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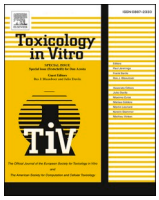

Review

Unravelling the toxicity of carbon nanomaterials – From cellular interactions to mechanistic understanding

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ABSTRACT

The application of carbon nanomaterials in diverse fields has substantially increased their demand for commercial usage. Within the earliest decade, the development of functional materials has further increased the significance of this element. Despite the advancements recorded, the potential harmful impacts of embracing carbon nanomaterials for biological applications must be balanced against their advantages. Interestingly, many studies have neglected the intriguing and dynamic cellular interaction of carbon nanomaterials and the mechanistic understanding of their property-driven behaviour, even though common toxicity profiles have been reported. Reiterating the toxicity issue, several researchers conclude that these materials have minimal toxicity and may be safe for contact with biological systems at certain dosages. Here, we aim to provide a report on the significance of some of the properties that influence their toxicity. After that, a description of the implication of nanotoxicology in humans and living systems, revealing piece by piece their exposure routes and possible risks, will be provided. Then, an extensive discussion of the mechanistic puzzle modulating the interface between various human cellular systems and carbon nanomaterials such as carbon nanotubes, carbon dots, graphene, fullerenes, and nanodiamonds will follow. Finally, this review also sheds light on the organization that handles the risk associated with nanomaterials.

1. Introduction

The nanotechnology industry has experienced significant growth in recent years, with analysts predicting a value of $125 billion by 2024 (Zarbin, 2018). Carbon nanotubes, valued at $4.55 billion in 2018, are anticipated to reach $9.84 billion by 2023. Additionally, the graphene market, worth $42.8 million in 2017, is projected to expand by 38% by 2025 (Zarbin and Orth, 2019). Nanomaterials (NMs), valued for their small size and aspect ratio, find applications in various fields, including agriculture, biology, cosmetics, communication, medicine, and pharmacy (Xue, 2017). Carbon-based Nanomaterials (CNMs), comprising of carbon blacks, carbon nanodots, carbon nano-onions, carbon nanofibers, carbon nanotubes, fullerenes, nanodiamonds, nano-size graphite, and graphene (as depicted in Fig. 1) (Adorinni et al., 2021), are widely used in water filtration (Nasrollahzadeh et al., 2021), fuel cells (Jaleh et al., 2022), batteries (Geng et al., 2020), solar panels (Hadadian et al., 2020), supercapacitors (Kakaei et al., 2021), and memory chips (Russo et al., 2017).

Carbon nanomaterials, such as carbon nanotubes (CNTs), possess distinctive physicochemical properties with high specific surface area, high carrier mobility, high electrical conductivity, flexibility, and optical transparency (Speranza, 2021) mechanical, thermal, magnetic, electronic, optical, and catalytic (Joudeh and Linke, 2022) that make them versatile for various applications in nanotechnology (Chufa et al., 2021). Researchers are intrigued by their nanoscale size and excellent electrical, mechanical, and optical properties that make them acceptable for direct interaction with biological systems (Debnath and Srivastava, 2021). Their hybridization states, allotropy, and dimensions can affect their toxicity, aggregation, and dispersibility. However, the extensive use of these materials raises environmental concerns because they

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inevitably end up in aquatic ecosystems and the atmosphere. Studies have demonstrated that they can have harmful effects on human cells, particularly carbon nanotubes (Silva et al., 2019). The toxicity of nanomaterials is a significant concern for the environment, aquatic systems, food products, and consumer goods because of high-dose consumption, production failures, environmental leakage, and occupational exposure (Dekkers et al., 2016; Gubala et al., 2018; Roy et al., 2016). With the widespread use of nanomaterials in commercial products and their exposure to humans and other organisms, concerns regarding health risks are growing. NMs can enter the environment through air, soil, and water, posing a threat to aquatic life and human health. Nanoparticles can gain access to organisms via ingestion, inhalation, or skin causing toxic effects on organs and tissues.

Considering the concerns above, this review aims to provide an overview of numerous studies that have reported various CNMs and their toxicity. Emphasis has been placed on the relationship between their physicochemical properties and mechanisms of toxicity in human cell lines. Furthermore, this review strives to give a thorough overview of current research on the consequences of the toxicity of CNMs and the potential public health and environmental risks associated with them, which may not have been covered in other reviews. Moreover, critical discussions are also aimed at optimizing the properties of CNMs for a safer nanomaterial with less toxicity.

2. Nanotoxicity: An overview

Nanotoxicology delves into the potential toxicity of materials at the nanoscale to living organisms and biological systems, making it a specialized field of study within nanoscience. Experts in this field assess these materials' physical and chemical properties, including particle active surface groups, catalytic activity, charge, size, shape, structure, solubility, surface coating, and surface area (Fig. 2), to comprehensively understand their potential impact (Sukhanova et al., 2018; Yuan et al., 2019). Nanoparticles can potentially interact with humans throughout the various stages of their life cycle including production, use, and disposal. The body's interfaces for transporting NMs include the skin, gastrointestinal (GI) tract, and respiratory system. Due to their small size, CNMs in the air can get into the body via the respiratory tract, passing through the alveolar section of the lungs and eventually entering the bloodstream and lymphatic system (Ganguly et al., 2018). Various treatments, medications, and creams incorporate NMs such as quantum dots and nanodiamonds (Abdellatif et al., 2022). These tiny particles can get into the body via the skin and gastrointestinal tract. While the skin usually serves as a barrier, it can allow nanomaterials to pass through (Ganguly et al., 2018). Similarly, the epithelial cells in the GI tract can absorb these particles, making it another route of entry. To assess the

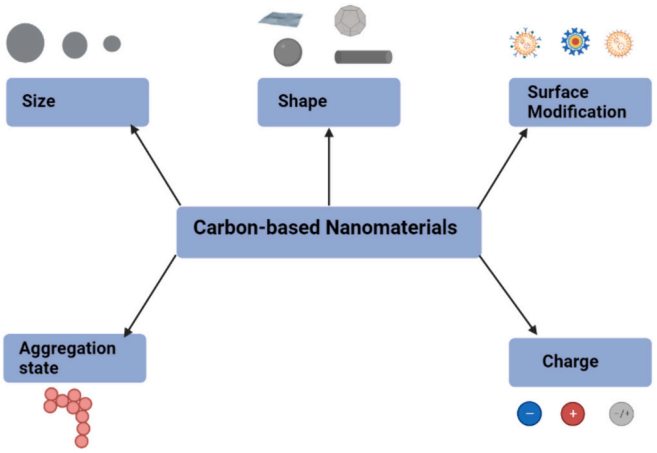

Fig. 2. The different physicochemical properties (size, surface modification, surface charge, shape, and aggregation state) that affect the toxicity of nanomaterials. Figure was created using https://www.biorender.com/

effect of CNMs on environmental and human health, it is crucial to assess their fate and potential toxicological effects (El-Kady et al., 2023). Understanding the interplay between nanomaterials and cells is vital for monitoring health and identifying nanotoxicity effects. These effects can range from physical damage to lipid peroxidation, DNA damage, mitochondrial damage, protein misfolding, and membrane damage caused by oxidative stress, surfactant interaction, and membrane damage (Lenz E Silva et al., 2019).

While many published reviews acknowledge the potential toxicity of carbon nanomaterials, they primarily concentrate on the physicochemical properties of carbon materials that impact toxicity. Nevertheless, the interaction between materials and cells that triggers toxicity and how their physicochemical properties correlate with toxicity remain inadequately understood, leading to ongoing debates. That is why it is essential to meticulously evaluate carbon-based nanomaterials' fate and potential toxicological repercussions on living organisms. We expect the field to continue to grow over the next few years and significantly influence the creation of safer nanomaterials with lower toxicity.

2.1. Toxicity of carbon-based nanomaterials to humans

Research has shown that exposure to CNMs can pose numerous health risks, such as carcinogenicity, cytotoxicity, genotoxicity, and lung inflammation (Barbarino and Giordano, 2021). Inhaling CNMs can lead to pulmonary granuloma, fibrosis, or inflammation, especially with

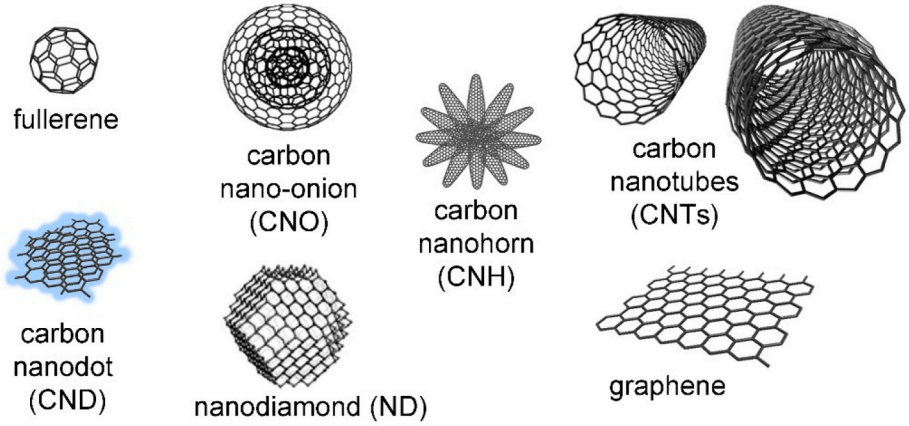

Fig. 1. Various types of carbon-based nanomaterials used in many applications. Figure adapted with permission from Ivyspring International Publisher (Adorinni et al., 2021).

multi-walled carbon nanotubes (MWCNTs), which can cause an inflammatory response and disrupt the mechanics of the lungs and airway epithelial function (Russ et al., 2019). Moreover, the smaller the size and the larger the size of the CNTs, the more challenging it becomes for macrophages to destroy them swiftly (Peng et al., 2020). When CNTs come into contact with alveolar epithelial cells and macrophages, it increases the likelihood of lung inflammatory cell bursts (Boyles et al., 2015). Furthermore, CNMs can infiltrate and permeate organs, such as the skin's dermis, with graphene also crossing the air-blood barrier to reach the liver and spleen (Li et al., 2021; Mao et al., 2016). However, research on the neurotoxicity of graphene materials and their capability to cross the blood-brain barrier is limited (Liu et al., 2015; Su et al., 2016; Tabish and Narayan, 2021). Additionally, there is a significant concern that carbonaceous nanomaterials can breach the placental barrier and harm the fetus since the placenta does not significantly hinder the transmission of nanomaterials. Therefore, the presence of CNMs in the fetus is a significant concern due to their small size (Teng et al., 2021).

3. The impact of carbon-based nanomaterial properties on their toxicity

Several researchers have investigated how crucial the physical and chemical properties, such as size, shape, surface area, topography, surface charge, and surface functionalization, concentration can influence the toxicity of nanomaterials (Nezakati, Cousins, and Seifalian 2014). These factors can impact the potential health risks and biomedical applications of the materials, including their ability to pass through biological barriers like the blood-brain barrier (Kafa et al., 2015). For example, the surface charge and functionalization of carbon nanotubes can affect how they are taken up by cells and dispersed throughout the body, as well as their potential toxicity (Tabish and Narayan, 2021). Similarly, graphene's surface area and crystallinity can affect its catalytic activity and potential biomedical applications (Georgakilas et al., 2016). The topography of materials may also play a role in their cellular uptake and toxicity (Gulumian et al., 2021). For a summary of these different properties and their potential toxic effects, please see Table 1.

4. Carbon-based nanomaterials exposure to cells: Potential toxicity effects

Research on the toxicity of CNMs has yielded valuable insights into the potential risks associated with exposure to these materials. Tables 2 to 6 in the sections below present a comprehensive summary of the existing knowledge on the types of nanomaterials, their physicochemical properties, and their effects on cells. However, there are still gaps in our comprehension of the health effects of carbon nanomaterials. Further research is needed to determine exposure's long-term effects and understand the mechanisms by which they can cause harm. It is also vital to consider the potential for synergistic effects between different types of nanomaterials or with other environmental factors, such as pollutants or stressors. Investigating the interactions between carbon nanomaterials and other pollutants could also shed light on their toxicity. Ongoing research on the toxicity of CNMs is crucial to ensure their safe and responsible use in various applications.

4.1. Carbon nanotubes

The rapid advancements in nanotechnology have brought about a pressing need for large-scale commercial carbon nanotube manufacturing. An increasing number of industrial-scale facilities are producing affordable MWCNTs to meet this demand. Researchers have studied the absorption and potential toxicity of CNTs, specifically MWCNTs and single-walled CNTs (SWCNTs), in humans and other biological systems. The toxicity of CNTs can vary depending on several factors, including exposure conditions, the model or test organism, the

Table 1
Properties of carbon nanomaterials and their toxic effects.

Properties of Nanomaterials	Effects	Ref
Size	The fibre length in carbon nanotubes plays a crucial role in determining their ability to penetrate biological barriers and their potential toxicity toward cells and tissues. Carbon nanotubes with fibre lengths exceeding 20 μm cannot be absorbed by macrophages, leading to frustrated phagocytosis, and hindering their clearance. Similarly, layered graphene nanoplatelets with a diameter of over 15 μm cannot be adequately phagocytosed by immortalized human monocytic cells, resulting in phagocytosis inhibition and eventual failure. Graphene, characterized by platelet morphology and lateral width ranging from less than <10 nm to>20 mm, promotes frustrated phagocytosis. Nanosized CB particles had a greater tendency to cause cytotoxicity, inflammation, and changes in phagocytosis in human monocytes compared to their larger micron-sized counterparts.	(Boyles et al., 2015; Kafa et al., 2015; Sahu et al., 2014; Samadian et al., 2020)
Shape	The physical structure of nanomaterials plays a vital role in their potential toxicity. Carbon nanoparticles with a high aspect ratio tend to cause more inflammation and lung damage. Long-aspect ratio particles, such as MWCNTs pose a greater risk to lung health than spherical particles. The potential toxicity of nanomaterials can vary based on their dimensions, morphology, and distribution.	(Abbasi et al., 2023; Cosnier et al., 2021; Turcheniuk and Mochalin, 2017)
Concentration	The study assessed the susceptibility of human alveolar basal epithelial cells to GO, considering its concentration. The nanoparticles of fullerene soot coated with dextran (Dex-FS) were modified and examined on C6 glial cells. The study revealed that Dex-FS displayed toxicity that varied in intensity based on the dosage, and it induced the generation of reactive oxygen species (ROS) in a manner that was influenced by both the dosage and duration of exposure. In addition, the study assessed the lysosomal activity and mitochondrial membrane potential after treatment with Dex-FS by employing acridine orange and rhodamine-phalloidin staining techniques.	(Ahamed et al., 2020; Athira et al., 2020a, 2020b; Gatoo et al., 2014)
Surface charge	Their surface charge influence carbon nanotubes' cellular uptake, biodistribution, and	Havrdova et al., 2016

(continued on next page)

Table 1 (*continued*)

Properties of Nanomaterials	Effects	Ref
	toxicity. Research suggests that negatively charged pristine CDs (CDs-Pri) can increase proliferation and oxidative stress. Contrary to positively charged CDs (CDs-PEI) are the most cytotoxic, penetrating the cell nucleus and causing significant G0/G1 phase changes.	
Surface functionalization	Graphene oxide (GO) and reduced graphene oxide (rGO) exhibit distinct surface oxidation states, with the hydrophilic nature facilitating its absorption by HepG2 cells, while the hydrophobicity of rGO leads to adsorption and aggregation. A study conducted by Suarez-Kelly et al. in 2017 examined the impact of nanodiamonds (FNDs) on various types of immune cells, including T cells, B cells, natural killer (NK) cells, and monocytes. The findings revealed that treating these immune cells with FNDs led to a substantial and dose-dependent absorption of FNDs. Importantly, this uptake did not compromise the viability of the cells and also resulted in the activation of the immune cells. The carbon black nanoparticle (CBNP) had an effect on rat lung and human bronchial epithelial cells that varied depending on the duration and dosage. Carbon-based nanoparticles (CBNPs) caused pulmonary fibrosis in a manner that was influenced by both the duration of exposure and the amount of nanoparticles administered. The development of pulmonary fibrosis caused by CBNPs was influenced, to some extent, by the activation of the NLRP3 inflammasome, which is regulated by miR-96 targeting the Forkhead transcription factor class O (FOXO3a).	(Chatterjee et al., 2014; Suarez-Kelly et al., 2017; Zhou et al., 2020)
Surface area	Its surface area and crystallinity can affect graphene's catalytic activity and biological functionality. The surface modification of nanomaterials such as graphene and graphene oxide can decrease their toxicity. Polyethylene glycol GO (PEG-GO), poly(acrylic acid)-functionalized GO (GO-PAA) were less harmful than pristine GO both invitro and Invivo	(Georgakilas et al., 2016; Xu et al., 2016)
Aggregation	The toxicity of nanomaterials is dependent on their aggregation states, which are guided by characteristics such as composition, size, and surface charge. Carbon nanotubes, for instance, have been found to assemble in the liver, lungs, and spleen with no immediate toxicity but can cause cytotoxicity over time due to their accumulation in aggregates. Moreover, agglomerated carbon nanotubes have been observed to be more toxic than those distributed and have been known to contribute to increased lung interstitial fibrosis.	(Gatoo et al., 2014; Zhao et al., 2015)
Topography	Entry of graphene multilayer sheets through cell membranes of primary human keratinocytes and human lung epithelial cells is initiated at corners or asperities that are abundant along the irregular edges of fabricated graphene materials	(Li et al., 2013)

form of the carbon nanotube, its origin, state of dispersion, modification processes, medium, and concentration (Donaldson et al., 2010; Lopes et al., 2021). However, they are commonly used in healthcare to improve performance, resulting in occupational and public exposure. Therefore, it is crucial to analyze toxicity and determine effective solutions to address concerns (Mohanta et al., 2019). Table 2 presents a summary of in vitro toxicity studies.

The cytotoxic effects of six CNT forms were studied on human chondrocyte stem cell precursors. The study examined SWCNTs and MWCNTs, including pristine, carboxylic and hydroxylic forms. The results showed that carboxylic SWCNT and MWCNT were the slightest toxic, with 90% and 82% cell viability, respectively, even at high concentrations of 100 g/mL (Aghaleh et al., 2021) Another study on human keratinocytes revealed that SWCNTs increased oxidative stress, inhibited cell growth, and activated NF-B in a dose-dependent manner (Palmer et al., 2019). Pristine multiwalled carbon nanotubes (P-MWCNTs) were also found to reduce cell viability in human lung epithelial cells due to oxidative stress in a study conducted by Azari et al. (Azari et al., 2020a, 2020b). The toxicity of pristine single-walled carbon nanotubes (P-SWCNT) and carboxylic functionalized single-walled carbon nanotubes (C-SWCNT) in the human neuronal cell line LN18 was depending on the dose and duration of exposure. The latter (C-SWCNT) exhibited increased toxicity compared to the former (P-SWCNT). Comparatively, C-SWCNT exhibited higher toxicity in terms of cell survival and oxidative stress than P-SWCNT (Vijayalakshmi et al., 2022). Similarly, a different study found that the presence of SWCNT resulted in a hazardous effect on HEK293 cells grown in culture, with the severity of the damage being directly correlated to the concentration of SWCNT. The observed cytotoxicity was associated with an increase in oxidative stress. In addition, when HEK cells were exposed to SWCNT at concentrations of 10 and 100 mg/mL, it caused damage to the cell membrane in a manner that depended on the dose. This exposure also led to an increase in the synthesis of IL-8, higher levels of thiobarbituric acid reactive compounds such as malondialdehyde, and a drop in intracellular GSH levels (Reddy et al., 2014).

Carbon nanotubes have a rope-like structure, which can pose a problem when inhaled as they may cause inflammation and apoptotic responses in lung cells (Sanpui et al., 2014). A study examined the cytotoxicity of two types of MWCNTs on lung epithelial cells and hepatocytes. One MWCNTs had residual iron, while the other had undergone heat treatment, resulting in fewer surface defects. Both types of MWCNTs decreased cell viability and caused membrane damage, as indicated by increased LDH leakage. The heat-treated MWCNTs were

Table 2
Toxicity of carbon nanotubes on cells as reported in the literature.

Nanomaterials	Properties	Cell type	Toxicity effects	Ref
CNTs		Small airway epithelial cells (SAEC)	Induce inflammation and apoptosis.	(Sanpui et al., 2014)
MWCNTs and MWCNTs-Fe	Dose	Human epithelial lung cells (A549) and Human hepatocellular carcinoma cells (HepG2)	Cell viability decreases dose- and time-dependent, with LDH leakage indicating membrane damage.	(Requardt et al., 2019)
P-MWCNTs		A549 cells	Cytotoxicity and oxidative stress cause cellular damage and reduce lung cell viability in A549 cells.	(Azari et al., 2020a, 2020b).
MWCNTs	Size	Human umbilical vein endothelial cells (HUVECs)	The release of cytokines, adhesion of monocytes, and production of intracellular reactive oxygen species all significantly increased.	(Zhao et al., 2019).
SWCNT	Dose	Human epidermal keratinocyte cells (HaCaT)	The presence of SWCNT particles caused oxidative stress and hindered the growth of keratinocytes. Applying small amounts of MWCNTs directly to the skin can cause damage to keratinocytes and worsen allergic skin conditions, depending on the presence of carboxylation.	(Palmer et al., 2019)
SWCNTs	Dose	Human Embryonic Kidney 293 (HEK293) cells	Exposure to SWCNT caused a cytotoxic effect in cultured HEK293 cells, which was directly proportional to the concentration of SWCNT. This cytotoxicity was linked to an elevation in oxidative stress.	(Reddy et al., 2014)
carbon black, CNT and nano-graphite (NG)	Physical dimensions, Surface chemistry, surface areas	RAW 264.7 macrophages	Functionalized CNMs triggered a slight cytotoxic effect comparable to that of pristine CNMs.	(Figarol et al., 2015)
Pristine-CNTs, carboxylic-CNTs, and hydroxylic SWCNTs and MWCNTs	Response surface methodology (RSM)	Human chondrocyte stem cells	At a concentration of 100 g/mL, the carboxylic SWCNT and MWCNTs exhibited negligible toxicity. The single-walled nanotubes showed 90% cell viability, while the multi-walled nanotubes showed 82% cell viability.	(Aghaleh et al., 2021)

more toxic and caused cell cycle arrest in lung epithelial cells dose-dependently (Requardt et al., 2019). In another study, the toxicity of three commercially available MWCNTs of different sizes (XFM4, XFM22, and XFM34) was evaluated on human umbilical vein endothelial cells (HUVECs) (Fig. 3), and it was found that XFM4, exhibiting the lowest diameter, was much more cytotoxic than the other two MWCNTs (Zhao et al., 2019).

When exposed to multiwall carbon nano-onions (MWCNOs) and MWCNTs, human skin fibroblast cells exhibited cytotoxic levels, leading to cell cycle arrest and enhancement of apoptosis/necrosis. These nanoparticles affected various cellular pathways, including the activation of transport, metabolism, and stress response genes. It was observed that MWCNTs triggered immunological and inflammatory responses, while MWCNOs were more focused on external stimuli. The induced signal transduction was found to be critically dependent on interferon and p38/ERK-MAPK cascades (Ding et al., 2005).

4.2. Carbon dots

Studies on cytotoxicity have indicated that carbon dots (CDs) can negatively affect cell viability, mortality, and proliferation (Havrdova et al., 2016). The use of CDs for cell labelling has been known to cause a slight reduction in cell viability at the concentrations employed (Hola et al., 2014). Despite carbon being an inherently non-toxic element, CDs' unique material and structural properties pose potential health risks that require thorough investigation (Bagheri et al., 2018). CDs' toxicity depends on the production method and is typically observed at higher dosages. CDs are taken up by cells through a process called endocytosis, and they become more concentrated in the cytoplasm, with minimal levels detected in the nucleus (Havrdova et al., 2016; Pierrat et al., 2015). A summary of the toxicity studies conducted on CD is presented in Table 3.

Researchers conducted a study to explore physicochemical factors' effects on CDs' safety. To create a diverse library of 35 CDs, unconventional materials and processes were employed. The findings revealed that CD toxicity is influenced by various factors, such as size, aggregation, charge, nitrogen content, passivation agent, and synthesis technique. Consequently, making accurate predictions regarding CD safety based on a single characteristic is difficult. (Fan et al., 2019). In 2019, a study was conducted on N-doped chitosan-based CDs using human skin fibroblasts. The study found that cell viability was 94% after 48 h (Janus et al., 2019). Another study by S. Cong et al. investigated the cytotoxicity of CDs produced from roast duck using PC12 cells and determined that cell viability was 91.19% after 36 h (Cong et al., 2019). According to research, exposure of laboratory-produced CDs to light can cause

Table 3
Toxicity of carbon dots toxicity on cells reported in the literature.

Nanomaterials	Properties	Cell type	Toxicity effect	Ref
CDs-Pri, CDs-PEG, CDs-PEI	Surface functionalization	Human umbilical cord-derived mesenchymal stem cells (HUC-MSCs)	Negatively charged carbon dots (CDs-Pri) and positively charged CDs-PEI were the most cytotoxic.	(Havrdova et al., 2016)
Nitrogen doped carbon quantum dots (NCQDs)	Concentration	Cervical cancer cells	NCQDs showed negligible to no toxicity against cervical cancer cells.	(Singh et al., 2019)
CD	Chemical	Human skin fibroblasts	Cell viability was determined to be 94% after 48 h.	(Janus et al., 2019)
CQDs	Time	PC12 cells	The cell viability of PC12 was determined to be 91.19% after 36 h.	(Cong et al., 2019)
CDs	Chemical	Normal (HEK-293) and malignant (HeLa and HepG2) human cells	Commercial CDs share photodegradation-induced cytotoxicity despite their chemical composition.	(Liu et al., 2021)
CDs	Concentration	Breast cancer cells	CDs had low cytotoxicity after 24 h of cell exposure.	(Esfandiari et al., 2019)
CD	Charge	Macrophages	Negatively charged CDs were shown to exhibit low toxicity.	(Lategan et al., 2018)
CQDs CDs-Pri CDs-PEI	Surface charge	HUC-MSCs	Negatively charged CDs-Pri boosted proliferation and increased oxidative stress.	(Havrdova et al., 2016)
CD	Concentration	Fibroblast	The minimal concentration of the CD solution is hazardous to human dermal fibroblasts.	(Golderova et al., 2022)

Table 4
Toxicity of graphene oxide on cells reported in the literature.

Nanomaterials	**Properties**	**Cell type**	**Toxicity effect**	**REF**
GO rGO	Fuctionalization	CaCO-2	GO and rGO exposure to Caco-2 cells resulted in cell death due to oxidative stress and apoptosis.	(Cebadero-Domínguez et al., 2022)
GO	exfoliation extent, size, shape, oxygen content, and surface charge	Red blood cells (RBC)	GO can trigger prolonged inflammatory and immunological reactions in mice glomerular nephritis (GNs) and lead to the destruction of RBC and impaired blood coagulation. These findings indicate that GO have the potential to produce muscle and haematological toxicity when present in high concentrations.	(Sun et al., 2024)
Graphene	Dose	Colonic human tissue	The results provided information on toxicity assessment using a human colon model, laying the groundwork for future bioapplication.	(Lahiani et al., 2021)
GO	Dose	Human multiple myeloma RPMI 8226 cells	GO is dose-dependent cytotoxic to RPMI 8226 cells and increases oxidative stress.	(Wang et al., 2014c)
GO, TRGO, and CRGO	Size Functional group	Human lung cells, bronchial epithelial cells (BEAS-2B), A549 cells	The toxicity intensity increases as the lateral dimension decreases and functional groups increase, indicating higher toxicity for TRGO and GO.	(Mittal et al., 2016)
GO	Dose	HEK293 cells	The experiment showed that the toxicity increased with the dosage.	(Gurunathan et al., 2019)
GO	Dose Functionalization	human fibroblast cells (THP-1) cells	At concentrations >50 lg mL^{-1}, GO exhibited cytotoxicity. Both GO and r-GO stimulated a pro-inflammatory reaction in A549 cells.	(Xu et al., 2016) (Di Ianni et al., 2021)
GO		alveolar epithelial cells (A549) and activated THP-1 macrophages (THP-1a)	GO induced a higher level of genotoxicity in THP-1a cells.	
GO and rGO	Surface charge	HepG2 cells	HepG2 cells can readily uptake GO based on its hydrophilicity. As the lateral dimension decreases and the number of functional groups increases, toxicity also increases, suggesting that TRGO and GO are more toxic.	(Chatterjee et al., 2014)
rGO	Dose	A549 cells	A549 cells displayed concentration-dependent sensitivity to GO, resulting in cytotoxicity.	(Tabish et al., 2017)
Graphene Nanoparticles (GNPs)	Dose and time	A549	Toxicity of GNPs in A549 cells influenced by dosage and exposure time.	(Nasirzadeh et al., 2019)
Graphene nanoribbons	Dose Time	HeLa cells, NIH-3 T3 cells and breast cancer cells (SKBR3, MCF7)	The decrease in the number of viable cells depended on the duration and dosage of exposure.	(Chowdhury et al., 2013)
GO, TRGO and CRGO	Lateral size and functional group density	BEAS-2B and A549 cells	Both cell types of experienced internalisation and oxidative stress-mediated cytotoxicity when exposed to GO. The toxicity level was directly proportional to the decrease in lateral dimension, and the presence of more functional groups indicated that TRGO and GO have a more significant potential for toxicity.	(Mittal et al., 2016)
GO	Particle size, morphology, exfoliation extent, oxygen content, and surface charge	Human Erythrocytes and Skin Fibroblasts	GO exhibited the highest haemolytic activity at the smallest size, whereas the lowest activity was observed in aggregated graphene sheets. Coating GO with chitosan resulted in a significant reduction in hemolysis.	(Liao et al., 2011)
GO	Dose electronic charge on the surface	Human lung fibroblast (HLF) cells	GO showed concentration-dependent cytotoxicity and genotoxicity on HLF cells, with more severe genotoxicity than cytotoxicity.	(Wang et al., 2013)

Table 5
Toxicity of fullerenes toxicity on cells as reported in the literature.

Carbon nanomaterial	Properties	Cell type	Toxicity effect	REF
Fullerenols	Dose	human epidermal keratinocytes (HEK)	The concentration of $C_{60}(OH)_{24}$ decreased significantly after 24 h, while the concentration of $C_{60}(OH)_{32}$ decreased significantly after 48 h.	(Saathoff et al., 2011)
$C_{60}(OH)_{24}$	Dose	endothelial cells	The cells were internalized, and their viability decreased in a dose-dependent manner.	(Yamawaki and Iwai, 2006)
C_{60}		A549 cells	Increase in ROS	(Wang et al., 2014a)
dFSNPs, DCFH-DA	Dose	A549	When observed under a fluorescence microscope, it was found that there was a significant free radical scavenging activity and a noticeable change in the cellular morphology.	(Athira et al., 2020a, 2020b)
C60 fullerene aqueous colloid solution	Dose	human embryonic kidney (HEK293) cells	The substance exhibited minimal toxicity when administered at doses ranging from 3.6 to 144 g/mL.	(Prylutska et al., 2019b)
F-828		human embryonic lung fibroblasts	ROS levels change intricately over time, causing necrosis, DNA breaks, and activating NF-kB and p53 transcription factors.	(Ershova et al., 2016)
nC_{60}	Size	A549	The impact of size can be demonstrated by the translocation of apoptosis-related fluorescent protein fused Bax at 20-fold lower and noncytotoxic doses.	(Song et al., 2012)

them to degrade into hazardous compounds for both normal and cancerous human cells (HeLa and HepG2). The molecular study identified 499 cytotoxicity-related chemicals, 212 of which had benzene, glucose, or polyethylene glycol, structures. Furthermore, the study revealed that all commercial CDs, irrespective of their chemical composition, exhibited identical cytotoxicity profiles and photodegraded products. This suggests that photodegradation-induced cytotoxicity is a common phenomenon among all CDs. The study also revealed that the CDs had low cytotoxicity after 24 h of cell exposure, with only high-quantum yield CDs showing substantial toxicity at higher concentrations. Additionally, the CDs displayed photo-induced cytotoxicity dependent on concentration and irradiation period (Liu et al., 2021).

The cytotoxicity of carbon dots with various surface functionalization was examined, and the results showed that the choice of surface passivation molecules affected their cytotoxicity, as illustrated in Fig. 4 (Havrdova et al., 2016). The study found that CDs-Pri (negatively charged carbon dots) and CDs-PEI (positively charged carbon dots with polyethyleneimine) were highly cytotoxic, causing significant changes in the G0/G1 phase of the cell cycle and penetrating the cell nucleus (as shown in Fig. 4). On the other hand, neutral CDs-PEG (polyethyleneglycol) did not cause any changes in cell shape, intracellular trafficking, or the cell cycle at a concentration of up to 300 μg/mL (Havrdova et al., 2016).

In a toxicological investigation conducted in vitro, researchers sought to establish a correlation between toxicity and concentration of positively charged CD over varying exposure durations. The study involved five experimental groups and one control group, with CD solution administered at increasing concentrations ranging from 24.15 to 120.75 μg/mL. The fifth and sixth groups showed signs of fibroblast destruction at solution concentrations of 96.6 and 120.75 μg/mL, respectively, with notable devastation in the center of the visual field and fragments of damaged cells on the periphery. Damaged fibroblasts accounted for over 20% in the fifth group and over 30% in the sixth group. Based on these findings, the researchers concluded that the minimal concentration of the CD solution that poses a hazard to human dermal fibroblasts is 96.6 μg/mL (Golderova et al., 2022).

4.3. Graphene

Graphene materials are known to have a wide range of physical and chemical properties, including size and chemical functional groups (Nezakati et al., 2014). GFNs, a form of graphene nanomaterial, are commonly employed in commercial products, particularly in biomedical applications. However, their use heightens the danger of human exposure. GFNs accumulate in tissues and organs, causing toxicity via lesions or functional impairment. They may also cause cytoskeletal abnormalities and organelle malfunction (Xiaoli et al., 2020) (Table 4). Smaller GO particles generate more oxidative stress and cytotoxicity than larger GO particles (Mittal et al., 2016). Thermally reduced graphene oxide (RGO) is more toxic than chemically reduced graphene oxide (Emadi et al., 2017).

The properties of GO, such as its purity, physical attributes, and chemical modifications, play a crucial role in assessing its impact on healthy cells. The biocompatibility of graphene-related materials is influenced by factors like particle size, shape, level of exfoliation, oxygen content, and surface charge, which can affect biological reactions in red blood cells. The degree of toxicity also depends on the exposure environment and the mechanism of cell contact (Ayreen et al., 2024). Through their research, Zhang et al. discovered that the absorption of graphene sheets is size-dependent, with 2 μm and 350 nm GO sheets significantly impacting macrophage absorption (Kurapati et al., 2018). Despite degradation by immune cells and phagocytes, graphene nanosheets can self-assemble into resilient structures (Cong et al., 2014). However, their hydrophobic nature can disrupt hydrophobic protein-protein interactions and cause forced separation, potentially leading to cell metabolism impairment and death (Luan et al., 2015). Another study explored the interaction between three types of graphene derivatives (GD-GOs) and human lung cells, revealing that GD-GOs internalize and cause oxidative stress-driven cytotoxicity in both cell types. The toxicity level was higher when the lateral size was reduced, and the functional group increased (Mittal et al., 2016). Additionally, GO and carboxyl graphene nanoplatelets exhibited dose- and time-dependent

Table 6
Toxicity of nanodiamonds on cells as reported in the literature.

Carbon nanomaterial	Properties	Cell type	Toxicity effect	Ref
ECNs		Microglial (BV-2) and A549 cells	When examining the decline in cell viability as a function of increasing ECN concentrations, we observed identical cytotoxic effects of ECN in both cell lines.	(Lazzarino et al., 2018)
nanodiamonds		Normal lymphocytes, non-small cell lung cancer cell line (NSCLC) human colorectal adenocarcinoma cell line (HT29)	The cell survival was lower when serum-free medium was used than the control.	(Adach et al., 2016)
Nanodiamond		Bovine serum albumin and fibronectin protein	These findings highlight the importance of understanding the chemical composition of the corona for predicting the fate of nanoparticles in the body.	(Khanal et al., 2020)
NDs	Concentration	BEAS-2B	In serum-free media, NDs demonstrated concentration-dependent cytotoxicity and were toxic to BEAS-2B, a human lung epithelial cell line.	(Chen et al., 2019)
NDs, Carbon black, MWCNT, SWCNT		Neuroblastoma cells and macrophages	Macrophages exposed to MWNT or SWNT produced up to five times more reactive oxygen species than neuroblastoma cells.	(Zhu et al., 2012)

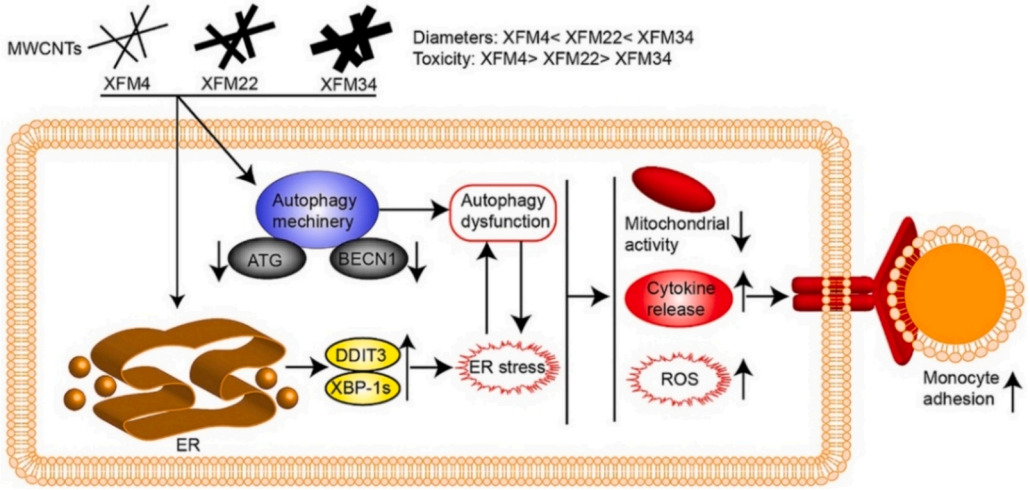

Fig. 3. The proposed toxicity mechanism of MWCNTs to HUVECs. MWCNTs alter the autophagy-ER stress pathway in HUVECs, causing reduced viability, inflammation, and oxidative stress. Figure adapted with permission from Elsevier (Zhao et al., 2019).

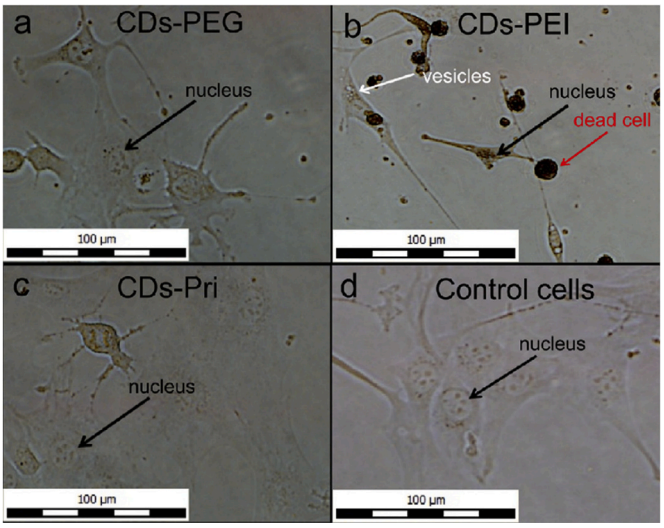

Fig. 4. Toxicity of CDs-PEG did not affect the cell morphology, however CDs-PEI, entered the cell nucleus and CDs-Pri affected the morphology (Havrdova et al., 2016).

toxicity against human hepatoma cells, with plasma membrane disruption and oxidative stress induction as fundamental mechanisms (Buskaran et al., 2021). Research indicates that the surface charge of GO has a direct impact on the way they are absorbed and internalized into cells (Yue et al., 2012). GO's interaction with cell membranes can cause morphological changes and even lead to cell death (Wang et al., 2013). This is due to the electrostatic interactions between the negatively charged oxygen surface groups of GO and the positively charged phosphatidylcholine on the outer surfaces of red blood cells. Additionally, the negative charge of GO can contribute to platelet activation and aggregation, whereas the positive charge does not have a significant effect (Liao et al., 2011). The harmful effects of GO are attributed to oxidative stress, with the surface electrical charge playing a critical role in its toxicity to haemoglobin-releasing factor (HLF) cells (Wang et al., 2013).

According to research conducted on human primary endothelial cells, it was discovered that graphene induces oxidative stress, which leads to apoptosis/necrosis-mediated cell death. Using cDNA microarray gene expression further revealed that graphene downregulates genes that play a crucial role in DNA damage response and repair pathways, indicating its potential to cause DNA damage(Fig. 5) in primary human cells (Sasidharan et al., 2016). Additionally, it was found that GO is cytotoxic to HepG2 cells by disrupting the plasma membrane and causing oxidative stress. However, it only poses a significant danger to human fibroblast cells (HDF) at high levels (Gurunathan et al., 2013; Lammel et al., 2013).

A recent analysis delved into the toxicity of GO on RPMI 8226 and revealed that GO displayed concentration-dependent cytotoxicity and genotoxicity. As doses increased, severe genotoxicity and decreased viability indicated oxidative stress (Wang et al., 2014c). Another study found that exposing HEK293 cells to varying doses of GO for 24 h led to

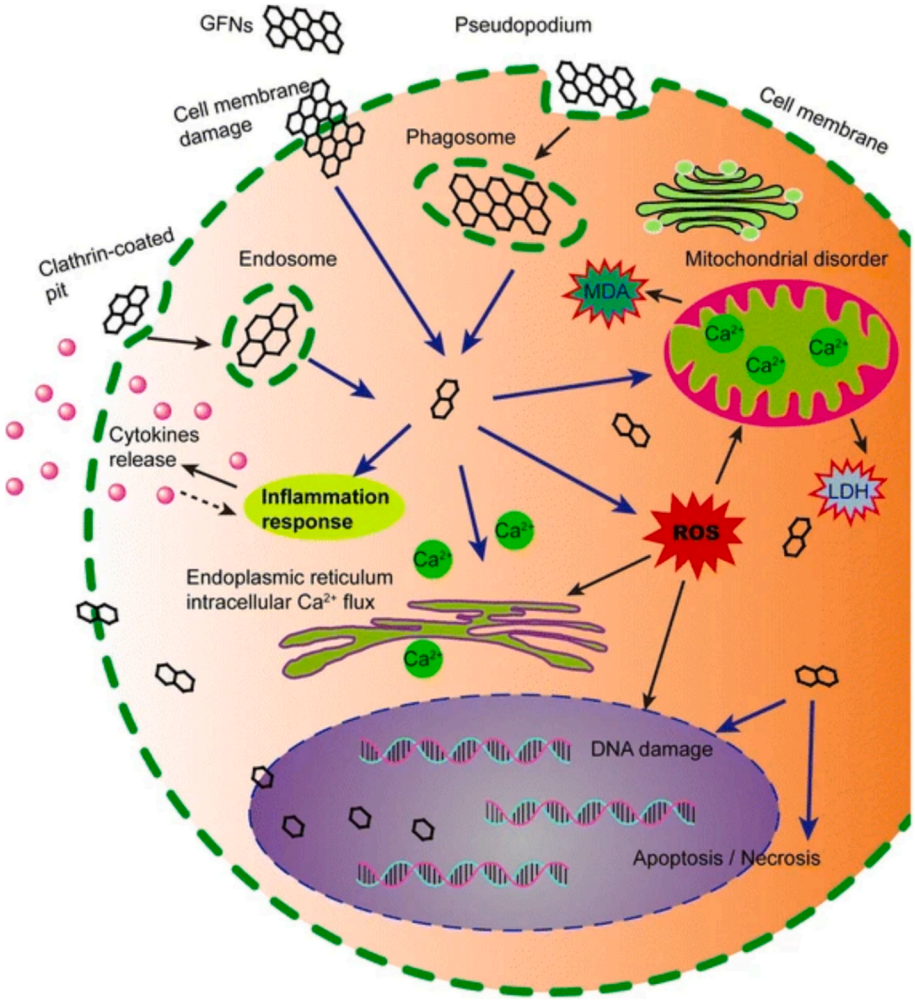

Fig. 5. Graphene-based nanomaterials can cause cytotoxicity by generating ROS, increasing LDH and MDA levels, and releasing Ca2+, leading to DNA Damage. Figure adapted with permission from Springer (Ou et al., 2016).

significant cytotoxicity, reducing cell survival and proliferation. This was attributed to increased LDH leakage, ROS formation, oxidative stress markers, mitochondrial membrane potential reduction, ATP generation, DNA damage, and caspase 3 activations (Gurunathan et al., 2019). GO may enter the cytoplasm and nucleus of human lung fibroblasts causing reduced cell adhesion, and cell death (Xu et al., 2016).

Other studies have demonstrated that GO causes cell death and oxidative damage in BF-2 cells. This effect is dependent on the dosage and duration of exposure, with even modest concentrations of GO (40 μg/mL) and 24 h of incubation leading to cytotoxicity and oxidative stress (Srikanth et al., 2018). Furthermore, the size of the GO particles also plays a role in triggering the production of reactive oxygen species (ROS) in the mitochondria (Srikanth et al., 2018).

4.4. Fullerenes

Fullerenes have been observed to engage with biological systems through diverse mechanisms, including enzyme modulation, phototoxic reactions, scavenging reactive oxygen species and free radicals, and initiating or catalyzing free radical reactions. The nanoparticulate system poses minimal toxicological risks when exposed orally, topically, or through inhalation in the short term. However, there is a possibility of long-term concerns due to the accumulation of these particles in the body. There has been a lack of extensive research on the repeated dose toxicity, carcinogenicity, and reproductive toxicity of these substances. The toxicity of fullerenes is contingent upon the dosage, with the quantity of fullerenes introduced into the body determining the occurrence of either deleterious or advantageous effects. The toxicity of fullerenes is determined by various factors, including their water solubility, electronic properties, functional groups, surface area, chemical composition, and shape. The electronic characteristics are contingent upon the chemical composition and the course of the reaction, both of which can influence the attachment of biomolecules to fullerenes (Shah et al., 2020).

Researchers conducted a study on fullerenol, which is a derivative of fullerene that is soluble in water. They found that F24-28 had lower toxicity and better antioxidant activity due to its higher solubility (Kovel et al., 2021). Rouse and colleagues conducted a study on the immunomodulatory properties of water-soluble fullerenol ($C_{60}(OH)_{20}$) on immune cells like T cells and macrophages in vitro (Yamawaki and Iwai, 2006). While it did not impact their survival, it did enhance the production of cytokines, particularly tumor necrosis factor-alpha (TNF-α), which plays a crucial role in eliminating abnormal cells during the cellular immune response (Liu et al., 2009). A summary of the toxicity of various fullerenes derivatives is summarised in Table 5.

Various concentrations of fullerenols ($C_{60}(OH)_{20}$, $C_{60}(OH)_{24}$, and $C_{60}(OH)_{32}$) were used to expose human epidermal keratinocytes (HEK) for 24 and 48 h to determine their potential toxicity. After 24 h, $C_{60}(OH)_{32}$ at 42.5 μg/mL significantly reduced viability. While normalised IL-8 concentrations were not different for $C_{60}(OH)_{20}$, they were lowered for $C_{60}(OH)_{24}$ and $C_{60}(OH)_{32}$ after 24 and 48 h (Saathoff et al., 2011). Additionally, in vitro studies on endothelial cells exposed to

$C_{60}(OH)_{24}$ showed a dose-dependent decrease in cell viability and impaired cell adhesion and growth after a 10-day treatment (Yamawaki and Iwai, 2006). The acute toxicity of surface-functionalized fullerene soot nanoparticles (dFSNPs) in A549, a model for lung exposure, was assessed by Athira et al. The comprehensive study (Fig. 6) validated the dose-dependent toxicity of dFSNPs (Athira, E. T. Biby et al., 2020). Hydroxylated fullerenes significantly reduce cell viability and cause cell cycle arrest in some cells while having minimal effects on viability and cell cycle in other cells (Su et al., 2010). Prylutska et al., 2019a, 2019b investigated the harmful effects of a nanocomplex generated by the noncovalent interaction of C60 fullerene with Cisplatin (Cis—Pt) on Lewis lung cancer (LLC) cells in contrast to the free drug. The nanocomplex dramatically reduced cell viability, degraded shape and adhesion, impeded migration, and caused proapoptotic accumulation (Prylutska et al., 2019a).

When C60 NPs were introduced to A549 cells, ROS levels increased, which triggered the activity of glutathione reductase to restore the balance of cellular oxidation-reduction and activate autophagic responses to maintain cellular health (Wang et al., 2014a). The toxicity of an aqueous C60 fullerene colloid solution was examined, and it was found that C60 fullerene had modest toxicity against HEK293 cells at concentrations ranging from 3.6 to 144 μg/mL, with an IC50 value of 383.4 μg/mL (Prylutska et al., 2019b). F-828, a soluble fullerene derivative, has been investigated as a potential nano vector and therapeutic agent; however, its toxicity is a concern. In vitro studies have shown that F-828 generates necrosis, DNA breaks, an increase in the transcription factors NF-kB and p53, and complex time-dependent changes in ROS levels. During necrosis-induced cell death, TGF-, RHOA, RHOC, ROCK1, and SMAD2 expression levels rise (Ershova et al., 2016).

According to the research, there is a correlation between the size of nC_{60} nanomaterials and their impact on DNA polymerase suppression and cytotoxicity. The study indicates that smaller nC_{60} aggregates may pose a greater risk at high exposure dosages (4-6 mg/L). Additionally, the research reveals that apoptosis-related fluorescent protein exhibits size-dependent behaviour, as evidenced by Bax translocation at doses 20 times lower than noncytotoxic ones (Song et al., 2012).

Fullerene derivatives with reversed surface charges are prepared in aqueous solutions to assess their toxicity. The effectiveness of cationic C60-EDA and anionic C60-(EDA-EA) was evaluated. Due to the influence of membrane potential (with a negative charge inside) in both the cell and mitochondria, C60-EDA is absorbed by cells and transported into mitochondria at a faster rate compared to C60-(EDA-EA), which is more concentrated in lysosomes. Due to its high cellular uptake and mitochondrial enrichment, C60-EDA demonstrates superior antioxidation abilities in laboratory settings compared to C60-(EDA-EA), suggesting its enhanced efficacy in treating diseases caused by oxidation (Ma et al., 2021). A study discovered that using dextran-coated C70 resulted in the preservation of cell viability of L929 at a level above 80% following a 24-h treatment. The cells that underwent treatment exhibited preserved mitochondrial membrane potential and intact lysosomes. The integrity of actin filaments and the nucleus was also preserved. The findings indicate possible medical uses for dextran-coated C70 (Ashtami et al., 2019). Another study comprehensively investigates cell viability assays, morphological evaluations, organelle functionality analysis, live-dead assays, and nuclear integrity measurement. The study affirms the toxicity of the nanomaterials, which increases as the dose increases. It advises the implementation of appropriate precautions when exposed to these materials (Suku et al., 2020).

4.5. Nanodiamonds

Researchers have conducted various studies on the toxicity of nanodiamonds, examining aspects such as cellular uptake mechanisms, intracellular localization, cytotoxicity, genotoxicity, immunotoxicity, and long-term effects. They aim to understand the factors contributing

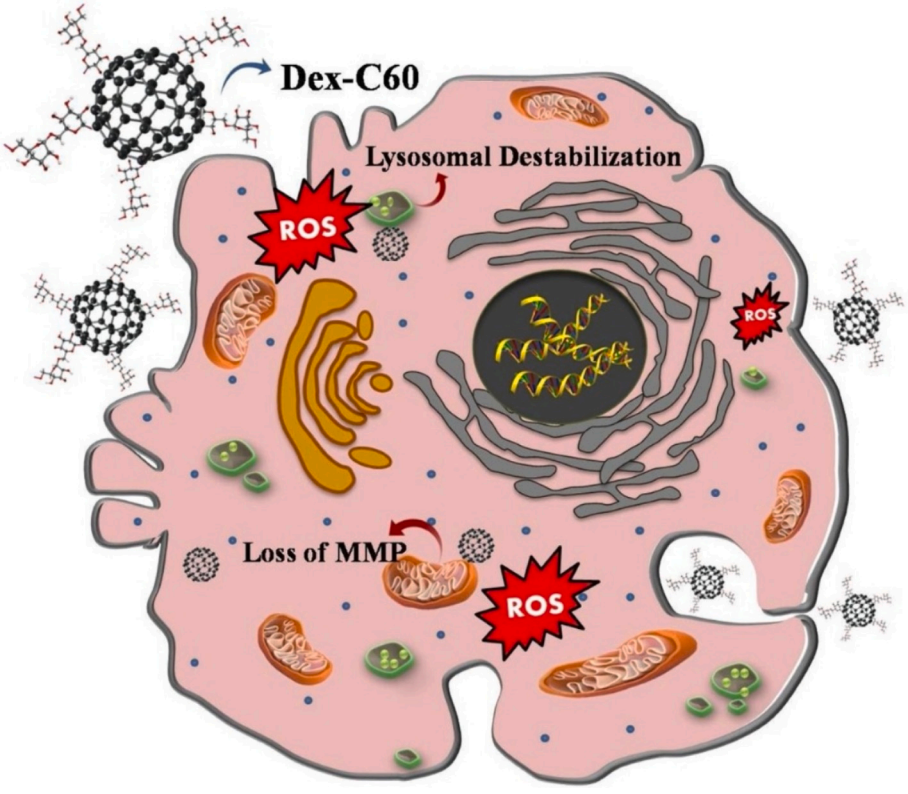

Fig. 6. Dex-C_{60} nanoparticles cause toxic reactions in C_6 glial cells by penetrating deeper into the cells. Figure adapted with permission from Elsevier (Biby et al., 2020).

to potential nanodiamond toxicity and the underlying mechanisms involved. One study by Prabhakar et al. focused on how cells monitor the low but potentially harmful effects of nondegradable fluorescent nanodiamonds (FNDs) through intracellular tracking over time. The study found FNDs in different cellular compartments, such as early endosomes and lysosomes near the plasma membrane. These findings suggested that FNDs were internalized into the cells via endocytosis and potentially exocytosis via lysosomal degradation. Fig. 7 from the study provides visual evidence of the endocytosis and exocytosis processes occurring in tandem (Prabhakar et al., 2017).

The level of air oxidation plays a significant role in the toxicity of detonation nanodiamonds (DNDs) in human airway epithelial cells, resulting in a pro-inflammatory response. To reduce the bioactivity in human airway epithelial cells (HAECs), surface modifications such as increased oxygen content, formation of carboxylic groups, decreased unpaired electron content, and negative zeta potential are recommended. These discoveries are essential for comprehending the chemical and molecular processes contributing to carbonaceous nanomaterials' inhalational toxicity (Adach et al., 2016). Numerous studies have demonstrated that surface-modified NDs, which are carbon nanomaterials, can potentially cause oxidative stress and DNA damage in various cell types. For instance, Dworak et al. discovered that continuous exposure to NDs can damage lymphocytes' DNA due to oxidative stress (Dworak et al., 2014). Additionally, a study by Keremidarska et al. found that exposure to a commercial nanodiamond preparation can increase IL-8 expression in human airway epithelial cells due to oxidative stress. The researchers also examined the cytotoxicity of nanodiamond particles produced by explosion and purified using various oxidizers. They discovered that rat mesenchymal stem cells (rMSCs) were more susceptible to the cytotoxic effect of nanodiamond particles than MG-63. Furthermore, smaller NDs were found to be more cytotoxic than larger ones, as they inhibited cell proliferation more effectively in MG63 and rat rMSCs (Keremidarska et al., 2014).

The research investigated how engineered carbon nanodiamonds (ECNs) affect microglial and alveolar basal epithelial cells in terms of cell survival, nitric oxide (NO) and ROS production, and energy metabolism. The study found that non-cytotoxic ECN dosages increased NO and ROS generation, leading to oxidative stress and mitochondrial malfunction (Lazzarino et al., 2018). Additionally, the research explored the cytotoxic effect of nanodiamonds on lymphocytes, lung cancer cells, and HT29 colorectal adenocarcinoma cells, revealing no effect on cell survival but decreased survival in serum-free mediums (Adach et al., 2016). Furthermore, the study delved into the mechanism of interaction between NDs and human serum albumin (HSA), a serum protein, discovering that NDs were cytotoxic to human lung epithelial cells BEAS-2B in a concentration-dependent manner in a serum-free medium (Chen et al., 2019). However, in full cell culture conditions, NDs exhibited no detectable toxicity toward Hela cells, and ND cytotoxicity was correlated with serum proteins in the culture medium (Hemelaar et al., 2018). Finally, Zhu et al. explored the acute toxicity of NDs delivered through intratracheal instillation. They concluded that a histomorphology investigation and accompanying biochemical markers indicated dose-dependent toxicity of NDs in the lungs, liver, kidneys, and blood (Zhu et al., 2012).

Wierzbicki et al., explored the toxic effects of diamond nanoparticles on different types of endothelial cells, including human umbilical vein endothelial cells (HUVEC), human mammary epithelial cells (HMEC), and the HS-5 cell line, by assessing the extent of cell exposure. The interaction between the surface of the nanoparticles and endothelial cells resulted in significant toxicity. Cells experienced ROS synthesis and NO depletion as a result of mechanical interaction (Wierzbicki et al., 2023). A study conducted by Fusco et al. examines the impact of NDs on the functionalization of human peripheral blood mononuclear cells (PBMC) and evaluates their compatibility with blood. NDs-COOH and NDs-NH2 modified NDs exhibited excellent compatibility with blood and stimulated immune responses. Nevertheless, NDs-COOH exhibited more noticeable reactions, inducing significant regulation of immune-modulatory transcripts (Fusco et al., 2020).

5. The underlying mechanism of toxicity of carbon-based nanomaterials

There are various ways in which nanomaterials can be harmful leading to cytotoxicity effects, such as generating reactive oxygen species (ROS), DNA damage, lysosomal damage, mitochondrial dysfunction triggering immunological responses and eventual cell death via apoptosis or necrosis (Yuan et al., 2019). Oxidative stress is an essential mechanism behind nanomaterial-induced toxicity resulting from increased reactive chemical species. In model cell lines, graphene is cytotoxic, with cellular uptake and ROS formation believed to be the primary causes (Gurunathan et al., 2019).

5.1. Oxidative stress

The prevailing theory regarding the toxicity of manufactured nanomaterials is that they may produce ROS directly or indirectly, leading to oxidative stress in target cells (Sengul and Asmatulu, 2020) (Fig. 8). Research has suggested that the production of ROS in target cells could be a potential mechanism of graphene toxicity (Zhang et al., 2016). ROS are a byproduct of mitochondrial respiration, phagocytosis, and

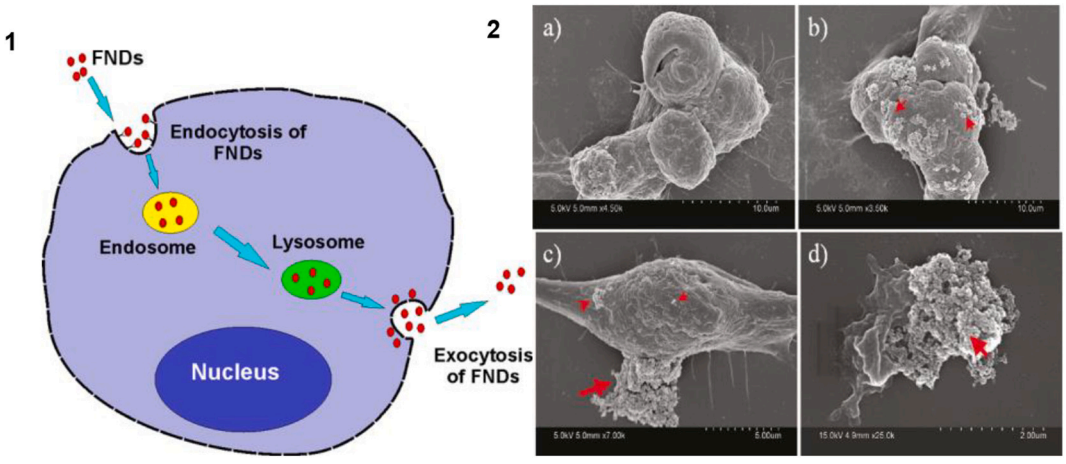

Fig. 7. 1. The diagram shows fluorescent nanodiamonds in early endosomes and lysosomes. 2. SEM photos display different cell morphology, including densely covered, varying-sized, and collapsed cells. Figure adapted with permission from ACS (Prabhakar et al., 2017; Xing et al., 2011).

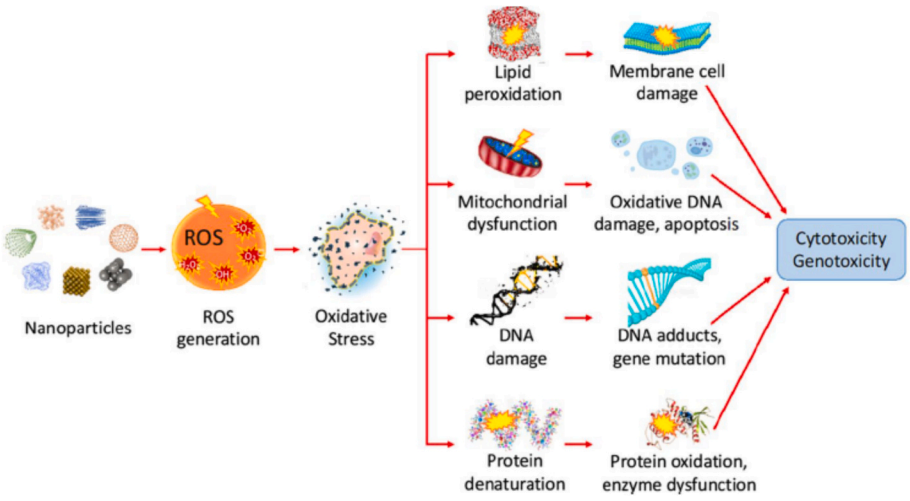

Fig. 8. The toxicity of carbon-based nanoparticles via the induction of ROS, which can be generated by mitochondria and result in lipid peroxidation, DNA damage, and protein denaturation. Figure adapted with permission from Springer (Sengul and Asmatulu, 2020).

metabolism. However, excessive ROS buildup can lead to oxidative stress linked to various clinical conditions (Banerjee et al., 2020). Induction of ROS is considered one of the primary ways that inorganic nanomaterials cause toxicity (Li et al., 2014).

Cellular homeostasis maintains a delicate balance between the production of ROS and their removal or decrease by antioxidant enzymes. When antioxidant activity fails to lower ROS levels, macromolecules such as DNA, membrane lipids, and proteins may suffer damage, leading to cellular harm. Certain graphene family nanomaterials (GFNs) with high hydrophobic surface areas may interact with membrane lipids, causing direct physical toxicity or by adsorbing biological molecules, which can result in indirect toxicity (Obeagu, 2018). Studies reveal that ROS production following GFM exposure occurs in a concentration- and time-dependent manner, indicating an oxidative stress mechanism (Kim et al., 2020). Oxidative stress is the predominant cause of DNA damage and apoptosis in Human Lung Fibroblasts (HLF) cells after fullerene exposure (Ershova et al., 2016). In pheochromocytoma (PC12) cells, GO exhibited cytotoxicity, with ROS playing a crucial role in this cytotoxicity, as discovered by Zhang et al. Subsequently, other researchers demonstrated the cytotoxicity of GO in various tumor cells, identifying oxidative stress as a crucial mechanism. The GO accumulation in the cytoplasm caused significant morphological changes and reduced the phagocytosis ability of toll-like receptor 4 (TLR4) (Kang et al., 2017).

Additionally, increasing ROS levels has been observed to contribute to macrophage necrotic cell death (Robinson et al., 2019). Hu and colleagues have revealed that direct interactions between the cell membrane and graphene oxide nanosheets result in physical damage to the cell membrane, causing cytotoxicity. It is worth noting that the duration of exposure does not affect cytotoxicity, which primarily occurs during the initial contact (Tian et al., 2017). Furthermore, Yan et al. discovered that graphene induces cytotoxicity by decreasing mitochondrial membrane potential and increasing intracellular ROS levels, activating the mitochondrial pathway, and leading to apoptosis. The activation of caspase 3 and downstream effectors is triggered in graphene-treated cells through the activation of mitogen-activated protein kinases (MAPKs) and Transforming Growth Factor-Beta (TGF-β) signalling pathways (Yan et al., 2017).

The underlying cause of CNT toxicity is oxidative stress, which triggers inflammation by activating transcription factors sensitive to oxidative stress. Prolonged exposure to CNTs can result in inflammation, fibrosis, and fibre- or secondary-mutation-induced cancer development. Despite differences in their characteristics, various types of CNTs have been found to elicit similar toxicity, albeit with different levels of potency (Møller et al., 2014). In a study by Zhu et al., the toxicity of various carbon nanomaterials on neuroblastoma cells and macrophages, such as NDs, CB, MWNT, and SWCNT, was compared. The results revealed that toxicity followed the order of SWCNT > MWCNT > CB > ND. Moreover, when exposed to MWNT or SWNT, macrophage cells produced significantly higher levels of ROS than neuroblastoma cells, indicating a more pronounced impact of carbon nanomaterials on macrophages (Zhu et al., 2012).

Additionally, research has revealed that CDs exhibit oxidative activity, which leads to photo-induced cell damage and the disintegration of biofilm matrices by generating ROS, resulting in cell auto-apoptosis (Wang et al., 2015b). Multiple studies have demonstrated that CDs can cause DNA damage in fibroblast cells and dose-dependent ROS production in HeLa cells. It is primarily the properties of the nanomaterial itself, rather than the coated polymers, which are associated with the formation of ROS and CD toxicity (Havrdova et al., 2016). Furthermore, CDs have been found to display phototoxicity by elevating intracellular ROS levels when exposed to blue light. Still, they can also scavenge free radicals in the absence of light, as evidenced by Chong et al. (Chong et al., 2014). It is worth noting that nanomaterials have the potential to accumulate not only in organs, tissues, and cells but also in cell organelles such as mitochondria and nuclei. This can disrupt cell metabolism and result in DNA damage, mutations, and even cell death. Furthermore, the cytotoxicity of nanomaterials could impede cell differentiation and protein synthesis, trigger the activation of pro-inflammatory genes, and provoke the production of inflammatory mediators (Barua and Mitragotri, 2014).

When exposed to carbon nanomaterials, macrophages can cause various cellular and molecular changes, such as ROS production, lysosome destruction, and activating apoptotic, inflammatory, and pyroptotic pathways. One significant effect is the activation of the ROS-activated Mitogen-activated protein kinase (MAPKs) pathway, which can lead to mitochondrial-dependent apoptosis. Additionally, ROS can activate transcription factors like NF-B, which control inflammation. As shown in Fig. 9, carbon nanoparticles can also cause lysosomal membrane permeabilization (LMP) and subsequent cathepsin translocation. Furthermore, ROS and LMP can mutually trigger each other in an amplification cycle. LMP can disrupt autophagy and initiate inflammasome-dependent pyroptosis, characterized by caspase 1 cleavage and IL-1 release (Yuan et al., 2019).

5.1.1. *DNA damage*

The small size and large surface area, coupled with a charge, make GO capable of causing severe DNA damage. Although it cannot infiltrate the nucleus of a cell, it can interact with DNA during the mitosis phase,

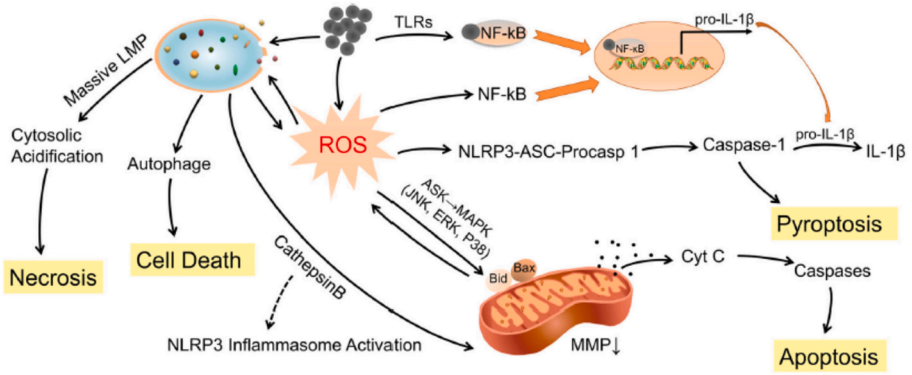

Fig. 9. Diagram illustrating how carbon-based nanoparticles generate macrophage cytotoxicity. Figure adapted with permission from Springer (Yuan et al., 2019).

increasing the possibility of defects. The stacking interaction between GO and hydrophobic DNA can lead to segment deformation and breakage (Chatterjee et al., 2016; Ivask et al., 2015; Wang et al., 2015a). Numerous scientific studies have demonstrated that damage to DNA is the underlying cause of CNT genotoxicity. Such damage leads to the production of ROS and reactive nitrogen species (RNS), which react with DNA bases, causing oxidative and nitrative DNA damage (Fig. 10) (Hiraku et al., 2016). ROS, such as hydroxyl and oxygen radicals, are particularly harmful to DNA as they can induce DNA oxidation, DNA strand breakage, 8-hydroxyguanine production, and DNA adducts resulting from lipid peroxidation (Andrés Juan et al., 2021). MWCNTs can cause DNA damage in human endothelial cells and affect cellular redox status, increasing ROS (Long et al., 2017). Aggregated diamond nanorods and nanodiamonds have been shown to increase DNA repair protein expression in embryonic stem cells, but their surface chemistry affects DNA damage. It is important to note that DNA damage is dose-dependent, as evidenced by the formation of yH2AX foci after a 12-h treatment with QDs (Xing et al., 2011).

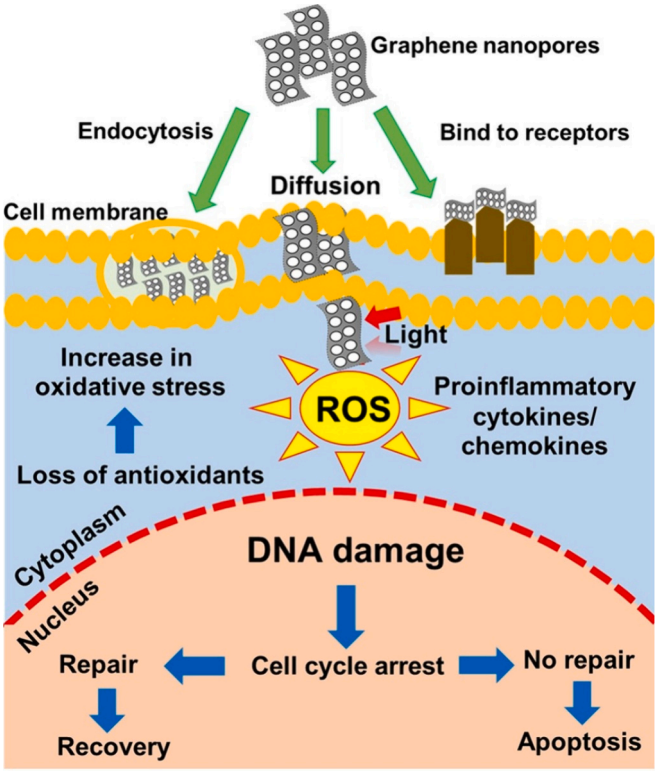

Fig. 10. Schematic depicting putative action of graphene nanopores' (GNPs). Figure adopted with permission from Elsevier (Tabish et al., 2018).

CQD was found to increase ROS production and can be used as ROS scavenger, the induction of ROS and formation of yH2AX foci were reduced. These findings suggest that the DNA damage caused by QD may be attributed to ROS generation (Li et al., 2022a; Liang et al., 2020). On the other hand, DF-1, a C60 derivative, protected both human lymphocytes and rat intestinal crypt cells against radiation-induced DNA damage, as evidenced by the decrease in MN generation. Furthermore, DF-1 significantly decreased ROS levels in crypt cells, indicating its ability to provide robust protection against the harmful biological effects of irradiation in mammalian systems, including cell death, DNA damage, oxidative stress (Theriot et al., 2010).

5.1.2. *Mitochondrial damage*

GFN exposure harms mitochondrial function by increasing oxygen consumption, altering mitochondrial membrane potential, and initiating apoptosis via the mitochondrial pathway (Seabra et al., 2014). Additionally, studies have shown that GO increases mitochondrial electron transport complex activity, which produces ROS during mitochondrial respiration, causing oxidative and thermal stress, impairing mitochondrial respiration, and inducing toxicity (Fig. 11) (Gualtieri et al., 2021). CNTs, such as SWCNT and MWCNT, have been found to accumulate selectively in normal and tumor cells, disrupting mitochondrial function in both cell types and causing cytochrome *c* release and mitochondrial dysfunction (Wang et al., 2014b; Wang et al., 2012). As discussed

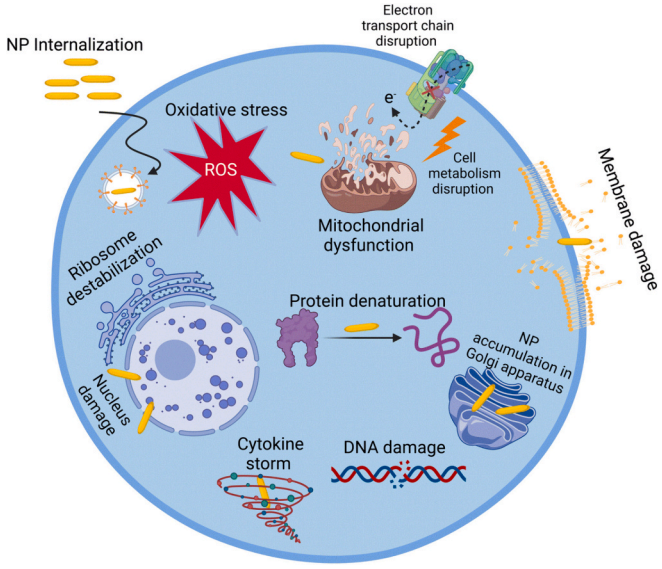

Fig. 11. Schematic illustration of the various modes of action of engineered nanomaterials on cells. Figure adapted with permission from Royal Society of Chemistry Publishing (Awashra and Młynarz, 2023).

earlier, the release of cytochrome *c* is a crucial component of CNT-induced mitochondrial dysfunctions. Cytochrome c is essential to the mitochondrial respiratory chain between the cytoplasm's inner and outer mitochondrial membranes (Shukla et al., 2022). Studies have shown that functionalized MWCNT can impact the cellular redox state and open the mitochondrial permeability transition pore (PTP) via the mitochondrial pathway created by MWCNT (Snyder, 2020). Typically, oxidative stress triggers the activation of the carbon nanomaterial-regulated mitochondrial pathway (Yan et al., 2017), causing cytochrome *c* to be released from mitochondria into the cytosol (Zhou et al., 2024). After being released, cytochrome *c* can combine with other molecules to form the apoptosome. The apoptosome then activates a series of enzymes, including caspase-9, leading to cell death (Zhou et al., 2024).

5.1.3. Inflammatory response

GFNs have been known to trigger notable inflammatory reactions, such as infiltration of inflammatory cell, pulmonary edema, and granuloma formation, mainly when introduced intravenously or intratracheally in substantial amounts (Kong et al., 2024). By releasing cytokines and chemokines that attract immune cells and encourage the production of Type 1 and Type 2 T helper cytokines, GFNs can prompt inflammation and harm to tissues (Reshma et al., 2016).

CNTs can trigger inflammation by binding to binding to toll-like receptors (TLRs), triggering the NF-κB signalling cascade. This increases the production of specific cytokines and chemokines such as IL-8 and MCP1 (Keshavan et al., 2021; Turabekova et al., 2014). Studies have shown that MWCNTs stimulate human cells' IL-8 gene expression and NF-B activation as indicated in Fig. 12. At the same time, SWCNT activates stress-related kinases through dose-dependent activation of NF-B in human keratinocytes (Thai et al., 2024). Exposure to carbon black, asbestos, and MWCNTs has been linked to an increased inflammatory response in mice. MWCNTs and asbestos cause polymorphonuclear leukocytes and protein exudation, and carbon black induces a typical foreign body reaction. Additionally, long MWCNTs can cause “frustrated phagocytosis” in macrophages, while short MWCNTs can cause chromosomal damage. In some cases, CNTs can induce necrosis, apoptosis, and chromosomal damage in mouse macrophages due to ROS without any significant inflammatory response observed (Nel, 2023). GQDs markedly enhanced the phosphorylation of p38 MAPK and p65, facilitating the translocation of nuclear factor-κB (NF-κB) into the nucleus. Collectively, these findings demonstrate that GQDs stimulate the production of ROS, apoptosis, autophagy, and an inflammatory reaction through the activation of p38MAPK and NF-κB signalling pathways in THP-1 macrophages (Qin et al., 2015).

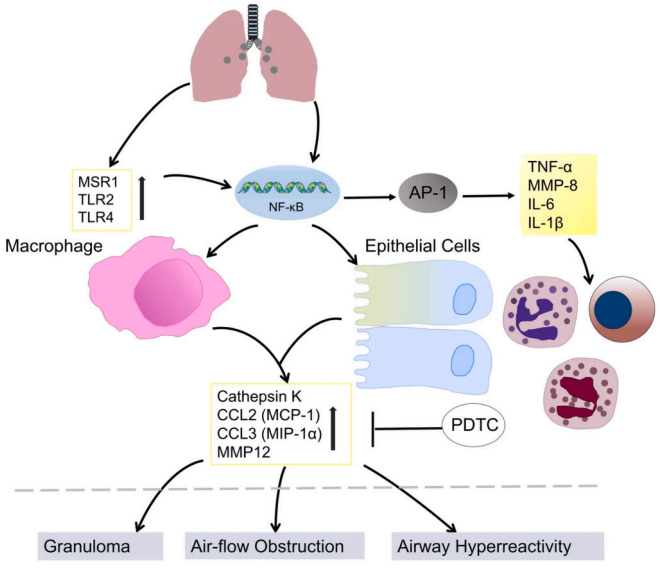

Fig. 12. Diagram depicting how CNT can trigger inflammation by binding to toll-like receptors (TLRs), initiating the NF-κB signalling cascade. Figure adapted with permission from Springer Nature (Yuan et al., 2019).

5.1.4. Apoptosis

The process of cell self-destruction, known as apoptosis, can be initiated by graphene and GO through physical damage to cell membranes, changes in mitochondrial membrane potential, and increased outer mitochondrial membrane permeability (Ou et al., 2016). This can lead to the activation caspase-3 through mitochondrial-dependent apoptotic pathways, resulting in cell death (Fig. 13) (Feng et al., 2022). Moreover, rGO has been found to induce apoptosis through both death-receptor and traditional mitochondrial mechanisms at low dosages and early time points (Chatterjee et al., 2014). When there are high levels of ROS present in mitochondria, it can lead to damage of the membrane phospholipids, leading to depolarization of the mitochondrial membrane. This can restrict the number of electrons leaving the mitochondrial chain leading to their reaction with molecular oxygen to produce O_2. The O_2 can further combine with molecular oxygen to form H_2O_2 or partially reduce to toxic OH. One way to achieve the desired result is by either restricting the electron transport chain or by improving the electron transfer to molecular oxygen. NP can accelerate O_2 synthesis (Napolitano et al., 2021).

Upon exposure to carbon nanotubes, certain types of cells, including T lymphocytes and HEK293 cells, undergo apoptosis. The expression of various genes involved in apoptosis (such as p16, bax, hrk, bak1, p53, p57FGFR2, TGF beta receptor1 (TGFbetaR1), and TNFAIP2) is observed to increase in the presence of CNTs (Chen et al., 2015a). According to experts, CNT toxicity arises due to extracellular matrix protein signalling, which causes alterations in cell structure, organelle displacement, membrane deformation, and apoptosis (Mohanta et al., 2019). Moreover, researchers have investigated the result of surface functionalization on MWCNT-activated macrophage toxicity and found that MWCNTs-PEG were limited cytotoxic and correlated with decreased apoptotic cell death compared to MWCNTs-COOH. In addition, MWCNTs-PEG were found to decrease the production of ROS and NADPH oxidase activity. These findings suggest that surface functionalization of CNTs can potentially alter ROS-mediated cytotoxicity and apoptosis by modifying apoptotic signalling pathways (Zhang et al., 2015).

5.1.5. Necrosis

Necrosis is cell death activated by inflammatory reactions or cellular damage. This type of cell death is characterized by a rapid breakdown of plasma membrane integrity, which can result in the release of endogenous molecules known as damage-associated molecular patterns (DAMPs) (Amarante-Mendes et al., 2018; Sangiuliano et al., 2014). Research has shown that a high graphene concentration can cause cell apoptosis and necrosis (Siqueira et al., 2022). Additionally, GO therapy has been found to activate Toll-like receptor 4 (TLR4) signalling and generate autocrine tumor necrosis factor (TNF)-alpha production, leading to macrophage necrosis (Hsu et al., 2021). Furthermore, when GO is combined with cisplatin (CDDP), it can produce necrosis in murine colorectal carcinoma cells by altering the levels of receptor-interacting protein 1 (RIP1) and RIP3, chaperone by the release of high mobility group B1 (HMGB1) from the nucleus into the cytoplasm (Chen et al., 2015b). CBNPs cause rapid cell death by rupturing lysosomes, and the release of mitochondrial DNA (mtDNA) from the dead cells plays a crucial role in triggering inflammation characterized by an influx of neutrophils in the lungs (Fig. 14) (Yuan et al., 2020). Human monocyte-derived macrophages (HMMs) have been exposed to purified SWCNTs, resulting in a slight necrosis-like cell death. To analyze the appearance and structure of necrotic cells, transmission electron microscopy (TEM) images were utilized, which revealed that huge bundles of SWCNTs were

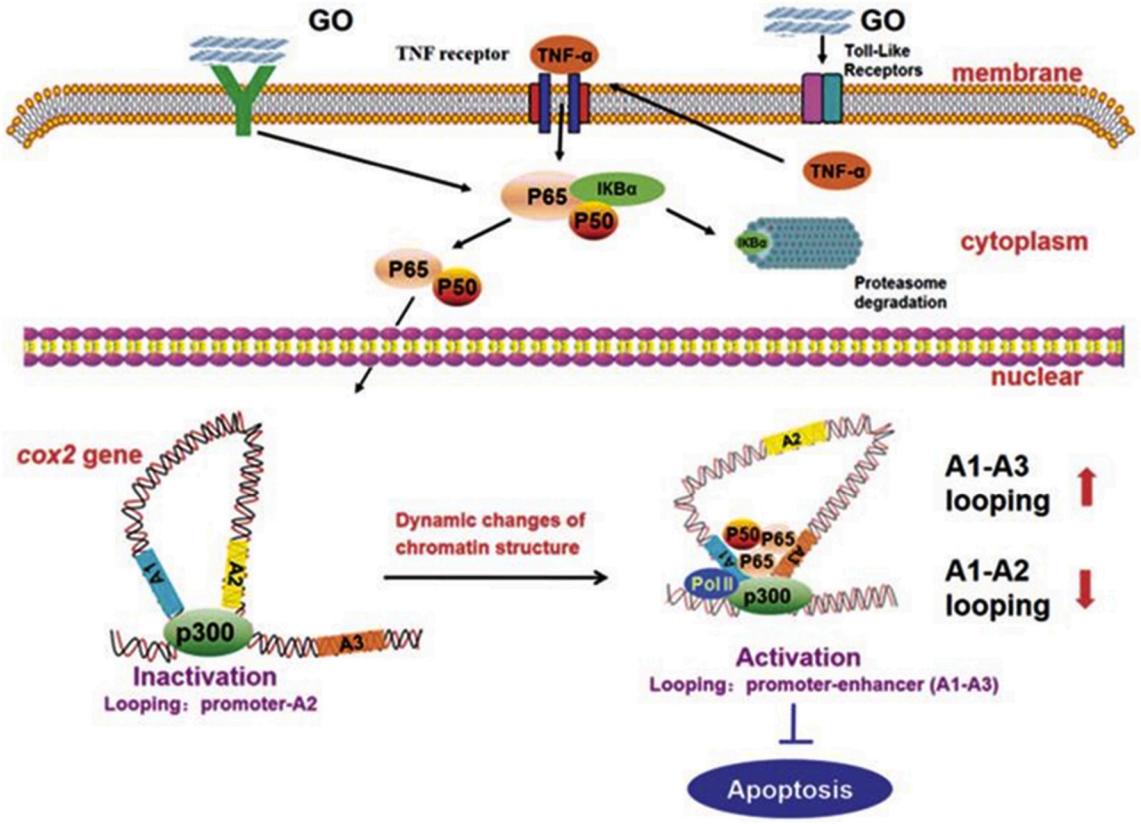

Fig. 13. The underlying mechanism behind the dynamic chromosomal changes and cox2 activation mediated by GO via TNF-α? Figure adapted with permission from Elsevier (Madannejad et al., 2019).

consumed by HMMs and found in lysosomes or cytoplasm (Ong et al., 2016).

6. Risk assessment

There is growing concern over nanotechnology's potential negative impacts on public health. While extensive research has been conducted on the toxicity of nanomaterials, their ability to infiltrate cells and influence biochemical activity also gives them great potential as molecular tools. However, while certain nanomaterials can be highly beneficial in targeting cancer cells or pathogenic bacteria and viruses, they may also have unintended repercussions for human health and the environment. For example, nanomaterials used to eliminate cancer cells may have side effects elsewhere in the body. Similarly, those utilized in soil remediation and water treatment may have unforeseen effects once they enter the body. The rapid development of nanotechnologies has resulted in an increasing number of occupational exposure assessments for engineered nanomaterials (ENM). However, our understanding of environmental exposure is less developed (Xiaoli et al., 2020). The development and commercial introduction of novel nanomaterials necessitates a thorough risk assessment of such products, as well as appropriate risk communication strategies (Laux et al., 2018). The European Commission (EC) has proposed a definition of “nanomaterial” for regulatory reasons. A substance is termed a nanomaterial if it comprises at least 50% unbound, agglomerated particles with one or more exterior dimensions ranging from 1 to 100 nm. Fullerenes, graphene flakes, and single-walled carbon nanotubes are excluded from this regulation. In certain circumstances, the 50% threshold may be reduced to 1% for particles ranging in size from 1 to 100 nm due to environmental, health, safety, or competitiveness issues (Laux et al., 2018).

6.1. The toxic effects of carbon-based nanomaterials on organs/tissues

6.1.1. Pulmonary toxicity

Carbon nanomaterials have been associated with the development of lung tumours, cellular inflammation, abnormal neural function, and pulmonary toxicity, as reported by (Lee et al., 2021; Peng et al., 2020). The main way people are accidentally exposed to harmful substances is by breathing them in. This can lead to various health problems such as asthma, fibrosis, cancer, and necrosis of lung tissues (Ghumman et al., 2021; Omari Shekaftik et al., 2022; Svadlakova et al., 2022). CNTs and CNFs pose a substantial risk as they have been consistently demonstrated to cause pulmonary toxicity by inducing chronic inflammation and fibrilization of lung tissue (Bergamaschi et al., 2021). Soliman et al. discovered that prolonged exposure to MWCNTs leads to persistent pulmonary granulomatous inflammation (Soliman et al., 2020). A separate investigation employed lung organoids to compare the impacts of carbon-based nanomaterials, revealing that MWCNTs elicit detrimental effects and promote the development of a fibrotic phenotype (Issa et al., 2024). In a comparative study on the toxicity of graphite and carbon nanotubes in lung cells, it was discovered that MWCNTs caused cell death by oxidative stress. The toxicity of the nanotubes was found to be influenced by their size(Azari et al., 2020a). Weiss et al. introduced a hypothetical Adverse Outcome Pathway (AOP) to explain the lung toxicity of CDs, employing both in vivo and in vitro experimental methods. CDs cause the rapid onset of lung inflammation and specifically affect airway macrophages. In laboratory conditions, CDs stimulate cellular reactions, which may result in the development of acute lung injury (Weiss et al., 2021). In a study conducted by Mahor et al., it was found that the administration of nanodiamonds through the trachea resulted in minimal toxicity in mice's lungs (Mahor et al., 2021). Furthermore, there was a gradual reduction in the presence of nanodiamonds in the alveolar region over time. CBNPs act as ROS producers,

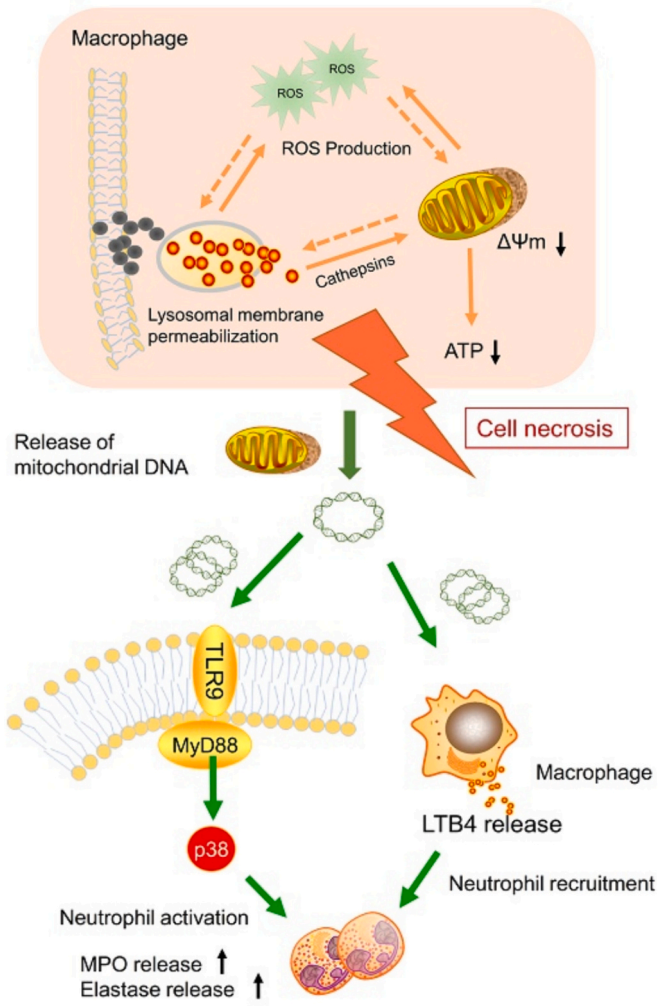

Fig. 14. CBNPs cause rapid cell death by rupturing lysosomes. The release of mitochondrial DNA (mtDNA) from the necrotic cells plays a crucial role in triggering inflammation characterized by an influx of neutrophils in the lungs. (Yuan et al., 2020).

initiating oxidative stress and inflammation in the lungs (Samadian et al., 2020). According to Rodrigues et al., the presence of micrometric-sized GO sheets leads to the development of granulomas, whereas nanometric-sized GO sheets do not cause any harmful effects on the lungs (Rodrigues et al., 2020). The introduction of micrometric GO sheets resulted in initial lung inflammation and genotoxicity. However, subsequent studies have shown that the murine lungs can recover from these effects (Loret et al., 2022; de Luna et al., 2022). Carbon fibres with a diameter of less than one micron showed harmful effects on the lungs and cells, and the size of the fibres played a significant role in causing these effects (Fujita et al., 2022). carbonaceous nanoparticles (GO, CB, and CNTs) elicit inflammation and acute phase response in the lungs and livers of mice. The signalling pathways of TLR2 and TLR4 were involved in the response to certain nanoparticles, as indicated by (Danielsen et al., 2021).

6.1.2. Cardiovascular toxicity

Carbon Nanomaterials are extensively utilized and can be found in the environment, posing a risk of toxicity to the heart. They can induce alterations in heart rate, arrhythmias, impaired cardiac contractility, and abnormal blood flow. Exposure of mothers to nanomaterials can result in cardiovascular abnormalities in their offspring, affecting the development of the heart (Cheng et al., 2021). Cardiotoxicity has been observed as a result of exposure to carbon nanotubes and graphene oxide. Nanoparticles can enter the body through the respiratory and digestive tracts, as well as through direct contact with the skin(Cheng et al., 2021). Nanomaterials induce cardiotoxicity by disrupting the heart's homeostasis, leading to myocardial cell death, electrophysiological disturbances, and mitochondrial dysfunction. The precise mechanism underlying the cardiotoxic effects induced by nanomaterials remains incompletely elucidated (Cheng et al., 2021). Kuijpers et al. discovered a correlation between being exposed to carbon nanotubes and nanofibers in the workplace and an elevation in biomarkers indicating oxidative stress and cardiovascular disease (Kuijpers et al., 2018). It seems that ICAM-1 is a reliable indicator of both exposure and disease in humans who have been exposed to nanocarbon, according to (Vlaanderen et al., 2017). Recently, an investigation evaluated the potential harm to the heart caused by GO and rGO through a combination of laboratory tests conducted in vitro and in vivo. According to Zhang et al., GO demonstrated less harmful effects on the heart compared to rGO. The toxicity of rGO may be caused by lipid peroxidation, oxidative stress, and mitochondrial dysfunction (Zhang et al., 2021). Furthermore, an extended duration of contact with carbon nanotubes has been discovered to induce cardiovascular toxicity, thereby presenting a potential effect to cardiac well-being (Shah et al., 2020). Airborne exposure to CNMs can impact cardiovascular functions through both direct and indirect routes, resulting in potential cumulative toxicity. Ultrafine combustion particles can penetrate the bloodstream through the lungs, leading to cardiac depression and functional deterioration. In addition, the rats' exposure to CB led to an increase in cardiovascular risk by causing hyperhomocysteinemia and platelet hyperactivity. CPs also initiate a ROS-dependent, inflammatory pathway associated with impaired blood vessel function, abnormal heart rhythms, and heart attack (Aslam and Roeffaers, 2022).

6.1.3. Dermal Toxicity

The exposure of the skin to nanomaterials during manufacturing or use can lead to dermal penetration (Basinas et al., 2018). Research indicates that nanomaterials of varying characteristics can permeate pig skin and gather in the epidermal and dermal layers within a timeframe of 8-24 h (Gimeno-Benito et al., 2021). Various factors that affect the permeability and toxicity of the skin include the level of hydration, compatibility with the lipids present in the skin, the ability to disrupt the outermost layer of the skin called the stratum corneum, as well as the size, flexibility, and elasticity of nanoparticles(Elmowafy, 2021; Khezri et al., 2018). Nanoparticle-infused cosmetic cream, lotion, and toothpaste are frequently applied to the skin, where they can amass in the stratum corneum and the dermis. According to Akçan et al., certain nanoparticles that are absorbed through the skin can also penetrate the bloodstream(Akçan et al., 2020). Research has demonstrated that nanomaterials, such as carbon nanotubes, can enter skin cells and induce negative consequences, including an inflammatory reaction and oxidative stress (Young et al., 2021). According to Aslam and Roeffaers, both diesel exhaust particles and cigarette smoke have the potential to damage skin tissues (Aslam and Roeffaers, 2022). Carbon-based materials, like carbon fibres, have been associated with irritant contact dermatitis and a higher occurrence of skin diseases (Fig. 15). However, research has shown that few-layer graphene presents lower health hazards than initially anticipated (Dalla Colletta et al., 2022; Moghimian and Nazarpour, 2020).

6.1.4. Hepatoxicity

The presence of free CNMs, such as CNTs, in the body, can lead to additional harm to the cardiovascular system, liver, and kidneys through their circulation in the bloodstream (Gao et al., 2024). There is a lack of in vitro studies on the hepatotoxicity of CNTs, but the few available studies have shown only minimal harmful effects on a human liver microtissue consisting of primary human hepatocytes and non-parenchymal cells (Fig. 16). Nevertheless, there are also investigations

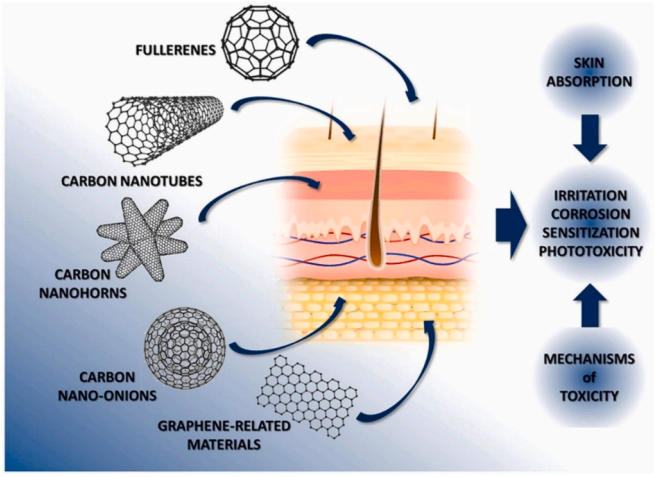

Fig. 15. Schematic illustration depicting the toxicity of different carbon-based nanomaterials on the skin. Figure adapted with permission from Elsevier (Dalla Colletta et al., 2022).

examining the hepatotoxic effects of these substances in living organisms after a single or brief period of exposure, even at low doses (Vilas-Boas and Vinken, 2021). A study assessed the hepatotoxicity of three different types of CQDs: diammonium citrate (AC)-based CQDs (CQDs-AC), spermidine trihydrochloride (Spd)-based CQDs (CQDs-Spd), and CQDs based on a combination of AC and Spd (CQDs-AC/Spd). The study concluded that the hepatotoxicity caused by CQDs-Spd seems to be linked to its surface charge. Cadmium quantum dots (CQDs) that possess positive surface charges are linked to heightened hepatocyte toxicity and elevated susceptibility to liver disease (Chen et al., 2024). Zhang et al. conducted a study to assess the safety of in-house synthesized cyclodextrins (CDs) in hepatocyte-like cells. Their research revealed that the cytotoxicity in these cells was moderate and dependent on the dosage of exposure to CDs, providing insight into the cellular response to CD exposure (Zhang et al., 2020b). In a separate study, adult Wistar rats were administered varying doses of GO. The findings demonstrated that GO induced toxicity in a manner that was dependent on the dosage, leading to alterations in the levels of specific enzymes in the serum and inducing changes in the liver tissue (Nirmal et al., 2021). Mouse hepatocytes and catalase (CAT) were utilized as specific receptors for investigating the cellular and molecular toxicity of UFCB, with a focus on size-dependent effects. The collective experiments demonstrate that the cellular absorption and distribution of UFCB play a crucial role in the variation of size-dependent cellular and molecular toxicity (Li et al., 2022b).

6.1.5. *Ocular toxicity*

The eyes possess a specific protective barrier, however, nanoparticles with diminutive particle sizes can breach the ocular surface barrier and access the innermost region of the eye (Yang et al., 2022). Consequently, NPs have the potential to induce cell death and provoke immune reactions throughout various parts of the eye, including the ocular surface, lens, retina, optic nerve, and macula (Zhu et al., 2019). The GFNs can penetrate the body through different pathways such as the eyes, skin, inhalation, and unintentional ingestion (Pelin et al., 2018). They have the potential to build up in organs such as the liver, lungs, kidneys, and reproductive organs, resulting in toxicity that varies depending on the dosage (Koyyada and Orsu, 2020). The ocular toxicity of GFNs is substantial as a result of heightened exposure. Studies conducted both in vivo and in vitro have demonstrated the harmful effects on human primary corneal and conjunctival epithelial cells. Additionally, reversible harm to the eyes has been observed in animal studies (Koyyada and Orsu, 2020; Yang et al., 2022). GO at low doses can maintain cell viability without observable cytotoxicity among embryonic stem cells (ESCs) (Yang et al., 2014). According to Yang et al., low doses of GO can preserve the viability of ESCs without causing any noticeable harm to the cells. An et al. discovered that mice exposed to a high concentration of reduced graphene oxide for 7 days did not experience any harmful effects on their eyes. However, exposure to GO resulted in notable inflammation within the eye and other related issues (An et al., 2018). The study investigated the cytotoxic effects of GO on human corneal and conjunctiva epithelial cells by inducing oxidative stress. The acute eye irritation tests conducted on albino rabbits demonstrated no cytotoxicity when exposed to GO occasionally. However, repeated exposure over a short period resulted in reversible eye damage caused by oxidative stress. This damage could be mitigated by the antioxidant GSH, as indicated by (Borandeh et al., 2021). An investigation assessed the detrimental impacts and toxic mechanisms of MWCNTs on ocular cells in humans. The study revealed that MWCNTs induced cellular harm and reduced cell viability in a manner that was dependent on the dosage. Exposure to MWCNTs also resulted in a rise in the number of cells undergoing apoptosis and cell death caused by necrosis. In addition, specific genes and long non-coding RNAs were found to be linked to exposure to MWCNT. The study conclusively demonstrated that exposure to MWCNTs caused cell death and led to an upregulation of specific genes and proteins in ocular cells(Luo et al., 2023).

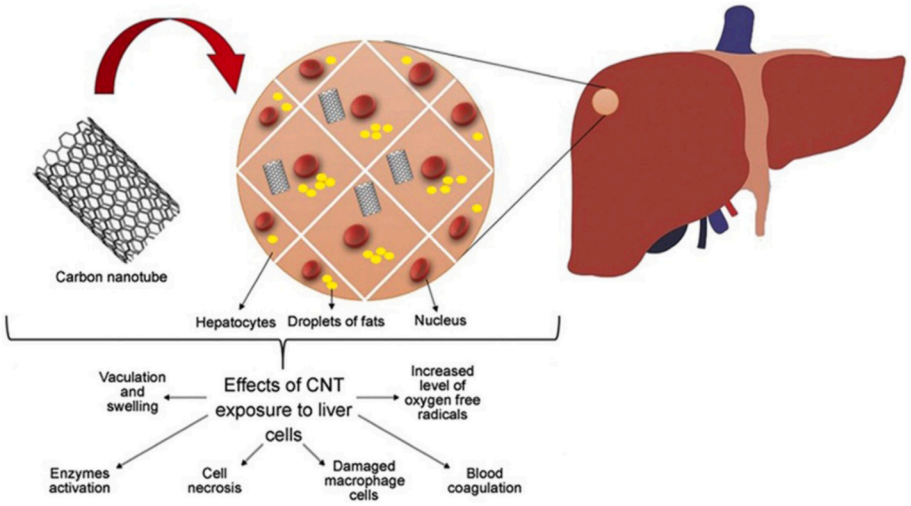

Fig. 16. The toxic effect of CNT exposure to liver cells. Adapted with permission from Frontiers (Gao et al., 2024).

6.1.6. Developmental and reproductive toxicity

Pregnant women may come into contact with NMs through respiration, ingesting, or contact with them on their skin. NMs can traverse the placenta, which may result in developmental toxicity (Aengenheister et al., 2021). There is debate regarding the extent to which the findings can be directly applied to human embryos and foetuses. In addition, NMs can have an indirect impact on development by influencing maternal and placental factors, such as oxidative stress and inflammation-induced placental dysfunction (Dugershaw et al., 2020). Nanoparticles can impact reproductive toxicology through two mechanisms: by disrupting pregnancy outcomes and impairing fertility. Research on the impact of nanoparticles on fertility yields inconclusive results due to differences in dosage and methods of exposure. However, studies on pregnancy outcomes indicate that the majority of nanoparticles are likely to have detrimental effects (Coimbra et al., 2022). Nanoparticles, such as CB NPs and CNTs (Bai et al., 2020), can penetrate the placental barrier and cause harm to the foetus, known as fetotoxicity. Exposure of mothers to nanoparticles can result in negative outcomes during pregnancy, including reduced birth weight, premature birth, miscarriage, foetal deformities, and developmental abnormalities (Teng et al., 2021). An instance of this is when nanoparticles are inhaled, they can lead to harm to the foetus in mammalian models by passing through the barriers between the mother and the foetus (Wang and Wang, 2020). The study conducted by Umezawa et al. found that exposure of mothers to CPs (Printex 90) in varying doses resulted in changes in the histology of different cell populations in the central nervous system (CNS) and also affected the open-field behaviour of the offspring in a mouse model (Umezawa et al., 2018). Exposure to CBNPs during pregnancy can directly cause inflammation, damage to the lungs, and genetic damage in the mothers, leading to abnormalities in their offspring. Exposure to CBNPs during pregnancy can increase the sensitivity to lipopolysaccharide (LPS) in both the first and second-generation offspring (F1 and F2). This effect across generations may be linked to the alteration of DNA methylation patterns caused by CBNPs (Onoda et al., 2014). Maternal exposure to CBNPs during pregnancy caused significant changes in maternal behaviours, delayed the development, and led to abnormal behaviours in offspring in the newborn period and adulthood, which were associated with changed levels of total m6A modification and its related genes in the cerebral cortex (Zhang et al., 2020a). Cohousidis et al. conducted a study to assess the impact of doping CQDs with different functional groups on the embryonic development of zebrafish. The CQDs caused considerable harm to the zebrafish in a manner that depended on the dosage, resulting in physical deformities. The N, S-doped carbon quantum dots exhibited the most prominent effects (Chousidis et al., 2020). The toxicity of CDs in zebrafish was evaluated, and notable impacts were detected at concentrations exceeding 200 μg/mL. These effects encompassed pericardial and yolk sac edoema, delayed growth, spinal cord flexure, and mortality. The presence of these concentrations was also linked to diminished locomotor activity, lowered dopamine levels, and organ damage (Liu et al., 2020).

International organizations such as the Organization for Economic Co-operation and Development (OECD) and the International Organization for Standardization (ISO), as well as developed nations such as the United States (US), the European Union (EU), and Japan, are collaborating to create guidelines and standards for evaluating the potential hazards of nanotechnology and implementing regulations. In the UK, the Health, and Safety Executive (HSE) recommends taking initiative-taking measures to mitigate risks and minimize exposure. In 2009, the HSE classified CNTs as "substances of very high concern," and the British Standards Institution (BSI) proposed a limit of 0.01 fibres/mL (Fries et al., 2012). As a result of the possible hazards correlated with nanomaterials, many developed nations are actively involved with international organizations that focus on this issue. These organizations include the OECD Working Party on Manufactured Nanomaterials (OECD WPMN), the International Organization for Standardization / Technical Committee 229 (ISO/TC 229), and the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Annex. In 2006, the Working Party on Manufactured Nanomaterials (WPMN) was established to develop nanomaterial testing recommendations. Additionally, countries like China participate in other organizations such as Sound Management of Chemicals (IOMC), Business and Industry Advisory Committee (BIAC), SO/TC 229, and NGOs. The goal of international collaboration on nanosafety legislation is to remove trade barriers, promote economic growth, and encourage the long-term advancement of nanotechnology (The Organization for Economic Co-operation and Development (OECD, 2017).

In 2005, the ISO established TC 229 for nanotechnologies, which, to date, includes 39 participating members and 17 observing members. The standardization process is overseen by several working groups (WG), of which some include WG 1 for terminology and nomenclature, WG 2 for measurement and characterization, WG 3 for health safety and environmental aspects, WG 4 for material specifications and WG 5 for products and applications. In the US, nanoregulations are managed by the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Consumer Product Safety Commission (CPSC) and follow the guidelines set by the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (Suh, 2014) (Hanson et al., 2011). Meanwhile, the European Union utilizes the REACH committee to register compounds produced or imported at more than one ton per year, which includes nanomaterials and substances with bioaccumulate, carcinogenic, mutagenic, persistent, reproductive, and toxic properties. Furthermore, the European Chemicals Agency (ECHA) must classify nanomaterials according to Classification, Labelling, and Packaging (CLP) regulations (Park and Yeo, 2016). Nordic Classification Group, a network of government officials and civil servants representing the Competent Authorities for the CLP Regulation, initiated a project under the auspices of the Nordic Chemical Group/ Nordic Council of Ministers to collect the perspectives of Nordic stakeholders on nanomaterial-related issues in relation to the CLP Regulation, which implements the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals (Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals (TDG-GHS), 2014). If a chemical has no effect in vitro, it may be regarded as non-genotoxic under some legislation (REACH, CLP, Cosmetics Directive), although others (pharmaceuticals, veterinary medications) typically require an in vivo follow-up examination. On the other hand, a positive in vitro result may necessitate confirmation through proper in vivo testing (Haase and Luch, 2016).

The REACH Implementation Project on Nanomaterials (RIP-oN) was developed in 2009 and has completed three phases: identification of nanomaterial substances, information requirements, and chemical safety evaluation. The Group Assessing Already Registered Nanomaterials (GAA RN) assessed human exposure and environmental and health concerns (European Commission, 2011). REACH initially considered carbon minimal risk, but in 2008, it was abolished for nanoscale forms. C60-Fullerene received a separate CAS registration number due to its unique properties. Unlike the EU, the US imposed stringent reporting requirements for carbon nanotubes in 2010 (The Commission of the European Communities, 2008). Despite their potential environmental benefits, a comprehensive life cycle analysis of CNTs is lacking. Limited data on ecotoxicity and exposure makes environmental risk assessment difficult. Current hazardous chemicals legislation and occupational health and safety rules lack guidance on handling CNTs. REACH standards may exclude manufacturers due to volume limits. CNT-specific properties are not adequately considered, and research and development are needed for analytical and detection procedures. Authorities recommend caution and minimizing exposure to protect employees (Fries et al., 2012).

Establishing consistent techniques and guidelines for comparing safety and toxicity evaluations among research organizations is crucial.

These approaches will harmonize the outcome of in vitro and in vivo studies and help predict prospective future impacts. In-depth research on the toxicity of CNMs is urgently required to facilitate the creation of government regulations for their use. The field of nanotoxicology requires further data to ensure that carbon nanoparticles are biocompatible and have minimal toxicity to blood components, protein structure, and cell survival. Understanding the biological interactions between CNMs, cells, proteins, and tissues is critical to producing safe nanoproducts. To determine the potential toxicity of carbon nanoparticles to human cells, it is necessary to provide detailed descriptions of their properties.

7. Conclusions and perspectives

In the present review, we detailed the in vitro studies on the toxicity of CNMs in human cells. Based on these findings, we examined the major physicochemical and toxicological characteristics of CNMs that regulate their toxicity. CNMs and their applications in several scientific and technological fields are increasing rapidly. As a result, the exposure risk to CNMs will continue to rise, which will have beneficial and harmful consequences on humans, animals, and the environment. CNMs, being one of the principal classes of nanomaterials, offer a vast array of applications among the various nanomaterial varieties. However, these chemicals' toxicity and adverse effects have recently gained widespread attention. The CNM toxicity study indicated that the level of toxicity is directly proportional to the substance's type, composition, diameter, length, and shape. It is plausible that CNMs provide numerous benefits to the human condition, yet they can also be harmful. Oxidative stress is the most common cause of CNMs' harmful mechanism. This analysis has also shed light on the toxicity of various carbon CNMs, including carbon dots, nanodiamonds, and fullerenes.

Carbon-based nanomaterials have garnered significant interest due to their distinct characteristics and diverse range of uses. Materials such as carbon nanotubes, graphene, and fullerenes possess outstanding mechanical, thermal, and electrical properties. This makes them extremely attractive for a wide range of industries, including electronics, medicine, and environmental remediation. The remarkable characteristics of carbon-based nanomaterials arise from their exceptional level of structural organization at the nanoscale, enabling precise manipulation of their properties and functionalities. Nevertheless, there have been concerns regarding the potential toxicity of these nanomaterials, especially when used in biological systems.

Studying the potential toxicity of CNMs is crucial due to their growing utilisation in diverse industries and consumer goods. This review has emphasised the intricate interplay between CNMs and biological systems, underscoring the significance of comprehending these interactions at both the cellular and molecular scales. The results indicate that the toxicity of CNMs is strongly influenced by various factors, such as their dimensions, morphology, surface modification, and concentration. At the microscopic level, carbon nanomaterials (CNMs) can cause oxidative stress, inflammation, and cytotoxicity, resulting in various negative consequences such as cellular demise. These effects are typically caused by the production of reactive oxygen species (ROS), damage to cellular membranes, and disruption of crucial cellular processes like mitochondrial function and DNA repair. Through the exploration of the fundamental processes that drive these reactions, scientists can strive to create nanomaterials that are less harmful and have fewer negative consequences. Furthermore, it is crucial to understand the factors that affect the way carbon-based nanomaterials behave in living organisms, such as their size, surface properties, and whether they are aggregated or not. This knowledge is necessary to evaluate the impact of these nanomaterials on living organisms. To make progress in the field of nanotoxicology and ensure the safe utilisation of nanomaterials in biomedical and environmental contexts, it is crucial to tackle these intricate interactions. To safely incorporate carbon nanomaterials into society, it is crucial to have a comprehensive understanding of their potential toxicological impacts, despite the significant potential they hold for technological progress. Further exploration of the mechanisms behind CNM toxicity will not only improve our capacity to reduce risks but also inform the creation of safer nanomaterials, ultimately promoting their sustainable and responsible utilisation.

Although there have been notable advancements in the examination of the toxicity of CNMs, there are still various constraints that impede a thorough comprehension of their potential health hazards. A significant constraint is the absence of standardized testing protocols, resulting in inconsistent and occasionally conflicting outcomes across various studies. Moreover, the extensive range of physicochemical characteristics exhibited by CNMs, including dimensions, morphology, surface modification, and level of impurities, hinders the generalisation of results obtained from one CNM variant to another. While in vitro studies are useful, they often do not accurately replicate the intricate interactions that occur within living organisms. On the other hand, in vivo studies are constrained by ethical concerns and the difficulties of conducting long-term exposure assessments. Moreover, the swift advancement of nanotechnology results in the constant creation of new carbon nanomaterials (CNMs), surpassing the capacity of toxicological research to keep pace. The existence of these limitations emphasises the necessity for more thorough, uniform, and multidisciplinary methods to more effectively evaluate and comprehend the toxicity of CNMs.

CNMs can potentially significantly improve wastewater treatment efficiency and effectiveness significantly. One promising application of these materials is removing pollutants from wastewater. CNMs can absorb and remove pollutants from water, resulting in a cleaner and safer discharge. Additionally, nanotechnology can create filtration systems that eliminate microscopic particles and pathogens. However, the toxicity of CNMs used in membrane filtration varies based on several factors, including the type of nanomaterial, production method, particle size and shape, and usage conditions. While extensive research has been conducted, there are still knowledge gaps regarding the potential impact of CNMs on human health and the environment over prolonged period, including their potential to accumulate in the environment and interact with biological systems. Further investigation is necessary to fully comprehend the potential risks associated with CNMs in water treatment and to establish safe usage standards. By better understanding these materials' toxicity, researchers and engineers can design more effective and safer ways to use CNMs in wastewater treatment.

Future research should give priority to the development of standardized protocols for toxicity assessment, which will allow for more dependable and comparable outcomes. Furthermore, there is a requirement for sophisticated in vitro and in vivo models that closely mimic human biological systems. These models would enable more precise forecasts of the behaviour and toxicity of CNMs in real-world situations, as well as predictions of the long-term health effects resulting from exposure to CNMs.

CRediT authorship contribution statement

Bveledzani P Makhado: Conceptualization and writing of the original draft. **Bveledzani P. Makhado**, **Adewale O. Oladipo**, **Nozipho N. Gumbi**, **Lueta A. De Kock**, **Charlene Andraos**, **Mary Gulumian**, and **Edward N. Nxumalo**: Conceptualization, reviewing and editing, and resources. All the authors have contributed by reading, editing, and confirmed to the publication of this review.

Declaration of competing interest

The authors declare that they have no financial or personal relationships that could have influenced the work reported in this paper.

Data availability

No data was used for the research described in the article.

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