Mutation Research-Reviews in Mutation Research 796 (2025) 108554

Contents lists available at ScienceDirect

Mutation Research-Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/mutrev

Review

Systematic review on toxicological effects of platinum nanoparticles: Towards their use as safe biomedical tools

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ARTICLE INFO

Keywords:
Platinum nanoparticles
Systematic review
Cytotoxicity
Genotoxicity
Embryotoxicity
Biocompatibility

ABSTRACT

Platinum nanoparticles (PtNP) have received considerable attention in the nanomedicine field due to their magnetic, catalytic, and optical properties. However, the potential toxicity of PtNP has not been properly evaluated yet, and current information on the possible risks related to their use is still limited. On this basis, the main objective of this systematic review was to gather available data on PtNP biological behaviour and potential harmful effects, as well as to highlight the gaps of knowledge that need to be filled in to progress in their use in clinical practice. A total of 441 studies were obtained and reviewed from the initial search; 108 fulfilled the selection criteria and were included in the revision. Mainly in vitro but also in vivo studies were reported using a variety of biological systems and animal models, with no data from human epidemiological studies published so far. All these studies were extensively evaluated to provide useful information on the PtNP biocompatibility and their potential to be employed for medical purposes. In particular, information on the physicochemical features of the PtNP influencing their biological behaviour, methods employed for toxicity evaluation, biological systems used, and outcomes addressed were analysed and discussed. In general, the results obtained showed a good biocompatibility of these NP, although some of them detected significant toxicity highly dependent of size, concentration/dose, coating, or exposed biological system. Furthermore, anticancer or protective effects were also described for PtNP in several revised studies. These findings encourage to continue exploring the benefits of PtNP for clinical practice.

1. Introduction

Due to their apparent biocompatibility, reported in some previous studies, their stability, and their surface properties, platinum nanoparticles (PtNP) have a broad application spectrum in several sectors including biomedical, biological, electronic, and chemical industries (Fig. 1). The most common utilization of PtNP is the catalysis of chemical reactions due to their high surface activity, in particular, they are integrated into the electrodes of fuel cells to facilitate the oxidation reaction of hydrogen into protons and electrons [1,2]. However, they are also important in the manufacture of other products such as fuels, oils, and other industrial chemicals including cosmetics, packaging agents, and food supplements [3].

In addition to their use in fuel cells and other chemical devices, PtNP have received considerable attention in nanomedicine due to their magnetic, catalytic, and optical properties with multiple potential applications in the diagnosis and treatment of several pathologies, including cancer [4–6]. Previous studies reported that PtNP present significant anticancer activity due to their cytotoxic properties that inhibit cell proliferation through activation of the apoptotic pathway,

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https://doi.org/10.1016/j.mrrev.2025.108554
Received 3 March 2025; Received in revised form 18 June 2025; Accepted 17 July 2025
Available online 6 November 2025

among others. Thus, Shakibaie et al. [7] revealed that PtNP synthesized by microwave-assisted methods have cytotoxic effects on MCF-7 breast cancer and A549 lung cancer cells mediated by induction of apoptosis. Moreover, PtNP combined with graphene-oxide (GO-PtNP) showed a significantly greater anticancer effect than platinum (Pt) alone [8]. PtNP have indeed gained immense attention due to their controlled therapeutic efficacy and apparent biocompatibility, which are superior to those of platinum-based drugs such as cisplatin [9,10]. PtNP can also be used for the production of biosensors based on field effect transistors for the early detection of breast cancer [11].

In addition, and given the current global public health threat posed by the antimicrobial resistance [12], PtNP may be also interesting in the biomedical field to explore potential new antibiotics, since they have shown to bear an important antibacterial effect due to their small size, so that they easily cross the bacterial wall, having an influence on a wide spectrum of gram-positive and gram-negative bacteria [13]. The antibacterial action of PtNP is likely associated with reactive oxygen species (ROS) generation, since they increase ROS levels in bacteria cells [14]. ROS include highly reactive radicals as OH^{-}, H_2O_2 and less toxic radicals as O^{2-}, able to affect DNA, RNA and proteins, causing the death of bacteria [15–17].

Still, despite their benefits in industry and medicine, the potential harmful effects of PtNP have not been properly evaluated yet and studies addressing their toxicity are still highly scarce; accordingly, information on the possible risks related to their use is often demanded in the literature [3].

Therefore, the main objective of this systematic review was to gather available data on PtNP biological behaviour and potential harmful effects, as well as to highlight the gaps of knowledge that need to be filled in to progress in this field. Consequently, we explored the biocompatibility and toxicological effects of PtNP by carrying out for the very first time a systematic evaluation of published studies addressing different aspects of PtNP toxicity, compiling and presenting the current knowledge on their effects. The physicochemical features of the NP, the methods employed for toxicity evaluation, the biological systems used, the outcomes addressed, the experimental conditions (including the protocol adaptations for preventing NP interference), and the observed effects were extensively evaluated and discussed to provide useful information on the biological behaviour of PtNP and their potential to be employed for biomedical purposes.

2. Method

To conduct and report this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [18] and the Rayyan web application for systematic reviews [19] was employed for the initial screening of the reviewed studies.

2.1. Bibliographic search

The identification and selection of studies to be included in the review was carried out through an extensive literature search using two databases: PubMed (National Library of Medicine, National Institutes of Health, Bethesda, MD, USA; http://www.ncbi.nih.gov/PubMed), and Web of Science (previously Web of Knowledge, https://www.webofscience.com/wos/). The systematic literature search was updated to July, 2024.

The search strategy developed comprised two terms that were intersected using the Boolean term “AND”. The first one was referred to the study nanomaterial “platinum nanoparticles” or “nanoplatinum” and the second one included descriptors related to different types of damage (‘toxic*, `cytotoxic*, `genotoxic*, `effects). All searches were initially focused on title or abstract.

Two reviewers, blinded for each other’s results, screened the titles and abstracts for eligibility by using the Rayyan web application. Disagreements were resolved by a third independent reviewer. Full text articles were then screened for eligibility.

2.2. Selection/exclusion criteria

This systematic review included studies addressing the potential toxic effects of PtNP. In particular, eligible studies were all nanotoxicity studies conducted in human, animal cells or organisms, written in

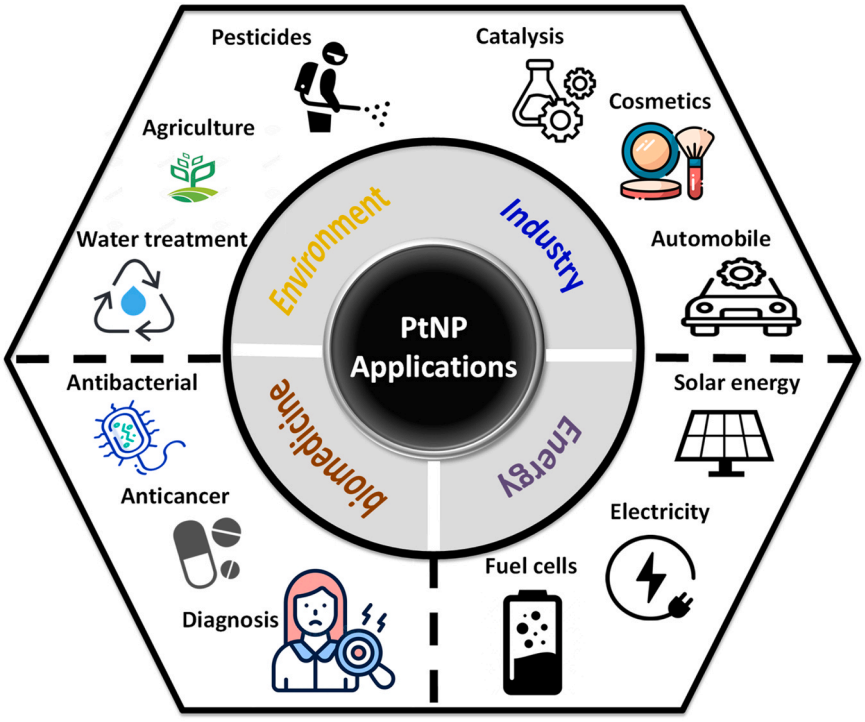

Fig. 1. Main applications of platinum nanoparticles (PtNP).

English, French or Spanish, investigating PtNP effects. We initially excluded narrative or systematic reviews, theses, books or book chapters, and conference proceedings. Exclusion criteria also considered studies performed in plants or microorganisms (e.g. testing the antimicrobial potential of PtNP), ecotoxicity studies aimed to evaluate their environmental impact, articles focused on PtNP synthesis with no specific evaluation of PtNP toxicity or biocompatibility, and studies employing PtNP to reduce or protect from the harmful effects induced by a third agent. Also, in order to avoid additional noise, only studies testing single constituent PtNP, either naked or surface-modified were included, excluding articles testing complexes of PtNP with any other nanomaterial (e.g. carbon nanotubes-PtNP, graphene oxide-PtNP, bimetallic gold-PtNP, etc.).

Four hundred and forty-one citations (after excluding duplicates) were initially obtained and manually reviewed (Fig. 2). Among them, 327 were excluded and 114 resulted eligible after an initial inspection of title and abstract. Full texts of these publications were reviewed, confirming that finally 103 studies did fulfill the selection criteria. Other five additional publications were identified and included in the revision after reviewing the references section of published articles.

3. Results and discussion

The systematic literature search identified 108 studies that fulfilled the selection criteria. They were all published in the last two decades, between 2008 and 2024, even though engineered PtNP are being synthetized since 1996 [20] and were introduced to the market in the late 20th century. To identify the country of origin of an article, the affiliation of the first author was used. The studies were mostly conducted in Asia (67.3 %), Europe (23.6 %), and USA (7.3 %); the majority of them were carried out just *in vitro* using a variety of cell types (74 studies, 68.5 %), whereas 12 out of 108 employed animal models (11.1 %), and 22 both *in vitro* and *in vivo* systems (20.4 %). Epidemiological studies evaluating the potential PtNP effects on human exposed populations have not been reported so far.

The great majority of the PtNP tested were spherical; 50 out of 108 studies employed just uncoated PtNP (when no specification was indicated for PtNP coating, we considered them as uncoated), whereas the remaining studies used PtNP coated with a variety of compounds, mostly citrate (15.52 %) or polyvinylpyrrolidone (PVP) (27.7 %). Other coatings included folic acid and different peptides.

3.1. *In vitro effects of PtNP*

Results from all *in vitro* approaches are collected in Table 1. Since differences in the synthesis method may lead to differences in physicochemical characteristics, cellular uptake and biological responses, the PtNP origin was also considered in this review. Most studies employed newly synthetized PtNP (87.1 %), either by chemical or green synthesis, and only in 14 cases (12.9 %) the PtNP were purchased from a commercial supplier. The *in vitro* systems most frequently employed to test PtNP were cell lines from both human (76.8 %) or murine (15.9 %) origin, but also primary cells from other different organisms were employed in some cases (7 studies, 7.3 %). Breast, hepatic, lung, and

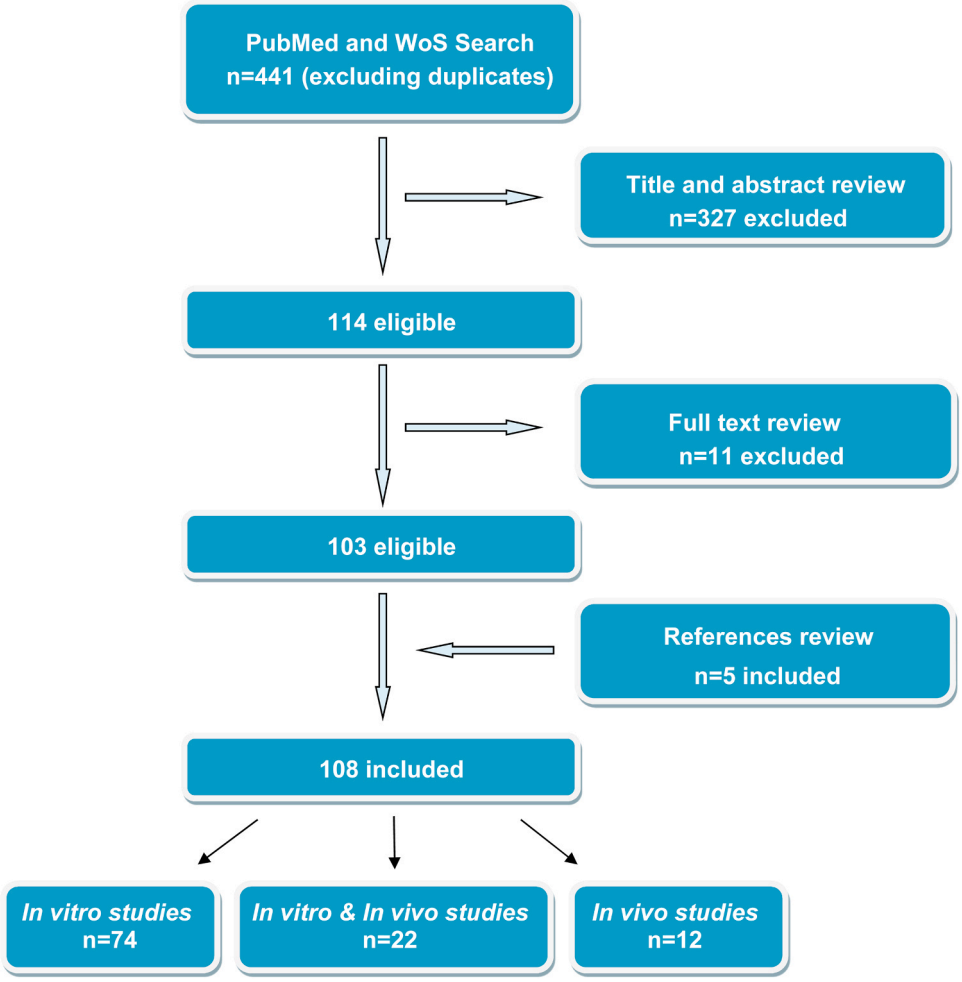

Fig. 2. Flow chart: selection of the literature.

Table 1
In vitro studies evaluating PtNP potential toxicity.

Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
Abed et al. (2022) [24]	*Ziziphus spina christi and Cordia myxa L.* leaf extract capped PtNP (30 nm)	MCF−7	2.5–40 μg/mL for 24 h	MTT assay, apoptosis analysis	Significantly increased cytotoxicity and apoptosis, enhanced by NIR: Higher effect with PtNP prepared by *Cordia myxa* leaf extract compared to *Ziziphus spina-christi* leaf extract -PtNP
Ali and Mohammed (2021)[25]	Polyphenols stabilized- PtNP (30–45 nm)	SKO−3 and SK-GT−4	1.25×10^{-3}–10^{-2} M for 72 h	MTT assay, morphological assessment	Concentration-dependent decrease in cell proliferation followed by morphological changes and reduction in the number of cell colonies
Almarzoug et al. (2020)[26]	PtNP (6.30 ± 2.4 nm)	CHANG and HuH−7	10–300 μg/mL for 24 and 48 h	MTT assay, NRU assay, morphological assessment, ROS generation analysis, GSH test, LPO test, MMP assay, chromosome condensation and caspase−3 activity assessment, comet assay, RT-PCR	Morphological alterations and decrease in cell viability in a concentration-dependent manner in both cell lines. Overexpression of pro-apoptotic genes and downregulation of anti-apoptotic genes
Almeer et al. (2018)[27]	*Azadirachta indica L.* leaf extract capped-PtNP (24.6 ± 3.4 nm)	HEK293	20–360 μg/mL for 6, 24, and 48 h	MTS assay, morphological assessment, NRU assay, GSH assay, MMP assay, ROS generation analysis, Cell Lysate assay, chromosome condensation and caspase−3 activity assessment, comet assay, RT-PCR	Morphological changes, increased ROS production, and cellular stress with decreased MMP and lysosomal function, apoptotic markers and significant DNA damage.
Alshatwi et al. (2015)[28]	Tea polyphenol (TPP) functionalized- PtNP (30–60 nm)	SiHa	25–200 μg/mL for 24 and 48 h	MTT assay, cell cycle analysis, apoptosis analysis	Significant time and concentration-dependent decrease in cell viability with morphological changes and cell cycle arrest in the G_2/M phase
Alyami et al. (2022)[29]	Lycopene stabilized- PtNP (124.3 nm)	HCT−116	0.01–100 μM/mL for 24 h	MTT assay, cell cycle analysis, LDH assay, migration and invasion assay, ROS-related markers, ELISA	Concentration-dependent inhibition of cell proliferation, with an increase in pro-apoptotic proteins, antioxidant markers, and cell cycle arrest at G_2 phase
Armada-Moreira et al. (2018) [30]	Citrate capped-PtNP (2 nm)	SH-SY5Y	Microreactor to cell ratios 1:20, 1:10, 1:2, and 1:1 for 24 h	CCK−8 test, LDH assay	Decreased cell proliferation without alteration of membrane integrity, indicating mechanical stress inhibiting cell growth
Asharani et al. (2010)[31]	Polyvinyl alcohol capped-PtNP (5–8 nm)	IMR−90 and U251	10–160 μg/mL for 24, 48 and 72 h	Titer-Glo luminescent cell viability assay, comet assay, cell cycle analysis, ROS generation analysis, MN analysis, apoptosis/necrosis assay, colony formation assay, western blot	Increases in H_2O_2 and O_2 with lower production in IMR−90 compared to U251 cells., S-phase arrest, induction of apoptosis, and increased DNA damage
Aygun et al. (2020)[32]	PtNP (1–6 nm)	HeLa and MDA-MB−23	25–150 μg/mL	MTT assay, morphological assessment	Significant morphological alteration accompanied by increased inhibition of proliferation of both cell lines
Baskaran al. (2017)[33]	PtNP (20–50 nm)	MCF−7	7.8–1000 μg/mL for 24 h	MTT assay, morphological assessment	Morphological alterations and significant reduction in cell viability
Bayat et al. (2023) [34]	PtNP (4.55 nm)	HEK 293, Thle 2, MIApaC 2 and Hela	0.1–100 μg/mL for 24 h	MTT assay	Cell viability rate decreased with increasing PtNP concentration. Cytotoxicity was higher on cancer cell lines (HEK 293, MIApaC 2 and Hela) compared to epithelial cells (Thle 2)
Bendale et al. (2016)[35]	PtNP (size not reported)	A549	50–200 μg/mL for 48 h	MTT assay	Reduced cell viability, and dose-dependent cytotoxicity
Bendale et al. (2017)[36]	PtNP (size not reported)	A549, PA−1, Mia-Pa-Ca−2 and PBMC	50–200 μg/mL for 48 h	MTT assay, trypan blue assay, apoptosis analysis, cell cycle analysis, clonogenic survival assay	Significant decrease in viability of cancer cells, without cytotoxic effect on normal PBMC, and inhibited PA−1 cell colony formation in a concentration-dependent manner, accompanied by morphological changes such as chromatin condensation, increased apoptosis and altered cell cycle
Berger et al. (2023)[37]	PVP coated- PtNP (3 nm)	HEI-OC1 and SG	50–150 μg/mL for 48 h	Resazurin assay, cell viability analysis, TEM	No cytotoxicity observed in HEI-OC1 exposed cells; a slight decrease in SG survival at high concentrations, with a concentration-dependent reduction in neurite outgrowth
Borowik et al. (2019)[38]	PtNP (10–80 nm)	HaCaT and MelJuSo	0.2–40 μL/mL (final suspension of PtNP at 25.6 mg/L) for 72 h	Alamar Blue assay	Exposure did not affect non-cancerous HaCaT cells but reduced the proliferation of cancerous MelJuSo cells.

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Table 1 (*continued*)

Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
Brown et al. (2018)[39]	Lipid-polymer conjugate 1,2-distearoyl-sn-glycero−3-phosphoethanolamine and PEG-coated PtNP (70 nm)	4T1-luc-tdTomato, HepG2 and NIH3T3	1–40 μg/mL for 1, 4, 24 h	Alamar Blue assay, fluorescence-based LIVE/DEAD assay	No significant toxicity was observed at concentrations up to 10 μg/mL after 1 or 4 h of incubation, but significant toxicity was detected after 24 h at 40 μg/mL in the murine 4T1-luc-tdTomato and NIH3T3 cell lines
Buchtelova et al. (2017)[40]	PVP-capped PtNP (PVP-PtNP) (10, 14, 20 nm)	LNCaP, MDA-MB−231, GI-ME-N, PNT1A, RBC and HaCaT	0.01–50 μg/mL for 24 h	MTT assay, Haemocompatibility analysis, ROS generation analysis, comet assay, scratch test, SQ-RT-PCR, western blot	A concentration-dependent antiproliferative activity was observed, with a slight impact on GI-ME-N, and without hemolysis. Reduction in cell migration of MDA-MB−231 and LNCaP cells. Increase in ROS levels was observed in all the cell systems
Chen et al. (2016) [41]	Sodium citrate coated-PtNP (5, 30, 50 nm)	Hs27	5 μg/mL for 2 h	CCK−8 test, ROS generation analysis	Cells pretreated with PtNP and sodium L-ascorbate showed a substantial increase in ROS levels and a decrease in cell viability
Daneshvar et al. (2020)[42]	PtNP (12.2 ± 0.7 nm)	B16/F10	10–250 μg/mL 72 h	MTT assay, intracellular ROS analysis	A concentration- and time-dependent decrease in cell viability was observed. A slight increase in ROS levels was also detected.
Das et al. (2020) [43]	Uncoated PtNP (3.47 nm)	HepG2	10^9–10^{11} particles/mL for 24 h	MTT assay	No significant changes in cell viability.
Demir et al. (2020)[44]	Uncoated and PVP-coated PtNP (4–9 nm)	EPC and BF−2	3.125–200 mg/L for 24 and 48 h	CFDA-AM, Alamar Blue, and Neutral Red assays	No significant cytotoxic effects were observed for PVP-PtNP. However, a concentration-dependent cytotoxicity was noted for uncoated PtNP.
Estrela-Llopis et al. (2014) [45]	Polysaccharides coated PtNP (18–38 nm)	A2780	80 mg/dm^3 for 24 h	Trypan blue assay, heterocoagulation analysis, TEM	PtNP showed a tendency for heterocoagulation with cells, facilitated by their modified surface properties, which enhanced their adhesion to cells. Extracellular metabolites actively interacted with PtNP surface, modifying their charge.
Fahmy et al. (2021)[46]	PtNP (20.3 ± 1.9 nm)	MCF−7 and A−549	0.01–300 μg/mL for 72 h	SRB assay	PtNP decreased cell viability.
Gatto et al. (2017) [47]	Citrate coated- PtNP (5 nm)	THP−1 and HL60	25–100 μg/mL for 3 and 9 d (differentiation assay in THP−1 and HL60 cells, respectively), and for 6 or 24 h (rest of assays)	Differentiation assay, TEM and confocal microscopy, cytokine and chemokine release analysis, WST−8 assay, annexin V-PI assay, cell viability analysis evaluation by flow cytometry	PtNP did not alter THP−1 differentiation and the release of inflammatory cytokines and chemokines. Reduction of cell metabolic activity up to 35 % on previously differentiated THP−1 macrophages. No necrotic or apoptotic cell death in HL60 cells
Gatto et al. (2018) [48]	Citrate coated- PtNP (5 nm)	THP−1 and HL60	50 μg/mL for 2, 6 and 24 h	TEM, intracellular uptake by flow cytometry, annexin V-PI assay, WST−8 assay, receptor expression, cytokine and chemokine release analysis, DCFDH-DA assay, transcriptional profile	Efficient reduction of ROS without affecting cell viability. Expression of receptors, cytokines and chemokines was not compromised. Modulation of transcription of 60 genes
Gehrke et al. (2011)[49]	PtNP (< 20, < 100, > 100 nm)	HT29 and Caco−2	10^{-3}–10^3 μM for 1, 4, 24, 48 and 72 h	SRB assay, WST−1 assay, LDH assay, TEM, translocation assay	PtNP did not affect the growth or viability of HT29 cells. In contrast, a significant increase in Pt content associated with DNA was observed over time. In the translocation assay system, PtNP were not able to translocate through a Caco−2 monolayer
Gholami-Shabani et al. (2023) [50]	PtNP (2–25 nm)	HepG2	12–400 μg/mL for 24 h	MTT assay, morphological assessment, DNA fragmentation assay	Decrease in cell viability in a concentration-dependent manner with morphological alterations and apoptotic markers
Gulino et al. (2021)[51]	Sodium citrate coated PtNP (50 nm)	Rat neuronal slices	1 mg/mL for 24 h	Fluoro-Jade staining, immunofluorescence	Absence of significant neuronal cell loss with neuronal degeneration in the CA3 region
Gurunathan et al. (2019a)[52]	PtNP (10–22 nm)	U2OS cells	5–25 μg/mL for 24 h	CCK−8 test, LDH assay, cell proliferation assay, trypan blue, morphological assessment, MMP assay, ATP levels, oxidative stress marker assessment, antioxidative marker assessment, cytokine measurement, RT-qPCR)	Concentration-dependent decrease in cell viability. The combination with DOX showed effective synergy at low concentrations, increased cytotoxicity, produced signs of apoptosis and ROS generation, overexpression of pro-apoptotic genes, DNA repair genes, significantly greater loss of MMP compared to individual treatments

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Table 1 (*continued*)

Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
Gurunathan et al. (2019b)[53]	PtNP (1–2 nm)	THP−1	25–150 μg/mL for 24 h	Cell proliferation assay, cell mortality assay, CCK−8 test, LDH assay, MMP assay, oxidative stress marker assessment, antioxidative marker assessment, RT-qPCR, cytokine measurement	Decrease in cell viability and cell proliferation in a concentration-dependent manner, morphological changes, alteration in membrane integrity, increased ROS, decreased MMP levels, and a significant increase in pro-inflammatory cytokines and proapoptotic genes
Gurunathan et al. (2020a)[54]	PtNP (20–110 nm)	SH-SY5Y, A549, MDA-MB−231 and LNCaP	20–100 μg/mL for 24 h	CCK−8 test, cell proliferation assay, morphological assessment, MMP assay, ROS levels and anti-oxidative markers analysis, LDH assay, apoptosis analysis, 8-oxo-G levels, RT-qPCR	Concentration-dependent decrease in viability of all cell lines including SH-SY5Y, apoptotic alterations, increased ROS, reduced antioxidants, mitochondrial depolarization and loss of membrane integrity, promoting neurite differentiation. The combination of PtNP and retinoic acid amplified these cytotoxic effects
Gurunathan et al. (2020b)[55]	Anisotropic PtNP (25 nm)	THP−1	25–150 μg/mL for 24 h	CCK−8-test, cell proliferation assay, morphological assessment, LDH assay, MMP assay, cell mortality assay, oxidative stress marker assessment, antioxidative marker assessment, RT-qPCR, cytokine measurement	Decrease in cell viability and cell proliferation in a concentration-dependent manner, morphological changes, loss of membrane integrity, increased ROS, reduced antioxidants, mitochondrial dysfunction and an increase in pro-inflammatory cytokines and apoptotic genes
Hamasaki et al. (2008)[56]	PtNP (1–5 nm)	TIG−1, WI−38, MRC−5, HeLa and HepG2	0.1–50 mg/L for 24 h	WST−1 assay, ROS-scavenging analysis	Cytotoxicity was not observed in any of the cell lines. Levels of ROS and O^{2-} in HeLa cells were slightly reduced after incubation with 2 mg/L 60 min.
Hashimoto et al. (2015a)[57]	PVP-stabilized PtNP (7.0 ± 7.0 nm)	RAW264	1–400 μg/mL for 24 h	WST−8, MMP assay, RT-qPCR	Decrease in MMP in a concentration-dependent manner with morphological changes. Cell viability reduction from 100 μg/mL on. Absence of alteration in the expression of pro-inflammatory genes.
Hashimoto et al. (2015b)[58]	Polyacrylic acid (PAA) stabilized PtNP (3.8 ± 3.0 nm)	L929 and RAW264	1–400 μg/mL for 24 h	WST−8 test, comet assay, MMP assay, TEM	Significant decrease in cell viability and MMP; significant genotoxicity
Hashimoto et al. (2016)[59]	PVP-stabilized PtNP (7.2 ± 6.9 nm)	L929	1–400 μg/mL for 24 h	WST−8 test, MMP assay, LDH assay, TEM, RT-qPCR	Significant decrease in viability at concentrations above 100 μg/mL. Significant decrease in MMP activity from 10 μg/mL on. No significant upregulation of IL−1 and TNF-α
Horie et al. (2011)[60]	PtNP (5–10 nm)	HaCaT and A549	0.01–10 mg/mL for 6 and 24 h	MTT assay, oxidative stress analysis, caspase−3 activity assay, clonogenic assay, TEM	No alteration of mitochondrial activity in A549 cells but reduced in HaCaT cells. No induction of apoptosis or necrosis. No changes in ROS levels. Alterations in membrane integrity at high concentrations without significant effect on the colony-forming ability of HaCaT cells.
Hullo et al. (2021)[61]	PEGylated PtNP (3.2 nm)	MDA-MB−231 and T47D	0.5 mM for 24 h	Cell cycle analysis, oxidative stress analysis, γ-H2AX phosphorylation analysis, colony formation assay	No alteration of cell viability or growth, no disruption of the cell cycle, increased ROS levels in both cell lines, low DSB rate
Jameel et al. (2021)[62]	PtNP (3.8 nm)	HEK−293	12.5–150 μg/mL for 24, 48 and 72 h	WST−1 assay	No decrease in cell viability after 48 h; significant decrease after 72 h at any concentration tested
Jawaid et al. (2016)[63]	PtNP (size not reported)	U937	300 μM for 20 h	Trypan blue, morphological assessment, cells apoptosis analysis, γ-H2AX analysis, MMP assay, ROS formation analysis, cell cycle analysis western blot, DNA fragmentation assay	PtNP attenuated the effects of ultrasound on DNA, MMP, caspase−3, ROS, and the increase in the intracellular concentration of free [Ca^{2+}], but their combination reduced long-term cell survival despite decreasing apoptosis
Konieczny et al. (2013)[64]	PVP-coated PtNP (5.8–57 nm)	NHEK	6.25–25 μg/mL for 24 and 48 h	MTT assay, comet assay, cell cycle analysis, colony-reduction assay, Caspase-Glo 3/7 assay, caspase 9 analysis, translocation assay, western blot	Decrease in cellular metabolism without alteration of viability, migration or cell cycle. Only PtNP with small size were genotoxic, decreased activity of proapoptotic proteins, and increased phosphorylation of ERK1/2, JNK and Akt, which normalized after 24 h
Kumar et al. (2019)[65]	PtNP (22 nm)	HeLa	31.25–250 μg/mL for 24 h	MTT assay	Decrease in cell viability in a concentration-dependent manner

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Table 1 (*continued*)

Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
Kutwin et al. (2017a)[66]	PtNP (2–19 nm)	U87	0.14–0.65 μM/mL for 24 h	MTT assay, TEM, apoptosis analysis, comet assay	Decreased cell viability, shortened protrusions and altered mitochondrial structure, leading to decreased metabolic activity and vitality. Increased genotoxicity, apoptosis and increased cell death in a concentration-dependent manner
Kutwin et al. (2017b)[67]	PtNP (2–25 nm)	U87 and U118	0.14–1 μM for 24 h	Cell proliferation assay, morphological assessment, translocation assay, oxidative DNA damage	PtNP altered cell morphology and reduced proliferation, with loss of their migration capacity
Kutwin et al. (2019)[68]	PtNP (2–19 nm)	MCF−7, LNCaP, Hela B, HepG2, SW480, HT29, HCT116 and Colo205	5–100 μg/mL for 24 h	MTT assay, apoptosis analysis, morphological assessment, cell proliferation assay, RT-PCR	Significant cytotoxic effects on various cancer cell lines (MCF−7, LNCaP, HepG2, SW480, HT29, HCT116, and Colo205). HepG2 cells showed increased sensitivity and structural deformation, while Colo205 cells displayed a significant reduction in PCNA expression. In addition, the number of necrotic cells was significantly lower than in the control group
Kutwin et al., (2014)[69]	PtNP (2–19 nm)	RBC from Ross Line hens	2.6 μg/mL for 3 h	Morphological assessment, haemolytic assay	Exposure caused membrane damage, cell deformation, and loss of normal shape. PtNP showed haemolytic properties compared to the control group
Labrador-Rached et al. (2018) [70]	Citrate coated PtNP (70 nm)	HepG2	5–100 μg/mL for 24 h	MTS assay, oxidative stress analysis, inflammatory markers assessment, Akt and Erk signalling activation	Concentration-dependently decreased cell viability. Exposure upregulated ROS and actin expression, as well as the cytokines IL−1β, IL−8 and TNF-α, but did not affect IL−6 or Erk phosphorylation, specifically targeting the PI3K/Akt pathway.
Lebedová et al. (2018)[71]	Citrate coated PtNP (5, 50 nm)	HBEC3-kt	0.5–50 μg/mL for 48 h	Alamar Blue assay, comet assay, MN assay	No significant reduction in cell viability. Only the largest PtNP caused a slight increase in DNA damage. No clear induction of MN was observed
Li et al. (2022) [72]	Zwitterionic thiol-functionalized sulfobetaine stabilized PtNP (6.97 ± 1.44 nm)	HeLa and A549	12.5–200 μg/mL for 4 h	MTT assay	PtNP significantly reduced cell viability of HeLa and A549 cells
Liao al. (2021)[9]	Polyamidoamine dendrimer and PEG double-caged PtNP (1 nm)	TC−1	0–20 μM for 2 and 24 h	CCK8 test, oxidative stress analysis, RT-PCR	Effective cytotoxicity at acidic pH, significantly reduced H_2O_2 levels, but not intracellular ROS accumulation
Lin et al. (2019) [73]	Citrate coated PtNP (5, 70 nm)	Neonatal mice ventricular cardiomyocytes	10^{-9}–10^{-5} g/mL for 5 min	Patch clamp, intracellular ROS measurement, LDH assay	PtNP depolarized the resting potentials, suppressed the depolarization of action potentials and delayed the repolarization of action potentials in a concentration-dependent manner. Exposure decreased the current densities of sodium, potassium and transient outward potassium channels, but did not affect the channel activity kinetics. PtNP did not significantly increase the generation of ROS and leak of LDH
Liu et al. (2021) [74]	Liposomes loaded PtNP (VP@MLip-PtNP) (3–5 nm)	4T1 and RAW264.7	0.5–50 μg/mL for 4 h	CCK8 test, apoptosis analysis, ROS generation analysis,	Photodynamic therapy (PDT) with VP@MLip-PtNP significantly increased cytotoxicity against 4T1 in a concentration-dependent manner, resulting in more complete cell killing compared to PDT without PtNP
Loan et al. (2018) [75]	PtNP (5, 30 nm)	Raw 264.7	2–25 ppm for 24 h	MTT assay, morphological assessment, apoptosis analysis, western blot, DNA fragmentation assay	Size-dependent cytotoxicity (higher toxicity with decreased size). Exposure changed cell morphology and density, increasing apoptosis and causing nucleus fragmentation. Apoptosis was induced by the activation of caspase−3 and −7
Loan et al. (2019) [76]	PtNP (5, 30 nm)	Raw 264.7	2–50 μg/mL for 24 h	MTT assay, morphological assessment, western blot, measurement of nitric oxide production	Effective cytotoxicity in a concentration-dependent manner and morphological changes. PtNP suppressed nitric oxide production and the expression of iNOS and COX−2 proteins

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Table 1 (*continued*)

Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
López Ruiz et al. (2022)[77]	Poly-lactic-co-glycolic acid and poly-ethylene glycol – anti body anti Epidermal Growth Factor Receptor (EGFR) encapsulated (PLGA-PEG-EGFR) PtNP (45 nm±10 nm)	MDA-MB−231 and NHCF-V	10–200 μg/mL for 1, 3 and 5 days	MTS assay, live/dead assay	Non-significant decrease in cell viability after 24 h of treatment which increased after 3 and 5 days without significant differences after encapsulation of PtNP with PLGA–PEG–EGFR; free PtNP showed a stronger anticancer effect
Ma et al. (2020) [78]	Triphenylphosphonium coated PtNP (TPP-Pt) and amino group of Fmoc-Lys PtNP (Lys-PtNP) (<10 nm)	HepG2	14.4–24 μg/mL and 30 mg/L for 4 h	MTT assay, live/dead assay, apoptosis/ necrosis analysis	TPP-PtNP induced significant photothermal cytotoxicity only under light irradiation, with the highest rates of late apoptosis and necrosis; toxicity without irradiation was negligible. Lys-PtNP showed low rates of apoptosis and necrosis, with and without irradiation
Madlum et al. (2021)[79]	PtNP (10, 20 nm)	Hepa1–6 and MDCK	1.5–25 μg/mLExposure time not mentioned	MTT assay	Severe cytotoxicity, with a more pronounced toxicity by the 10 nm PtNP compared to those of 20 nm
Manikandan et al. (2013)[80]	PVP-stabilized PtNP (1–21 nm) with precursor (H_2PtCl_6) concentrations of 5–600 mg	Neuro 2 A	5–50 μg for 8 h	MTT assay, MALDI-MS analysis	All PtNP demonstrated a significant reduction in cell viability, even at low concentrations, and mass spectral profiles indicated that they interact and kill cells through the activation of the apoptosis pathway, with the exception of the PtNP with 200 mg of H_2PtCl_6, which showed remarkable biocompatibility and a mass spectral profile similar to that of the negative control
Manzoor et al. (2021)[81]	PtNP (113.6 nm)	MCF−7	7.8–500 μg/mL for 24 h	MTT assay, cell cycle analysis, wound healing assay	Morphological changes, progressive decrease in cell viability, significant inhibition of migration and wound healing, and notable cell cycle arrest in G_0/G_1 phase, with reduction of cells in G_2/M and S phases
Mironava et al. (2013)[82]	Folic acid coated PtNP (2.3 ± 0.5 nm)	DO33, SCC13, SCC12B, MCF7 and MCF10A	25–300 μg/mL for 12 and 24 h	MTS assay, morphological assessment, apoptosis analysis	PtNP were more effective against SCC13 and SCC12B cancer cells than against normal cells; decreased viability was observed in all cell lines, with increased apoptosis and necrosis, particularly notable in SCC12B and MCF7 cells. Morphological changes were noted in normal and cancer cells
Mitrevska et al. (2023)[83]	PVP-coated (10 ± 2 nm)	MDA-MB−231	0.01–25 μg/mL for 24 h	MTT assay	PtNP reduced cell viability by half at 25 μg/mL
Moglianetti et al. (2016)[84]	Citrate coated PtNP (5, 20 nm)	HeLa, MCF−7, Caco−2 and MEF	25–100 μg/mL for 24, 48 and 72 h	WST−8 test, LDH assay, TUNEL, oxidative stress analysis, antioxidant capacity analysis	No alteration of mitochondrial activity, cell membrane integrity or DNA integrity in HeLa cells, and no induction of any detectable increase in intracellular ROS levels, even at high concentrations. PtNP were able to down-regulate the altered levels of intracellular ROS in MEF cells
Mollania et al. (2024)[85]	PtNP (47 nm)	MCF−7 and 3T3	0.5–2.5 mg/mL for 24, 48 and 72 h	MTT assay	Significant concentration-dependent decrease in the cancer cell line MCF−7, while weak effect in the normal cell line 3T3 after treatment
Nakashima et al. (2019)[86]	PtNP (1 nm)	EVT, HchEpC1b-mStrawberry, HchEpC1b-ATG4B C74A, HTR8/SV40neo and HUVEC	12.5–50 μg/mL for 12 and 48 h	Comet assay, trypan blue assay, WST−1 assay, γ-H2A.X analysis, invasion assay, autophagy assessment, cell proliferation assay	PtNP inhibited cell proliferation, invasion and vascular structure formation in a concentration-dependent manner, with more pronounced effects in autophagy-deficient cells (HchEpC1b-ATG4B C74A). DNA damage was also more significant in autophagy-deficient cells
Nejdl et al. (2017) [87]	Liposome encapsulated PtNP (LipoPtNP) and PtNP (6.5 nm)	HFF and RBC	12.5–200 μg/mL for 2 h	Comet assay, haematological analysis, oxidative stress analysis, xCELLigence method, RT-PCR	More marked genotoxic and cytotoxic effect of LipoPtNP compared to naked PtNP. PtNP had no significant effect on erythrocytes and platelets, and oxidative stress remained stable

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Table 1 (*continued*)

Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
Nomura et al. (2011)[88]	PtNP (2 nm)	RAW264.7 and BMM	1–10 μM for 7 days	Cell viability analysis, RT-PCR	Concentration-dependent inhibition of ROS levels with complete inhibition at 100 μM, concentration-dependent reduction of osteoclast differentiation followed by downexpression of some genes essential for differentiation, without affecting the growth and survival of RAW 264.7 cells
Onizawa et al. (2009)[89]	Polyacrylate stabilized PtNP (2.0 ± 0.4 nm)	A549	50 or 100 μmol/L for 24 h	Alamar Blue assay	Concentration-dependent inhibition of the mortality of cells exposed to a toxic concentration of cigarette smoke extract. PtNP were two times more effective than N-acetylcysteine in reducing cell mortality
Pan et al. (2024) [90]	Nucleus-targeted Pt Nanoclusters (NC) with PEG and with PEG and TAT peptide (Pt@sPEG and (Pt@TAT/sPEG, respectively) (20–40 nm)	8505 C	20 μg/mL for 24 h	Apoptosis analysis, γH2AX analysis, ROS detection analysis, CCK−8 test, LDH assay, translocation assay, western blot	Pt@TAT/PEG demonstrated superior antitumor activity compared to cisplatin and Pt@sPEG, with enhanced cytotoxicity at pH 6.4, inducing overproduction of ROS, Pt-DNA adducts, enhanced apoptosis and DNA damage
Pandey et al. (2014)[91]	Novel self-assembling Cis-platinum nanoparticles (SACN) (>100 nm)	4T1	3–5 μmol/mL for 48 h	CellTiter 96 Aqueous One Solution assay, western blot	The treatment induced dose-dependent apoptosis, activated the PI3K pathway, and increased EGFR and AKT phosphorylation. Sequential SACN-PI828 treatment enhanced PI3K suppression, apoptosis, and reduced AKT phosphorylation
Pansare et al. (2016)[92]	PtNP (11 nm)	MDA-MB−468	1.179×10^{-7}–1.17910^{-4} M for 4 h	SRB assay, western blot, evaluation of interaction with BSA protein and HsDNA	Significant inhibition of cell growth. PtNP bind to BSA, and showed minor groove binding with HsDNA
Patel et al. (2021) [93]	PVP-PtNP (173.5 ± 0.28) and DOX conjugated PVP-PtNP, (DOX-PVP-PtNP) (231 ± 1.1 nm)	MCF−7, HEK−293 and MDA-MB−231	Not reported	MTT assay, western blot, RT-PCR	PVP-DOX-PtNP showed superior cytotoxicity than PtNP alone against breast cancer cells, inducing DNA damage, increased ROS, loss of mitochondrial potential, and apoptosis via inhibition of PI3K/AKT, activation of PTEN, and of the mitochondrial intrinsic apoptosis pathway
Pelka et al. (2009) [94]	PtNP (2–100 nm)	HT29	10^{-4}–10^{3} ng/cm^2 for 3 and 24 h	Trypan blue assay, comet assay, western blot, ROS generation analysis	Treatment did not induce ROS formation in cells, but resulted in decreased intracellular GSH levels and impaired DNA integrity, with an effect dependent on the concentration of PtNP, the incubation time, and the particle size in an inverse manner
Ramanathan et al. (2023)[95]	Chitosan stabilized PtNP (84 ± 4.65 nm)	MDA-MB−231 and HEK−293	25–100 μg/mL for 24 h	MTT assay, apoptosis analysis	Treatment significantly decreased viability of MDA-MB−231 cells, inducing apoptosis, while caused only a minor decrease in the viability of non-cancerous HEK−293 cells
Rehman et al. (2012)[96]	Pectin stabilized PtNP (2.4 ± 0.7 nm)	RAW 264.7	10–1000 μM for 24 h	MTT assay, intracellular ROS generation analysis, PCR, western blot	No effect on cell viability, significant inhibition of LPS-induced ROS and iNOS protein production. Concentration-dependent reduction of PGE_2 production, and levels of pro-inflammatory cytokines IL−6, IL−1β, and TNF-α, increased by LPS stimulation
Sadalage et al. (2022)[97]	PtNP (6–8 nm)	PBMC andRBC	1–300 μg/mL for 24 h	MTT assay, morphological assessment, hemolysis assay	PtNP did not show significant effects on PBMC at 150 μg/mL, but toxic effects were observed at higher concentrations. No signs of significant haemolysis were detected, although a change in cell shape was noted at higher concentrations
Şahin et al. (2018) [98]	PtNP (20.12 nm)	MCF−7	2.5–100 μg/mL for 1, 2 and 3 days	MTT assay, cell cycle analysis, apoptosis analysis, morphological assessment, comet assay	Dose-dependent decrease in cell viability and increase in apoptotic cells, causing oxidative stress, and reduction of cells in the G1 phase of the cell cycle, with significant DNA damage at 100 μg/mL

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Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
Sancho-Albero et al. (2022) [99]	PtNP loaded exosomes from 3 cell lines ($Exos^{hpMSC}$PtNP, ($Exos^{U251-MG}$PtNP, and ($Exos^{B16\text{-}F10}$ PtNP) (< 2 nm)	hpMSCs, B16-F10 and U251-MG	0.125–4 μg/100 μL for 48 h	Blue Cell viability test, cell cycle analysis, apoptosis/necrosis analysis, live/dead assay	$Exos^{hpMSC}$PtNP slightly reduced the viability of parental hpMSCs cells, while $Exos^{hpMSC}$PtNP obtained with higher precursor concentrations caused a significant viability decrease in viability accompanied by morphological changes. Exosomes from the same parental line significantly decreased G1 phase, but no differences were observed with exosomes from another line
Sankarganesh et al. (2017) [100]	2-((4,6-dimethoxypyrimidine−2-yl) methyleneenamino)−6-methoxyphenol) capped PtNP (58.64 ± 3.0 nm)	NHDF, MCF−7, HEp2 and HeLa	20–100 μg/mL for 72 h	MTT assay	PtNP showed higher cytotoxicity towards cancer cell lines compared to normal NHDF cells
Sathiyaraj et al. (2021)[101]	*Halymenia dilatata* capped PtNP (15 nm)	MDA-MB−231	5–100 μg/mL for 24 h	MTT assay, apoptosis analysis, morphological assessment	PtNP effectively inhibited cell growth; signs of apoptosis were observed, such as swelling and fragmentation of the nucleus
Shakibaie et al. (2021)[7]	PtNP (7.4–11.2 nm)	A549, MCF−7, 3T3 and RBC	0.25–640 μg/mL for 24 and 48 h	MTT assay, haemolytic assay	Dose-dependent haemolysis, but values remained below 5 %. Results showed lower toxicity of PtNP against A549, MCF−7 and 3T3 cell lines than hexachloroplatinic acid and cisplatin
Shim et al. (2017) [102]	PtNP (23–60 nm)	HEK−293	5–45 μg/mL for 24 or 48 h	Trypan blue assay	Cell viability decreased in a concentration-dependent manner and by prolonged incubation, by affecting cell proliferation, without noticeable changes in cell shape or size
Shiny et al. (2016) [103]	PtNP (20–35 nm)	A549	1–20 μg/mL for 24 h	MTT assay, Live/dead assay, morphological assessment, oxidative stress markers analysis, comet assay, cell cycle analysis, RT-PCR	Cell growth was blocked in G_2/M phase and the number of cells in S phase decreased. Up-modulation of apoptotic inducers, down-expression of anti-apoptotic genes, and nucleic acid damage were also observed
Shoshan et al. (2019)[104]	Peptide coated PtNP (2.5 ± 0.7 nm)	HepG2, HT−29, MCF−7, HeLa, PC3, A431, A549 and A2780	0.1–10 mg/L for 72 h	MTT assay	Treatment almost completely inhibited the growth of HepG2 cells (IC_{50} of 2.9 ± 0.3 mg/L), having less impact on non-cancer cells
Subramaniyan et al. (2018) [105]	PtNP synthesized under microgravity (MG-PtNP) and normal gravity (NG-PtNP) (8.5 and 15 nm, respectively)	C2C12	10–100 μg/mL for 24 h	MTT assay, apoptosis/necrosis analysis, western blot, trypan blue assay, ROS generation	PtNP significantly reduced mitochondrial activity and cell viability, inducing morphological changes and ROS production. PtNP promoted early and late apoptosis, with a more pronounced effect observed for MG-PtNP
Tanaka et al. (2019)[5]	PtNP-conjugated latex beads (P2VP) and Pt nanocomposite beads (PtNCP) (size not reported)	HSC−3-M3	6.25–100 μg/mL for 48 h	LDH assay, CCK−8 test, morphological assessment	PtNCP inhibited cell viability in a concentration-dependent manner and induced LDH leakage. Aggregation of the PtNCP on the cell membrane, destructionof the cell membrane and globular structures were observed. No effect on cell viability or morphological alterations were obtained after P2VP treatment
Teow and Valiyaveettil (2010)[106]	Folic acid–capped (Pt-FA, 10–15) nm) and PVP capped (Pt-PVP, 2–6 nm) PtNP	HeLa, MCF7 and IMR90	25–400 μg/mL for 24, 48 and 72 h	Apoptosis assay, Glo luminescent cell viability assay	Pt-FA effectively reduced cell viability and induced apoptosis in normal and cancer cells. Pt-PVP increased apoptosis without affecting cell viability
Ullah et al. (2017) [107]	PtNP (5 nm)	A549	8–128 μg/mL for 24 h	MTT assay	Cell viability decreased, and severe damage to cell morphology was observed with increasing concentrations of PtNP
Wang et al. (2015)[108]	Trifolium-like PVP-PtNP (TPN) (16 ± 3 nm)	NIH3T3, PC9 and HeLa	9.8–58.5 ppm	MTT assay, live/dead cell assay	Cells treated with TPN and NIR showed increased cell death compared to separate treatments
Wawrowicz et al. (2022)[109]	PEG-PtNP and trastuzumab-targeted bioconjugated PEG-PtNP (2 nm)	SKOV−3 and HepG2	50–400 μg /mL for 24, 48 and 72 h	MTS assay, apoptosis analysis, ROS generation analysis	Neither PEG-PtNP nor bioconjugates with trastuzumab inhibited SKOV−3 cell proliferation, while PEG-PtNP induced a reduction in viability in HepG2 cells at concentrations higher than 145 μg /mL. A slight increase in ROS was observed in SKOV−3, while the signal was doubled in HepG2, with S phase cycle arrest

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Table 1 (*continued*)

Study	PtNP tested (dry size)	Cell system	Exposure conditions	Methods	Results
Xiang et al. (2023)[110]	BSA and curcumine (CUR) decorated PtNP (Pt@BSA and Pt@BSA-CUR) (5–10 nm)	HFF−2, HepG2 and RBC	25–400 μg/mL for 4 and 12 h	MTT assay, hemolytic assay	Pt@BSA did not affect the haemolysis and viability of normal HFF−2 cells but promoted their proliferation. In contrast, Pt@BSA and Pt@BSA-CUR reduced the viability of HepG2 cancer cells in a concentration-dependent manner
Yang et al. (2017) [111]	Extract polyphenols capped PtNP (54 ± 2 nm)	HCT 116	5–50 μg/mL for 24 h	MTT assay	Cell viability decreased proportionally with increasing PtNP concentration (IC_{50}: 20 μg/mL)
Yin et al. (2017) [112]	Chondroitin sulfate capped PtNP (3–5 nm)	Osteoarthritis chondrocytes	10–100 ppm for 24 h	Trypan blue assay, apoptosis analysis	-Concentration-dependent cytotoxicity, with cell viability greater than 50 % even at high concentrations, accompanied by morphological changes in the nuclei
Yoshihisa et al. (2010)[113]	Polyacrylic acid capped PtNP(size not reported)	HaCaT	100 μM for 24 h	ROS generation analysis, DNA fragmentation assay, early apoptosis/ secondary necrosis assessment, MMP assay, TUNEL assay, northern blot, western blot	PtNP significantly inhibited UV-induced O_2 formation and reduced early apoptotic cells after UVB and UVC irradiation, while decreasing Bax expression. No alteration of secondary necrosis or the expression of Bax, Bcl-XL, procaspase−3 and Fas after UVA irradiation
Yoshihisa et al. (2011)[114]	Polyacrylic acid capped PtNP (size not reported)	U937 and HH	10–100 μM for 24 h	DNA fragmentation assay, MMP assay, ROS generation analysis, apoptosis analysis, western blot	PtNP reduced hyperthermia-induced DNA damage, decreased early apoptotic cells, inhibited hyperthermia-induced ROS (completely in U937 and partially in HH), prevented Fas receptor externalization, preserved MMP, and reduced caspase−3 activity
Zhang et al. (2021)[115]	PVP-coated PtNP (3 nm)	HEK293	12.5–200 μg/mL for 20 or 44 h	MTT assay, haemolysis assay, ROS/RNS scavenging analysis, apoptosis and necrosis analysis	PtNP significantly reduced intracellular levels of ROS and RNS in a concentration-dependent manner, prevented mitochondrial fragmentation, improved cell survival, and reduced apoptosis
Zhu et al. (2016) [116]	Diallyl dimethyl ammonium chloride coated PtNP (72 ± 18 nm)	U−87 MG	8–60 μg/mL for 24 h	MTT assay, LDH assay, morphological assessment	PtNP exhibited no cytotoxicity. However, a change in cell morphology was observed after pretreatment with PtNP followed by laser irradiation. The combined treatment resulted in a significant release of LDH, indicating that PtNP, under high irradiation, induced cell necrosis in photothermal therapy
Zhu et al. (2017) [117]	Hyaluronic acid-encapsulated PtNP (HA-PtNP) and alginate acid encapsulated PtNP (AA-PtNP) (38 ± 6 and32 ±6 nm, respectively)	NIH3T3 and MDA-MB231	1–200 ppm for 48 h	MTT assay, AO/EB staining assay, histopathological examination	Both PtNP exhibited no cytotoxicity on both cell lines, while when cells were irradiated with a NIR laser viability of cancer MDA-MB 231 cells was greatly reduced at high concentrations of HA-PtNP. These results were confirmed by AO/EB staining of NIR-irradiated NIH3T3 and MDA-MB231 cells

8-oxo-G, 8-oxo-7,8-dihydro-2'-deoxyguanosine; AKT, protein kinase B; AO, acridine orange; BSA, bovine serum albumin; CCK, cell counting kit; CFDA-AM, 5-carboxyfluorescein diacetate-acetoxymethyl ester; DCFDH-DA, 2′,7′-dichlorodihydrofluorescein diacetate; DOX, doxorubicin; DSB, double strand breaks; EB, ethidium bromide; ERK1/2, extracellular signal-regulated kinases 1/2; GSH, glutathione; HsDNA, herring sperm DNA; IL-1, interleukin 1; IL-6, interleukin 6; IL-8, interleukin 8; IL-1β, interleukin 1β; JNK, c-Jun N-terminal kinase; LDH, lactate dehydrogenase; LPO, lipid peroxidation; LPS, lipopolysaccharides; MMP, mitochondrial membrane potential; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NIR, near-infrared radiation; NRU, neutral red uptake; PBMC, peripheral blood mononuclear cells; PCNA, proliferating cell nuclear antigen; PCR, polymerase chain reaction; PEG, polyethylene glycol; PGE2, prostaglandin E2; PI, propidium iodide; PI3K, phosphoinositide 3-kinase; PVP, polyvinylpyrrolidone; RBC, red blood cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; RT-PCR, real time polymerase chain reaction; RT-qPCR, quantitative real time polymerase chain reaction; SQ-RT-PCR, semiquantitative reverse transcription polymerase chain reaction; SRB, sulforhodamine B; TEM, transmission electron microscopy; TNF-α, tumour necrosis factor α; TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling; WST, water-soluble tetrazolium.

cervical cancer cell lines were among the most frequent cell types.

Regarding the outcome evaluated, most *in vitro* studies, 82 out of 96 (85.4 %), addressed only cytotoxic effects, including viability decrease, apoptosis induction, membrane impairment or oxidative stress, with 14 out of 96 (14.6 %) addressing both genotoxicity and cytotoxicity. Fig. 3 outlines the main cellular effects observed in these studies. Among those evaluating cytotoxicity, the great majority (89 %) evaluated effects on cell viability by colorimetric assays, i.e. tetrazolium cell viability assays (MTT, WST, MTS), neutral red uptake (NRU), alamar blue (AB), or trypan blue, being MTT or related assays (WST, MTS) the most commonly used (72.8 %). However, even though potential interference of metal nanoparticles with colorimetric assays is well-documented in the literature [21–23], possible interference with reagents or detection methods was not addressed in any of those studies. Regarding genotoxicity, comet assay is the technique most frequently employed (in 13 out of 14 studies) to evaluate potential DNA damage induced by PtNP; however, it must be pointed out that in three of these studies, proper quantitative analysis of the comet assay results was not conducted, and just qualitative evaluation is provided. The Micronucleus (MN) test was used in two occasions, and other two studies evaluated the double strand break (DSB) induction by analysing the levels of H2AX phosphorylation.

Studies focused on the potential cytotoxic effects of PtNP on cell cultures reported that these nanomaterials may generate a panel of cell disruptions, mainly decrease in cell viability and excessive generation of ROS, which often results in oxidative stress and mitochondrial damage causing the activation of programmed cell death. It is also noticeable the number of studies finding antioxidant properties of PtNP (12 out of 32), even when this outcome was not included as a search descriptor [87,89, 93,94,96,113]. PtNP can induce different types of cellular damage, which have been described as function of concentration, exposure time and cell type, although in most studies, cytotoxicity was mainly expressed by a reduction in cell viability. For example, 20–50 nm sized PtNP (31.2 μg/mL) reduced the viability of human MCF-7 breast cancer cells by 52.77 % after 24 h of incubation [33]. Furthermore, a concentration-dependent inhibition of HEK 293, Thle 2, MIApaCa 2 and Hela cell proliferation was reported after exposure to 0.1–100 mg/mL PtNP [34]. Other studies have also reported effects on viability of different human carcinoma cell lines, including liver (HepG2), colon (HT-29), breast (MCF-7), cervical (HeLa), prostate (PC3), epidermoid (A431), lung (A549) and ovarian (A2780) cells [45,104].

However, effects on cell viability are usually less marked when non-cancer or primary cells are exposed, highlighting the selectivity of PtNP for cancer cells [94]. Indeed, no decreases in viability were observed after treating keratinocytes (NHEK cells), HaCaT cells [60], or peripheral blood mononuclear cells (PBMC) [97] with diverse PtNP at different concentrations and exposure times. This limited effect in non-cancer cells was also demonstrated in different studies employing simultaneously both non-cancer and cancer cells to investigate the potential anticarcinogenic ability of PtNP. Thus, 2-((4,6-dimethoxypyrimidine-2-yl)methyleneenamino)-6-methoxyphenol (DPMM)-PtNP were used to treat different cancer cell lines (MCF-7, HeLa and HEp-2) and normal human fibroblasts (NHDF), showing a more pronounced cytotoxicity in tumour lines [10]. Similarly, Bendale et al. [36] treated 567A5, PA-1 and Mia-Pa-Ca-2 cancer cells and normal PBMC with PtNP at 200 μg/mL for 48 h, and found a significant decrease of viability in all cancer cell lines but not in non-cancer cells. Peptide-coated PtNP also showed significantly greater toxicity against HepG2 hepatic cancer cells than against non-cancerous AML-12 liver cells [104], and against cancerous MelJuSo cells than against non-cancerous HaCaT cells [38]. The selectivity of PtNP for cancer cells over non-cancer cells could be related to differences in metabolism, membrane permeability, and signalling pathways between tumour and normal cells [10]. Accordingly, a doxorubicin–PtNP conjugate system was reported to down-regulate the PI3K/AKT signalling pathway and consequently activate the tumour suppressor gene *PTEN* [93]. All these observations support the suitability of PtNP to be potentially used in anticancer therapies.

Half-maximal inhibitory concentration (IC_{50}) values for PtNP were reported in several of the reviewed studies (Table 2). Three of them were carried out using MCF-7 breast cancer cells treated with green-synthesized PtNP. Baskaran et al. [33] evaluated the effects of PtNP (20–50 nm) biologically fabricated by *Streptomyces sp.* on MCF-7 cell viability by the MTT test, revealing an IC_{50} of 31.2 μg/mL at 24 h treatment. Şahin et al. [98] obtained an IC_{50} value of 17.84 μg/mL in the same cells incubated for 48 h with PtNP synthesized using an extract of *Punica granatum* crusts. More recently, Manzoor et al. [81] established an IC_{50} value of 167.2 μg/mL after 24 h of treatment with PtNP synthesized using an extract of *Psidium guajava* leaves. Similar IC_{50} values for peptide-coated PtNP (2.9 mg/L) and peptide-coated PtNP further functionalized with glucose (2.4 mg/L) were reported in hepatocellular carcinoma HepG2 cells incubated for 72 h [104]. However, the impact of the same PtNP variants on the viability of non-cancer liver AML-12 cells was limited, with an $IC_{50} > 100$ mg/L. Another issue to highlight is the influence of NP size on the observed effects. As previously reported in other studies [118,119], results from three studies using different PtNP on the same cell type, MCF-7, demonstrated an inverse relationship between NP size and the magnitude of induced cytotoxicity, i.e. the smaller the NP, the greater cytotoxic potential. In particular, Fahmy et al. [46] found an IC_{50} value of 10.9 μg/mL for 20 nm PtNP; Baskaran al. [33] reported a IC_{50} value of 31.2 μg/mL for medium-sized PtNP (20–50 nm), and Manzoor et al. [81] described a higher IC_{50} of 167.2 μg/mL, for larger PtNP (113.6 nm).

Excessive ROS production, frequently leading to oxidative stress and mitochondrial damage, has also been observed in a number of reviewed *in vitro* studies (20 out of 95). This increase in ROS generation was observed specifically in C2C12 cells treated with PtNP synthesized via a green mediated synthesis using cell-free culture filtrate as a reducing agent, leading to progressive oxidative damage, ultimately causing cell death [105]. Also, polyethylene glycol (PEG) and peptide-coated PtNP (Pt@TAT/sPEG) induced excessive ROS production thus facilitating the formation of Pt-DNA adducts, especially under acidic conditions, and disrupting DNA conformation [90]. Polymeric PtNP were also found to generate intracellular ROS directly related to mitochondrial membrane integrity alterations in breast cancer cells [93]. Another study revealed that citrate-coated PtNP induced ROS production in a concentration-dependent manner in HepG2 liver cells related to an increase in the expression of actin, a marker of cellular stress, which would indicate a significant stress response of these cells in the presence of the NP [70].

However, as previously pointed out, PtNP may act as antioxidant agents as well. Several reviewed studies reported antioxidant ability of PtNP on different cells systems. Rehman et al. [96] studied the effect of PtNP on lipopolysaccharide (LPS)-induced ROS generation in RAW 264.7 cells. Preincubation with PtNP at a concentration of 100 μM significantly decreased ROS generation. Similarly, the antioxidant capacity against hydrogen peroxide (H_2O_2)-induced oxidative stress of ultra-small (3 nm) polyvinylpyrrolidone (PVP)-coated PtNP (0–200 μg/mL) was evaluated in HEK293T cells, observing where a significant reduction in the intracellular ROS levels was observed [115]. One study reported pro-oxidant and antioxidant behaviour of PtNP, depending on the experimental conditions. In particular, PtNP increased the intracellular H_2O_2 and $O^{2\bullet-}$ levels in U937 cells when pretreated for 20 h before ultrasonication (1 MHz), but decreased the formation of the oxidant species when added immediately before ultrasonication [63]. Finally, polyacrylate-stabilized (PAA)-PtNP were found to be two times more effective than N-acetylcysteine, an antioxidant agent, in reducing the death of human lung cancer A549 cells exposed to a toxic concentration of cigarette smoke extract [89]. This pro-oxidant/antioxidant duality highlights the importance of exploring the specific conditions under which PtNP exert their effects, and the role of size and surface modifications, in order to better understand their mechanisms of action and optimize their use in therapeutic applications.

Exposure to PtNP also caused morphological changes in liver cells,

both normal (CHANG cells) and cancerous (HuH-7 cells), becoming fragmented and spherical, and detaching from the culture flask surface in a concentration- and time-dependent manner [26]. Exposure to these ultrasmall PtNP (~2 nm) induced significant changes in the morphology of human monocytic THP-1 cells, such as loss of uniformity and shrinkage around cell clusters, as well as impaired cell membrane integrity [53]. Severe morphological alterations were also observed in other cell lines, such as A549 human lung cancer cells [107], C2C12 myoblast cells [105], and RAW 264.7 macrophage cells [75]. On the contrary, PtNP did not cause visible alterations to MDM-MB-468 human breast cancer cells [92].

Among the observed cytotoxic effects, significant alterations in the cell cycle were reported in several studies. Şahin et al. [98] observed that the incubation of MCF-7 cells with PtNP for 48 h resulted in substantial changes in the cell cycle, specifically causing a loss of cells in the G_0/G_1 phase. Alyami et al. [29] demonstrated that PtNP induced a marked and significant cell cycle arrest of HCT-116 cells in the G_2 phase, while also reducing the population of cells in the G_0/G_1 and S phases. These results indicate that PtNP effectively inhibit the transition of cells to the S phase, thereby obstructing the cell division. In contrast, an evaluation of the impact of PtNP on the division of NHEK cells revealed no significant effects after either 24 or 48 h of incubation [64]. These variations in effects appear to be influenced by the specific characteristics of the nanoparticles tested, their concentrations, and the particular cell lines utilized.

The impact of PtNP on the differentiation process of THP-1 cells into macrophages was examined by exposing cells to a concentration of 50 μg/mL of 5 nm-sized citrate-coated-PtNP for 24 h, before being stimulated for cell differentiation using phorbol myristate acetate (PMA) [47]. Three days later, transmission electron microscopy (TEM) analysis revealed no notable differences in intracellular structures, cytoskeletal organization, or vesicular compartments between control and PtNP-exposed THP-1 macrophages, although efficient cellular uptake of the NP was confirmed [47]. The influence of citrate coated-PtNP on the osteoclast differentiation of RAW cells and bone marrow cells induced by the addition of RANKL was also tested [88]. The results revealed that the NP strongly inhibited the differentiation of osteoclasts in a concentration-dependent manner. The divergence of the results obtained in the two studies regarding the process of cell differentiation despite the similarity of the NP coating (citrate), highlights that the cellular response may vary depending on the cell type and the biological specificities [88].

Furthermore, anti-inflammatory properties have been already attributed to PtNP. Thus, PtNP treatment significantly attenuated LPS-induced inflammation in a concentration-dependent manner. Indeed, stimulation of RAW 264.7 cells with LPS resulted in a marked increase in the production of pro-inflammatory cytokines, including interleukin (IL)-6, IL-1β, and tumour necrosis factor alpha (TNF-α). Nonetheless, PtNP administration led to a notable reduction in these cytokines, suggesting that these NP possess a substantial anti-inflammatory effect in this cell model.

As previously pointed out, potential genotoxicity of PtNP has been much less addressed in the literature than their cytotoxicity. The main genotoxic effects observed after *in vitro* exposure to PtNP included (i) induction of primary DNA damage in a number of cell types, namely trophoblast EVT cells [86], liver normal (CHANG) or cancerous (HuH-7) cells [26], lung carcinoma A549 cells [103], IMR-90 fibroblasts, glial U251 cells [31], NHEK keratinocytes [64], colon carcinoma HT29 cells [94], and embryonic kidney HEK293 cells [27]; (ii) MN formation in human fibroblasts and glial U251 cells [31]; (iii) DSB induction in EVT trophoblast cells [86]; and (iv) oxidative DNA damage in colorectal adenocarcinoma HT29 cells [94]. But most of these effects were observed after long treatment times and/or high concentrations, likely far from being therapeutically relevant [26,27,64]. Moreover, several studies reported no induction of genotoxic damage [61,71,87] or gene expression alterations of IL6 and TNFα by PtNP exposure [58]. Still, in other cases, changes in the expression of genes related to inflammatory pathways [47], and of pro-apoptotic and DNA repair genes [52,68] were found after PtNP treatment of different cell types. It is also worth highlighting that in some studies PtNP showed genotoxic potential only when employed encapsulated in liposomes [87] or conjugated with TAT peptide [90], but not in its pristine form. This should be considered for further biomedical applications.

Potential effects of PtNP on DNA repair pathways were assessed in just one study, where the combined impact of PtNP and doxorubicin (DOX) on the expression of DNA repair genes in U2OS cells was investigated [52]. Individual exposure to PtNP and DOX increased the expression of DNA repair genes, and the effect was significantly more pronounced for the combined treatment, particularly 8-oxoguanine DNA glycosylase 1 (OGG1) and other repair genes, such as APEX1, CREB1, POLB, UNG, and GADD45A, were significantly upregulated. Results from this study suggest that PtNP would exert a genotoxic effect that stimulates the expression of genes involved in base excision repair (BER) pathway in U2OS cells. None of the reviewed studies addressed the potential antigenotoxic effects of PtNP.

Taking all these reviewed studies together, in vitro results obtained have demonstrated that PtNP show in general good biocompatibility and promising benefits for biomedical use under specific conditions; still more studies are necessary for their characterization (size, functionalization, concentration, route of exposure…), and particularly for understanding their dual pro-oxidant/antioxidant effect. Together with this potential good biocompatibility, PtNP were found to reduce the damage induced by other agents in a number of studies, encouraging that their potential benefits in biomedicine are worth exploring.

3.2. *In vivo effects of PtNP*

Complementing the first approach to biological effects of PtNP offered by *in vitro* systems, *in vivo* tests are crucial to understand the real effects of PtNP in complex biological conditions and to guide their future safe use. They provide essential information on the safety, efficacy and potential impact of these nanomaterials in various contexts, comprehensively assessing the interactions with living organisms at very different levels.

Despite their relevance, *in vivo* toxicity studies with PtNP remain relatively scarce. In this review, a total of 34 *in vivo* studies were obtained from the systematic search (Table 3). Most studies were performed employing vertebrates (88.2 %), with only 4 out of 34 (11.8 %) using invertebrates. The most frequently studied organisms were mice (67.6 %), mostly limited to C57BL6/J or BALB/c, but other organisms were also used, including hens (11.8 %), rats (5.7 %), the nematode worm *Caenorhabditis elegans* (5.9 %), the zebrafish (*Danio rerio)*, the fruit fly (*Drosophila melanogaster*), and the small seawater crustacean *Artemia nauplio* (1 study, 2.9 % each) (Fig. 4). In rodent studies, PtNP were administrated mainly intravenously, although other administration routes, i.e. oral, intranasal, subcutaneous, dermal, intraperitoneal and intratumoral administration vias, were also used. The results obtained generally focused on the assessment of physical (weight, size…), histopathological or biochemical outcomes, as well as oxidative stress, inflammation, behaviour, and mortality. Studies addressing potential embryotoxic effects used hen fertilized eggs [120] or zebrafish embryos [121]. No studies evaluating teratogenicity or reproductive toxicity in mammals were reported. Regarding PtNP biodistribution, several studies addressed the bioaccumulation and aggregation of PtNP in various body compartments. The following sections describe the main results of these studies, according to the type of organism and outcome addressed.

3.2.1. *Toxicity in mammals*

As previously indicated, the great majority of *in vivo* PtNP studies were conducted in mammals (73.5 %), particularly in rodents (mice and rats). Agreeing with in vitro results, some of these studies support the

good biocompatibility of PtNP reporting absence or low *in vivo* toxicity of these NP, usually with no alterations in body weight or clinical abnormalities in the exposed animals. According to the works by Yamagishi et al. [131] and Isoda et al. [124] in Balb/c male mice, the smaller the NP, the more damage they induce, again in line with the findings from *in vitro* studies. In Yamagishy's study [131], although less than 1 nm PtNP intravenously injected induced liver damage, including acute hepatic injury and increased levels of serum inflammatory cytokines, larger NP (15 nm) did not produce these abnormalities. Similarly, intravenous administration of PtNP induced significant hepatorenal toxicity and dose-dependent increases of inflammatory markers only after exposure to 1 nm PtNP but not to 8 nm PtNP [124]. Katsumi et al. [125] also found significant increases in lipid peroxidation, hepatic serum proteins and oxidative stress in male ddY mice treated with 30 nm PtNP but not in those treated with 106 nm PtNP.

Some *in vivo* studies reported PtNP biodistribution and accumulation in different organs and systems, mainly in liver. No Pt was detected in plasma of mice 24 h after injection of 10 mg of lipid-polymer conjugate 1,2-distearoyl-sn-glycero-3-phosphoethanolamine and polyethylene glycol (DSPE-PEG)-coated PtNP micelles, indicating that PtNP had either been excreted from the system or deposited in organs or tissues within that time period [39]. Indeed, about 27 % of the injected Pt was detected in liver and spleen after 24 h. Tumour-bearing mice accumulated about 3 % of the injected Pt in the tumour site, and slightly lower amounts in the liver and spleen compared to healthy mice. Accordingly, a rapid accumulation of NP in the kidneys of female BALB/c mice intravenously injected with polyvinylpyrrolidone (PVP) coated PtNP was observed just 2 h after administration, in both healthy and acute kidney injured animals. In addition, the NP were rapidly cleared from the blood, with a distribution half-life of approximately 2.27 h, and their excretion was faster in healthy than in ill mice [115].

As already pointed out, a number of *in vivo* studies reported no or limited adverse effects of PtNP in exposed animals. No significant toxicity was observed after intravenous injection of healthy female mice with single doses of DSPE-PEG-PtNP 5–20 mg Pt/kg bw as compared to a non-treated control group. The micelles were well tolerated, and no weight loss was observed at any dose tested. Mice were sacrificed after 21 days, and blood plasma was analysed for markers of toxicity. All results were normal, suggesting minimal organ stress or toxicity. Plasma biochemistry and histology supported the conclusion that the NP induced minimal toxicity *in vivo* [39]. Compared to other metal NP evaluated in the literature, these PtNP are better tolerated than silver [132] and copper NP [133]. Similarly, BALB/c nude mice injected intravenously with 4 mg/mL peptide-coated (TPP)-PtNP showed no significant changes in body weight after 13 days of treatment; liver and kidney function tests showed results within the normal range, without signs of toxicity, and organ morphological examination revealed no necrosis or lesions, highlighting the good tolerance of the animals to TPP-PtNP treatment [78]. Additionally, treatment with PVP-PtNP (25 mg/kg bw) intravenously injected [115] or PEG-PtNP (10 and 50 mg/kg bw) intraperitoneally injected [127] did not result in significant decrease in body weight or obvious pathological lesions in the organs of mice, supporting the good biocompatibility of PtNP.

Furthermore, anticancer or protective effects were described for PtNP in several animal studies. PtNP encapsulated in exosomes were administrated intravenously and intratumourally to female BALB/c nu/nu mice bearing tumours implanted 11 days before treatment. Tumour size in the control group continued to grow, while the tumours in PtNP-treated mice stopped growing and even shrank after the first administration. Moreover, unlike mice treated with cisplatin, animals treated

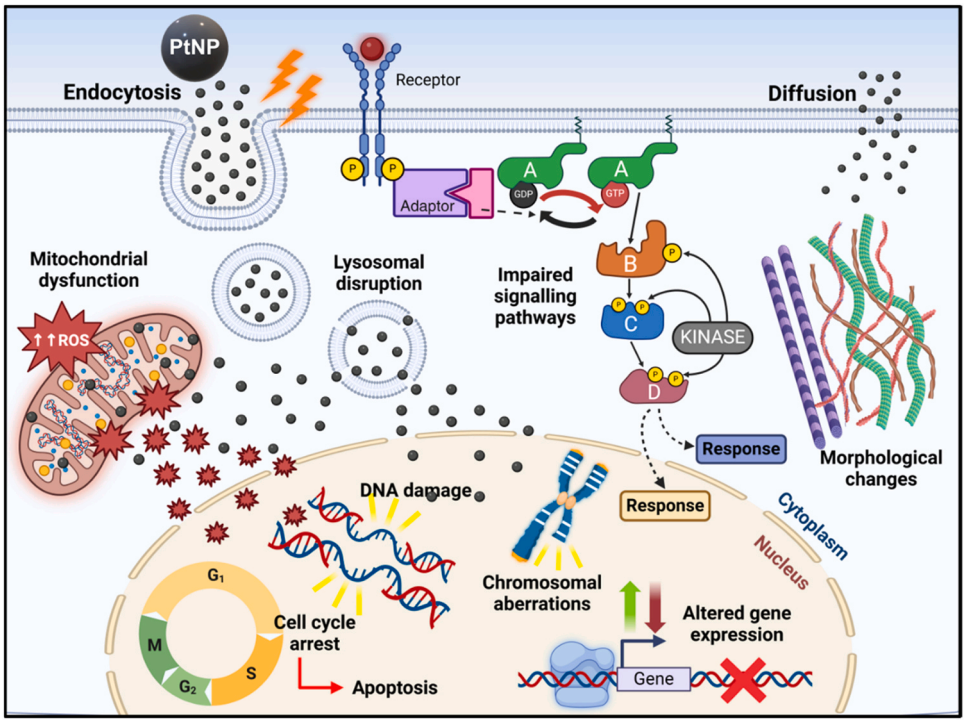

Fig. 3. Impact of platinum nanoparticles (PtNP) on cellular mechanisms and the integrity of biomolecules. PtNP can enter cells by endocytosis or passive diffusion across the plasma membrane. Once in the cytoplasm, they interact with various organelles including mitochondria, leading to disruption of ATP production and alteration of energy metabolism that induces overproduction of reactive oxygen species (ROS), causing oxidative stress. The latter disrupt essential cellular functions, by altering intracellular signalling pathways, modulating critical processes such as inflammation and cell cycle, thus promoting membrane dysfunctions. In addition, PtNP can enter the nucleus and directly interact with DNA, causing single (SSB) and double (DSB) strand breaks, as well as structural modifications such as interstrand cross-links. Also, the generated ROS can oxidize DNA bases accentuating genomic damage and instability, the appearance of chromosomal aberrations, such as deletions, translocations or breakages, as well as mutations in genes, such as oncogenes and tumour suppressor genes. The inability to effectively repair these damages often triggers apoptotic pathways, leading to programmed cell death.

with PtNP did not experience significant weight loss, severe clinical effects, or inactivity [99]. Intravenous injection of HepG2 tumour-bearing BALB/c nude mice with TPP-PtNP via tail vein revealed a high accumulation in the tumour site at as early as 0.5 h, with prolonged retention at 12 h [78]. Photothermal imaging revealed that tumour temperature of TPP-Pt-treated mice increased faster and higher than that of the control group, indicating a photothermal effect in the tumour site. Tumours in the TPP-PtNP treated group were slightly smaller than those in the control group, and histological analyses revealed severe cellular damage in the treated tumours, confirming the efficacy of TPP-PtNP [78]. Finally, PVP-PtNP were demonstrated to alleviate acute kidney injury symptoms in ill BALB/c mice more effectively than traditional treatments [115]. Intravenously treated animals partially prevented the severe weight loss and showed reduced levels of urea nitrogen and creatinine, tubular injury, cell apoptosis, and oxidative DNA damage, and inhibited renal ROS generation as well as increased levels of superoxide dismutase, an antioxidant enzyme. Furthermore, different PtNP reduced the epidermal inflammation induced by UV-light in mice [113], inhibited lung inflammation in mice exposed to cigarette smoke [88], and scavenged excessive ROS by showing antioxidant capacity or by mimicking activity of antioxidant enzymes [134,135].

3.2.2. *Embryotoxicity*

Potential embryotoxicity of PtNP was addressed in some studies that employed embryos from zebrafish (*Danio rerio*), red junglefowl (*Gallus gallus*), or Ross hen individuals. The assessment of the impact of PtNP (10–100 μg/mL) on zebrafish embryos was carried out by Asharani and colleagues [121]. Embryos exposed to NP during the early stages of development exhibited body accumulation of PtNP, hatching delays, as well as a concentration dependent drop in heart rate, touch response and axis curvatures. Additionally, no remarkable effects on the development of the circulatory system were observed, with only a mild increase in inflammatory markers and oxidative stress suggesting a better relative biocompatibility of PtNP than the other two types of NP studied (silver and gold) [121].

Similarly, fertilized eggs from Ross hens were exposed to PtNP administered by albumen injection at doses from 1 to 20 μg/mL [120]. The results showed normal development of embryos without visible alterations, and no significant changes were either observed in body weight or in the weights of brain, heart, spleen, and bursa of Fabricius, except for a slight variation in liver weight. In addition, biochemical indices measured in blood sera of embryos did not reveal any disturbances. However, histological and morphological analyses indicated pathological alterations in the brain structure of embryos treated with PtNP, including moderate degradation of the cerebellar molecular layer, neuronal loss in the cerebellar cortex, and astrocytosis. TEM examination revealed mitochondrial degradation, rounded nuclei with dispersed chromatin, and signs of functional and structural disruption induced by PtNP. In addition, immunohistochemical analyses revealed statistically significant increase in caspase-3 and decrease in the number of proliferating cell nuclear antigen (PCNA)-positive nuclei after *in ovo* injection, indicating that PtNP inhibit cell proliferation and promote apoptosis in the cerebellar cortex [120].

Table 2
Half-Maximal Inhibitory Concentration (IC_{50}) obtained for PtNP (in vitro studies, alphabetically ordered). See Table 1 for additional details on the studies.

Study	Size NP	Coating	Cell system	Exposure time	IC_{50} Value
Alyami et al. (2022) [29]	124.3 nm	Lycopene coated	HCT−116	24 h	14.62 μM/mL
Alshatwi et al. (2015) [28]	30–60 nm	Polyphenol coated	SiHa	24 and 48 h	18.34 μg/mL
Aygun et al. (2020)[32]	3.47 ± 1.31 nm	-	HeLaMDA-MB−23	24 h	36.86 μg/mL 19.83 μg/mL
Baskaran al., (2017) [33]	20–50 nm	-	MCF−7	24 h	31.2 μg/mL
Borowik et al. (2019) [38]	10–80 nm	-	HaCaT MelJuSo	72 h	102 μL/mL 23 μL/mL
Buchtelova et al. (2017) [40]	10, 29, 40 nm	PVP coated	MDA-MB−231, LNCaP, PNT1A, HaCaT	24 h	3.1–6.2 μg/mL
Estrela-Llopis et al. (2014)[45]	18 nm38 nm	-Polysaccharide coated	A2780	24 h	46 mg/dm^3 μg/mL12 mg/dm^3 μg/mL
Fahmy et al. (2021)[46]	20.3 ± 1.9 nm	-	MCF−7A−549	24 h	10.9 μg/mL6.7 μg/mL
Gholami-Shabani et al. (2023)[50]	2–25 nm	-	HepG2	24 h	184.07 μg/mL
Gurunathan et al. (2019)[52]	10–22 nm	-	U2OS	24 h	15 μg/mL
Gurunathan et al. (2020)[54]	25 nm	-	SH-SY5Y,	24 h	50 μg/mL
Kumar et al. (2019)[65]	20 nm	-	HeLa	24 h	90.78 μg/mL
Manzoor et al. (2021) [81]	113.6 nm	-	MCF−7	24 h	167.2 μg/mL
Mironava et al. (2013) [82]	23 ± 0.5 nm	Folic acid coated	DO33SCC13SCC12BMCF7MCF10A	24 h	106 μg/mL51 μg/mL61 μg/mL86 μg/mL124 μg/mL
Patel et al. (2021)[93]	22 nm	DOX and PVP coated	MCF−7MDA-MB−231	not reported	2.3 μg/mL DOX-PtNP and 0.3 μg/mL PVP-PtNP4.6 μg/mL DOX-PtNP and 1.0 μg/mL PVP-PtNP
Pandey et al. (2014) [91]	> 100 nm	-	4T1	48 h	14.93 μmol/L
Ramanathan et al. (2023)[95]	84 ± 4.65 nm	Chitosan	MDA-MB−231, HEK−293	24 h	85 ± 0.65 μg/mL 48.26 ± 0.65 μg/mL
Şahin et al. (2018)[98]	20.12 nm	-	MCF−7	48 h	17.84 μg/mL
Shiny et al. (2016)[103]	20–35 nm	-	A549	24 h	19.3 μg/mL
Yang et al. (2017)[111]	54 ± 2 nm	-	HCT 116	24 h	20 μg/mL
Yin et al. (2017)[112]	3–5 nm	-	Osteoarthritic chondrocytes	24 h	100 ppm

PVP: Polvinylpyrrolidone; PS: Polysaccharides; DOX: Doxorubicin.

Other studies on fertilized eggs addressed anticarcinogenicity of PtNP. In particular, fertilized eggs of *Gallus gallus* bearing glioblastoma tumours were treated by intratumoural injection of PtNP-hydrocolloids (8.45 μM/mL) and a significant decrease in tumour cell proliferation compared with the control group was observed [66]. In addition, analysis of tumour tissue revealed a significant increase in in 8-hydroxy-2′-deoxyguanosine (8-OH-dG) concentration compared with the untreated and cisplatin-treated groups, highlighting the efficacy of PtNP in inducing oxidative stress in tumour tissue and suggesting a promising perspective for tumour treatment. In the same study, it was also demonstrated that PtNP and cisplatin significantly reduced the volume and weight of the tumours compared to the control group. These treatments were followed by a loss of the compact structure of the tumour tissue, accompanied by atypical morphological alterations of nuclei and a deformation of the inner mitochondrial membrane. In addition, intratumoural injection of PtNP and cisplatin induced activation of the apoptotic pathway in glioblastoma tumours in eggs, thus increasing the expression of caspase-3 and messenger RNA of p53.

In a further work, the same authors demonstrated that treatment of *Gallus gallus* fertilized eggs with PtNP-hydrocolloids (8.45 μM/mL) also decreased cell migration, which affected the malignancy of glioma tumours [67]. Besides, evaluation of the migration potential of glioma cells indicated that treatment with PtNP or cisplatin reduced the metastasis of glioblastoma tumour cells by reducing the number of circulating tumour cells in the bloodstream.

The impact of PVP-coated PtNP on the growth of MDA-MB-231 xenografted tumours in fertilized chicken eggs was also evaluated [83]. A marked reduction in tumour size was observed after only 24 h of exposure to 250 μg/mL of 10 nm PtNP, accompanied by a disintegration of the adjacent chorioallantoic membrane. In addition, PtNP exerted a significant effect on the inhibition of metastasis and angiogenesis, with 10 nm PtNP demonstrating greater effects compared to 40 nm PtNP, and proving to be more effective than cisplatin.

3.2.3. *Effects on invertebrate organisms*

Only 4 out of the 35 revised *in vivo* studies evaluated the effects of PtNP on invertebrate organisms. None of them observed adverse effects at clinically relevant doses, but anti-inflammatory, antioxidant and tissue regeneration stimulating properties were reported in some cases, supporting their use as potential therapeutic agents. Bag et al. [123] explored the use of PtNP to improve wound healing in the fruit fly (*Drosophila melanogaster*). After the induction of wounds using a fine sterile needle on the third instar larvae, a significant acceleration of wound healing was observed when treated with different PtNP doses and exposure times. In particular, histological and immunohistochemical examination of a number of biomarkers, including the levels of expression of Ki-67, vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β), indicated that treated larvae showed a reduction in inflammation and a faster formation of granulation tissue around the wound area compared to the control groups, demonstrating that PtNP enhanced wound healing by increasing cell proliferation, improving cell adhesion, and promoting neovascularization and granulation tissue formation.

Also, after 24 h of exposure of the animal model *Caenorhabditis elegans* to biosynthesized PtNP, no alteration in the life cycle was observed. Both exposed individuals and untreated controls were able to develop to the adult stage and have a normal oviposition [38]. In another study in the same organism, administration of PVP-PtNP for 10 days reduced oxidative stress and cellular damage associated with aging and prolonged the lifespan of *C. elegans*, highlighting their potential as promising therapeutic tools [126]. Finally, the aquatic crustacean *Artemia nauplii* also showed no toxicity after being exposed for 24 h to PtNP synthesized from red algae *Halymenia dilatata*, keeping healthy appearance and survival rates always over 82 %, despite the demonstrated accumulation of NP around the mouthparts and in the gut of animals [101].

4. Conclusions and perspectives

After an exhaustive search of studies addressing the potential toxicity of PtNP, a total of 110 studies out of the 441 initially found fulfilled the inclusion criteria and were included in this systematic review. Mainly *in vitro* but also *in vivo* studies were reported in a number of biological systems and animal models, with no data on human epidemiological or environmental impact studies published so far. The results obtained from all these studies showed a variety of PtNP effects, harmful but also beneficial or absent in some cases, highlighting the inconsistence of the currently available data and the need for further research, so that the biomedical field can take advantage of their promising benefits and prevent undesirable effects on patients or exposed subjects. In general, results obtained from the *in vitro* and *in vivo* revised studies showed limited toxic effects, with some presenting significant lung or liver toxicity and others good biocompatibility. Furthermore, anticancer or protective effects were also described for PtNP in several studies, encouraging to continue exploring their benefits for clinical practice. It is worth highlighting the lack of long-term exposure studies in the reviewed literature, which are essential for assessing the hazards of chronic exposure to PtNP.

Variations in the observed effects of PtNP may be due to several factors, mainly to their properties, namely size, coating, synthesis method, and concentration, and the way they interact with biological systems. Indeed, the physicochemical characteristics of nanomaterials, as well as the formation of a biocorona, whose presence and composition directly depend on the biological environment, are thought to greatly influence their biological behaviour and toxicity profile [136]. Although NP shape is also known to determine toxicity, the great majority of the studies included in this review used spherical PtNP, so the effect of shape could not be analysed. Moreover, despite the demand from the scientific community for alternative nanotoxicity testing strategies and the international effort to agree on specific guidelines for nanomaterial testing [137], there is still a significant lack of validated official protocols and global consensus for nanotoxicity tests for regulatory purposes, especially considering the possible interferences of the nanomaterials with the test systems (reagents or detection methods), which can lead to false positive or negative results. As a result, the reviewed studies used different protocols, approaches, and experimental conditions, in addition to a number of different cells, tissues, or organisms, leading to divergent results. This variability in results, together with the fact that most published studies do not discard the interference of PtNP with the toxicity testing methods used, highlights the importance of a cautious approach when assessing the potential risks and benefits of PtNP use in various applications.

Exposure of a biological system to PtNP could lead to different types of outcomes – there are reports on nephrotoxicity, hepatotoxicity, and inflammatory responses as well as DNA damage induced by PtNP – but several studies reported also beneficial properties. This explains why the biological effects and toxicological behaviour of PtNP remain poorly understood. It seems difficult to get an overview and a definitive conclusion as several parameters are involved in the interpretation of the results. In order to obtain reliable and comparable results, it is necessary to develop standard protocols to study the toxicity of nanomaterials. Crucial parameters such as their physicochemical properties, the setup of the experimental conditions, and the methods for assessing the different toxicity outcomes should be considered in this standardization.

CRediT authorship contribution statement

A.T.: Methodology, Investigation, Writing – original draft preparation. L.R.-P.: Methodology, Investigation, Writing – original draft preparation. S.F.: Methodology, Investigation. N.F.-B.: Methodology, Investigation. B.L.: Conceptualization, Supervision, Formal analysis. V. V.: Conceptualization, Supervision, Funding acquisition, Writing –

Table 3
In vivo studies evaluating PtNP toxicity (alphabetically ordered).

Study	NP tested (dry size)	Organism	Conditions	Results
Amano et al. (2016)[122]	PtNP (5.4 nm)	Wistar male rats (8-weeks old)	10 mg/kg for 2 weeksIntratracheal administration	Aggregates of PtNP were observed in the lungs one day after administration, accompanied by bleeding and signs of emphysema
Asharani et al. (2010)[121]	Polyvinyl alcohol capped-PtNP (3–10 nm)	*Danio rerio* eggs	10–100 μg/mL for up to 72 hpfDispersed in egg water	PtNP increased mortality, turbidity of chorionic fluid at 24 hpf, reduced embryo hatchability, decreased heart rate at 48 hpf without significantly altering blood flow, and a decreased slightly sensitivity to tactile stimuli at concentrations > 100 μg/mL
Bag et al. (2023)[123]	PtNP (45–50 nm)	*Drosophila melanogaster* (larvae and 2–10 days old adults)	50–400 μg/mL for 3–10 daysOral administration	PtNP reduced DNA damage and ROS levels in intestinal epithelial cells, increased the number of mitochondria without damaging them, accelerated wound healing with less necrosis and better angiogenesis, without affecting the haemocyte cell membrane or inducing phenotypic defects in adult flies
Bendale et al. (2016)[35]	PtNP (size not reported)	SCID female mice (5–7 weeks old)	500–2000 mg/kg for 6 weeks Oral administration	No statistically significant changes in body weight were observed. PtNP at the mid and high doses effectively inhibited and delayed the growth of lung cancer in SCID mice
Borowik et al. (2019)[38]	PtNP (10–80 nm)	*Caenorhabditis elegans* (L4)	0.04–5.12 μg/mL for 24 h	PtNP did not induce significant alteration in the survival rate or life cycle, even at the highest dose, with the worms developing normally to adulthood and laying eggs, similar to the control group
Brown et al. (2018)[39]	Lipid-polymer conjugate 1,2-distearoyl-sn-glycero−3-phosphoethanolamine and PEG coated PtNP (2–4 nm)	BALB/c female mice (6 weeks old) (17–27 g)	5–20 mg/kg for 24 hIntravenous administration	PtNP demonstrated low in vivo toxicity, with no weight loss or clinical abnormalities, with prolonged accumulation in the liver and spleen, low renal and pulmonary retention, and slight architectural changes in the white pulp of the spleen at the highest dose
Isoda et al. (2017)[124]	PtNP (1, 8 nm)	Balb/c male mice (8 weeks old)	1–20 mg/kg for 3, 6, 12, 24, and 48 h Intravenous administration	Significant hepatorenal toxicity and injury were observed at doses of 15–20 mg/kg, with dose-dependent increases in serum markers of hepatorenal function as well as IL−6 and IL−1β levels, only after administration of 1 nm PtNP
Katsumi et al. (2014)[125]	Citric acid protected- PtNP (30, 106 nm)	ddY male mice (25–27 g)	50 μg/kg for 30 minIntravenous administration	Accumulation of both types of PtNP in the liver with little distribution to other organs; an increase in lipid peroxides, hepatic serum proteins and oxidative stress significantly only for 30 nm PtNP
Kim et al. (2008)[126]	PtNP (2.4 ± 0.7 nm)	*Caenorhabditis elegans* wild type N2 and mutant mev−1 (kn1)	0.1–1 mM for 10 days	Treatment with 0.5 mM decreased lipofuscin accumulation and ROS levels induced by paraquat with improved lifespan of N2 worms
Kutwin et al. (2017a)[69]	PtNP (2–19 nm)	*Gallus gallus* fertilized eggs	8.45 μM/mL for 2 daysIntratumour injection	Significant decreased in tumor volume and weight, decreased cell density after PtNP treatment Glioma disruption, apoptosis, reduced proliferation via caspase−3 and p53
Kutwin et al. (2017b)[67]	PtNP (2–25 nm)	*Gallus gallus* fertilzed eggs	8.45 μM/mL for 2 daysIntratumour injection	PtNP significantly reduced tumour tissue proliferation and density, while significantly increasing the concentration of 8-OH-dG in DNA
Li et al. (2022) [72]	Zwitterionic thiol-functionalized sulfobetaine stabilized PtNP SH-SB-PtNP (6.97 ± 1.44 nm)	KM female mice	3 mg/kg for 14 daysIntratumour injection	PtNP did not alter body weight, visceral indices or liver function of mice
Liao et al. (2021)[9]	PEG stabilized PtNP DCPN (1 nm)	C57BL/6JNal mice (5 weeks old)	0.5–40.3 mg/kg for 3 daysIntravenous administration	Suppression of tumour growth in nude mice bearing human mammary and ovarian tumours. No substantial body weight loss. Significant inhibition of hypoxia- and angiogenesis-related pathways in TC−1 tumours
Lin et al. (2019)[73]	Citrate-coated PtNP (5, 70 nm)	C57BL6/J adult male mice (18–20 g)	3–10 mg/kgIntravenous administration	PtNP (5 and 70 nm) reduced heart rate dose-dependently and induced complete atrioventricular block at high doses
Liu et al. (2021)[74]	Liposomes loaded with PtNP (VP@MLip-PtNP) (3–5 nm)	BALB/c female mice (6–7 weeks old)	5 mg/kg for 1, 4, 8, 12 and 24 hIntravenous injection	VP@MLip-PtNP without light activation prolonged the survival of mice. HIF−1 was significantly reduced, reflecting the significantly reduced hypoxia and no obvious histological toxicity according to histopathological examination
Ma et al. (2020)[78]	Triphenylphosphonium and lysine coated PtNP (TPP-PtNP and LysPtNP, respectively) (< 10 nm)	BALB/c nude mice	4 mg/mL for 13 daysIntravenous injection	TPP-PtNP showed effective tumour inhibition *in vivo* with prolonged retention in tumours and without notable systemic toxicity, in contrast to Lys-PtNP. The treatment effect was weak and had no notable variation in body weight for any group.
Mitrevska et al. (2023)[83]	PVP coated PtNP (10, 40 nm)	Fertilized chicken eggs	250 μg/mL for 24 hTopic administration	Significant decrease in MDA-MB−231 tumour xenograft size and notable tumour disintegration. PtNP 10 nm also showed the best inhibition of

(*continued on next page*)

Table 3 (*continued*)

Study	NP tested (dry size)	Organism	Conditions	Results
				MDA-MB−231 cell migration and metastatic colonization in embryonic tissues, outperforming PtNP 40 nm. Treatments with PtNP (10, 40 nm) reduced vascular density and inhibited angiogenesis in tumours
Mukherjee et al. (2021) [127]	PEG coated PtNP (2–1 nm)	C57BL6/J male mice (4–6 weeks old)	10 and 50 mg/kg for 2 weeksIntraperitoneal administration	Administration of PtNP at 10 mg/kg did not result in severe toxic symptoms, mortality, weight loss or significant behavioural changes. Slight signs of toxicity at 50 mg/kg, such as increased haematological parameters and serum protein. Histologically, at 10 mg/kg no tissue toxicity was observed, while renal and cerebral changes were observed at 50 mg/kg.
Onizawa et al. (2009)[89]	Polyacrylate stabilized PtNP(2.0 ± 0.4 nm)	DBA/2 male mice (7 weeks old)	0.1 μmol/body for 3 days Intranasal administration	PtNP concentration in the lungs increased 400x compared to controls and without detection in brain, heart, liver and kidney tissues. Intranasal administration of PtNP followed by exposure to cigarette smoke prevented antioxidant depletion in the lungs, reduced neutrophil infiltration into the lungs and reduced NFκB activation
Pan et al. (2024)[90]	TAT peptide and sPEG Pt nanoclusters (Pt@TAT/sPEG) (20–40 nm)	BALB/c athymic nude female mice (5–6 weeks old)	4 mg/kg for 15 daysIntravenous administration	Pt@TAT/sPEG significantly reduced tumour growth without causing weight loss or increased oxidative stress. No major changes were observed in blood indices nor pathological alterations
Pandey et al. (2014)[91]	Novel self-assembling cis-PtNP (SACN) (>100 nm)	BALB/c female mice (4 weeks old)	0.5 mg/kg for 3 daysIntravenous administration	Better antitumour efficacy of the combined treatment PI828 followed by SACN than SACN followed PI828, with a notable increase in caspase−3. The sequential treatment, where PI828 is administered after SACN, was more effective than the simultaneous administration
Park et al. (2010)[128]	PVP coated PtNP (21 nm)	ICR male mice (25 ± 1 g, 6 weeks old)	1 mg/kg for 1, 7, 14, 28 daysIntratracheal instillation	Treatment induced an increase in oxidative stress and proinflammatory cytokines at day 1, a redistribution of lymphocytes, an increase in MMP and heat shock proteins, as well as cellular infiltration and persistent microgranulomatous lesions in the lungs up to day 7
Prasek et al. (2013)[120]	PtNP (2–19 nm)	Eggs from Ross line chickens (56 ± 2.2 g)	1–20 μg/mL for 20 daysInjection into the albumen	Treated embryos exhibited pathological changes in brain tissue, mitochondrial degradation, neuronal loss, and astrocytosis, but with no differences in survival, body weight, and weight of the brain, heart, spleen and bursa of Fabricius. Significant reduction in caspase−3 at 20 μg/mL
Sancho-Albero et al. (2022) [99]	PtNP loaded exosomes (2 nm)	BALB/c nu/nu female mice (6–8 weeks old)	100 μg for 24 h, 96 h, 21 days Intravenous or intratumour administration	Treatment inhibited tumour growth, particularly effective by intravenous administration. Antitumoral properties observed were similar to that of cisplatin but with a strongly reduced or in some cases no toxic effect
Sathiyaraj et al. (2021)[101]	*Halymenia dilatata* biosynthesizes PtNP (15 nm)	*Artemia nauplii* (1 day old)	25–150 μg/mL for 24 hImmersion exposure	PtNP induced low mortality, that could be due to the aggregation in the intestine and around the mouthparts, with less accumulation at a concentration of 25 μg/mL. No disintegration of nauplii was observed, and their structure remained similar to that of the control group
Shatokhina et al. (2020) [129]	PVP-PtNP (4 ± 2 nm)	White outbred male rats (300–350 g)	1 mL suspension of PtNP (concentration not specified) for 2 hIntraperitoneal administration	PtNP exposure maintained physiological homeostasis, with appearance of markers of inflammation and stress response of the body, microcirculatory activation, and increased blood flow fluctuations in endothelial, neurogenic, and myogenic domains, without changes in blood pressure or cerebral flow
Takamiya et al. (2011)[130]	PVP-PtNP (2–3 nm)	C57/Bl6 male mice (8 weeks old, 24–27 g)	4 μmol/kg for 48 h Intravenous administration	Treatment produced stabilization of blood flow after having dropped after tMCAO. Treatment improved motor function, reduced cortical infarct volume, attenuated collagen IV degradation, decreased MMP−9 activation, and reduced superoxide levels, thereby showing protection against ischemic damage
Tanaka et al. (2019)[5]	Conjugated latex beads (P2VP) and platinum nanocomposite PtNP (PtNCP) (size not reported)	KSN/slc male mice (6 weeks old, 20–25 g)	10 mg/mL for 14 daysIntravenous injection	Tumour inhibition in mice treated with PtNCP was more effective than in P2VP treated group. Histologically, PtNCP induced more necrotic areas with pyknosis and neutrophil infiltration than P2VP treatment
Wang et al. (2015)[108]	Trifolium-like PVP-PtNP (TPN) (16 ± 3 nm)	Nude mice	9.8–58.5 ppm Intratumour injection	The combination of TPN and NIR significantly reduced tumour growth and increased tumour temperature, and also caused severe osteolytic lesions and bone matrix erosion. Despite stable

(*continued on next page*)

Table 3 (*continued*)

Study	NP tested (dry size)	Organism	Conditions	Results
				blood pressure and cerebral blood flow, fluctuations in blood flow were observed, related to inflammation and microcirculatory activation
Xiang et al. (2023)[110]	Bovine serum albumin and curcumine decorated PtNP (5–10 nm)	Balb/C mice	66.66–150 mg/kg for 30 daysIntravenous administration	No evidence of mortality. No signs of damage in organs or tissues
Yamagishi et al. (2013) [131]	PtNP (1, 15 nm)	BALB/c male mice (8 weeks old)	5 −20 mg/kg for 3, 6, 12, 24 and 48 hIntravenous administration	Acute hepatic injury, and increased levels of serum markers of liver injury and inflammatory cytokines after treatment with 1 nm PtNP. Administration of 15 nm PtNP did not produce these abnormalities
Yoshihisa et al. (2010)[113]	Polyacrylic acid capped PtNP (size not reported)	Balb//c male mice (8 weeks old)	0.3 g of 0.002 % for 24 hDermal administration	Reduction of UVB-induced inflammation and apoptosis and a reduction of UVB-induced pathoallergic signs (skin oedema, leukocyte infiltration, hyperplasia and expression of pro-inflammatory cytokines)
Zhang et al. (2021)[115]	PVP coated PtNP (PVP-PtNP) (3 nm)	BALB/c female mice (6–7 weeks old)	5 and 25 mg/kg for 2, 4, 8, 12 and 24 hIntravenous administration	Efficient clearance of PVP-PtNP from kidneys in acute kidney injury (AKI) and healthy mice. Treatment partially prevented weight loss and inhibited ROS production without renal damage of AKI mice, while no organ damage or impaired function were observed in healthy mice
Zhu et al. (2017)[117]	Hyaluronic acid-encapsulatedPtNP (HA/Pt) and alginate acid encapsulated PtNP (AA/Pt) (38 ± 6 and (32 ± 6 nm, respectively)	Balb/c nude mice (4 weeks old, average weight 20 g)	3 mg/kg for 12 and 24 hIntravenous administration	Significant tumour regression in mice treated with HA/Pt compared to AA/Pt after NIR. HA/Pt+NIR were significantly apoptotic without pathological or weight changes

HIF-1, hypoxia-inducible factor-1; hpf, hours post fertilization; IL-6, interleukin 6; IL-1β, interleukin 1β; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; NIR, near-infrared radiation; PEG, polyethylene glycol; sPEG, pH-sensitive poly (ethylene glycol) methyl ether-acryloyl-cysteamine; PVP, polyvinylpyrrolidone; ROS, reactive oxygen species; tMCAO, transient middle cerebral artery occlusion.

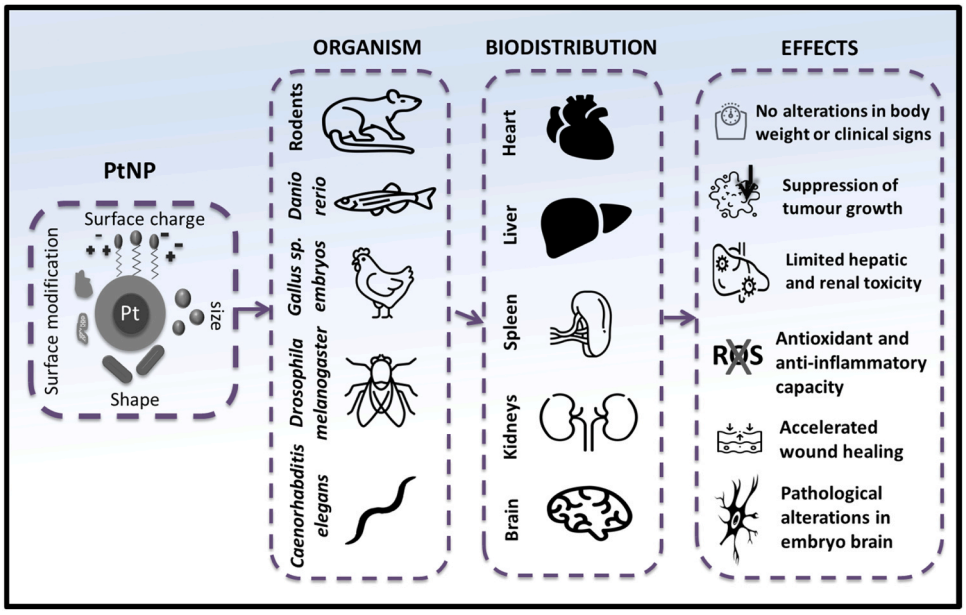

Fig. 4. Biological consequences of exposure to platinum nanoparticles (PtNP) *in vivo*. In the scientific literature, the *in vivo* evaluation of PtNP toxicity has been studied in different organisms, including rodents, zebrafish (*Danio rerio*), fruit fly (*Drosophila melanogaster*) and the nematode *Caenorhabditis elegans*. After exposure and systemic distribution via the bloodstream, several organs such as the liver, kidneys, heart, digestive system and brain showed signs of bioaccumulation. A number of *in vivo* studies reported no adverse effects of PtNP in exposed animals, while others showed some hepatic and renal toxicity. Also, PtNP inhibit tumour growth via oxidative stress or activating apoptotic pathways that reduces cancer cell viability. There are reports on nephrotoxicity, hepatotoxicity, and embryonic neurotoxicity induced by PtNP, but several studies reported also beneficial properties, such as an antioxidant, anti-inflammatory or wound healing capacity.

original draft preparation. All authors have reviewed and approved the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vanessa Valdiglesias reports financial support was provided by Spain Ministry of Science and Innovation. Lucia Ramos reports financial support was provided by Spain Ministry of Science and Innovation. Sonia Fraga reports financial support was provided by Portuguese Republic Government Ministry of Science Technology and Higher Education. Vanessa Valdiglesias reports financial support was provided by Government of Galicia. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was funded by Ministry of Science and Innovation: MCIN/AEI/10.13039/501100011033 (Grant PID2020–114908GA-I00), Xunta de Galicia (ED431B2022/16) and Foundation for Science and Technology – FCT (Portuguese Ministry of Science, Technology and Higher Education) under the projects POCI-01–0145-FEDER-031898, UIDB/04750/2020 and LA/P/0064/2020, with DOI identifiers https://doi.org/10.54499/UIDB/04750/2020 and https://doi.org/10.54499/LA/P/0064/2020. L. R.-P. was supported by a Ministry of Science and Innovation predoctoral fellowship (grant number FPU2023/03379). Funding for open access charge: Universidade da Coruña/CISUG.

Data availability

Data will be made available on request.

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