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Review article

Nanoparticle-mediated cardiotoxicity and nanomedicine interventions in cancer treatment

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ABSTRACT

Nanoparticle-based therapies have emerged as transformative tools in oncology, offering targeted drug delivery, improved pharmacokinetics, and minimised systemic toxicity. However, accumulating evidence suggests that whilst nanomedicines enhance therapeutic efficacy, they may inadvertently induce cardiotoxic effects through mechanisms including oxidative stress, mitochondrial dysfunction, immune activation, endothelial injury, and off-target accumulation in cardiac tissues. This narrative review synthesises current literature on the cardiotoxic potential of various nanoparticle classes, including liposomes, polymeric nanoparticles, metallic nanostructures, dendrimers, and carbon-based materials. Following an established narrative review framework, we examined how nanoparticle physicochemical properties, administration parameters, and patient-specific factors contribute to cardiac risks, evaluated current and emerging methodologies for detecting nanoparticle-induced cardiotoxicity, and explored mitigation strategies through nanomedicine design innovations and artificial intelligence integration. The assessment of nanoparticle-induced cardiotoxicity faces significant challenges, including absent standardised evaluation protocols, limited sensitivity of traditional diagnostic tools, and difficulties isolating nanoparticle-specific effects from concurrent cancer therapies. Promising solutions encompass advanced in vitro cardiac models (organoids, heart-on-a-chip), novel biomarkers (microRNAs, extracellular vesicles), molecular imaging technologies, and computational modelling. Preventative strategies involve surface modification, biodegradable or biomimetic materials, co-delivery of cardioprotective agents, and stimuli-responsive drug delivery systems. Artificial intelligence is enhancing nanoparticle design optimisation, toxicity prediction, and personalised monitoring through digital twin models and AI-assisted imaging. As nanomedicine advances cancer care, addressing cardiotoxic risks through interdisciplinary collaboration, improved regulatory frameworks, and precision cardio-oncology strategies is imperative for ensuring safe, effective nanoparticle use in cancer treatment.

1. Introduction

Cancer nanomedicine has revolutionised oncology by enabling targeted delivery of chemotherapeutics, improving drug solubility, enhancing pharmacokinetics, and reducing systemic toxicity. Nanoparticles (NPs) such as liposomes, polymeric micelles, metallic nanostructures, and dendrimers are increasingly employed to enhance the therapeutic index of anticancer agents [1]. The ability of NPs to selectively accumulate in tumours through the enhanced permeability and retention (EPR) effect or via active targeting ligands has expanded treatment options and opened new avenues for imaging and combined therapies [2]. Understanding nanoparticle behaviour in biological

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systems requires consideration of the protein corona, a dynamic layer of proteins that adsorbs onto nanoparticle surfaces upon contact with biological fluids, fundamentally altering their biological identity and interactions [3].

Despite these advantages, emerging evidence highlights that nanoparticle-based therapies may induce unintended cardiotoxic effects. Unlike classical chemotherapy agents whose cardiotoxicity mechanisms are relatively well understood, nanoparticles can induce complex cardiac injury through a combination of oxidative stress, inflammatory responses, endothelial dysfunction, and off-target accumulation [4]. The unique physicochemical properties of NPs, including their size, surface chemistry, and composition, modulate their interaction with cardiac tissue and contribute to potential toxicity [5]. Surface engineering strategies, including covalent coating methods, have emerged as critical approaches to enhance biocompatibility and reduce adverse cardiovascular effects [6]. Advanced surface modification techniques, such as those applied to MXene-based nanoplatforms, have demonstrated that rational surface engineering can simultaneously improve therapeutic performance while potentially mitigating toxicity through enhanced biocompatibility and controlled biological interactions [7].

The rationale for this narrative review stems from the critical gap between the rapid clinical translation of nanomedicines in cancer therapy and the incomplete understanding of their cardiovascular safety profiles. Whilst nanoparticle-based cancer treatments have demonstrated remarkable therapeutic benefits, cardiovascular complications represent a significant barrier to their optimal clinical implementation. Current literature lacks a comprehensive synthesis that bridges nanotoxicology, cardio-oncology, and advanced nanomedicine design strategies. Furthermore, the absence of standardised assessment protocols for nanoparticle-induced cardiotoxicity creates challenges for clinicians, researchers, and regulatory bodies in evaluating and managing these risks. Traditional morphological imaging techniques have proven insufficient for evaluating early therapeutic response and detecting subclinical cardiotoxicity, necessitating the integration of advanced molecular imaging modalities and multimodal imaging approaches that can visualize biological processes at the cellular and molecular level [8]. As the field of precision oncology continues to expand with increasingly sophisticated nanoformulations, there is an urgent need to systematically examine the cardiotoxic mechanisms, detection methodologies, and mitigation strategies to ensure patient safety whilst preserving therapeutic efficacy. Recent advances in bionanomaterials have demonstrated promising anticancer properties while addressing biocompatibility concerns, yet their cardiac safety profiles require rigorous evaluation [9].

This review offers several novel contributions to existing literature. Firstly, unlike previous reviews that primarily catalogue nanoparticle toxicity or discuss cancer-related cardiotoxicity separately, this work uniquely integrates fundamental nanotoxicology principles with clinical cardio-oncology practice through a mechanistic lens, explicitly connecting physicochemical nanoparticle properties to specific molecular pathways of cardiac injury. Secondly, this review goes beyond existing literature by critically examining clinically approved nanodrugs and their real-world cardiotoxicity profiles, providing actionable insights for current clinical practice rather than limiting discussion to experimental systems. Thirdly, we uniquely incorporate the emerging role of artificial intelligence and machine learning in predicting, detecting, and mitigating nanoparticle-induced cardiac injury with specific examples of successful clinical applications, reflecting the latest technological advances that have not been comprehensively reviewed elsewhere. Fourthly, this work synthesises cutting-edge methodologies including cardiac organoids, heart-on-a-chip platforms, novel biomarkers (microRNAs, extracellular vesicles), molecular imaging technologies, and digital twin technologies in the specific context of nanoparticle cardiotoxicity assessment, an integration absent in previous reviews. Fifthly, the comprehensive examination of preventative strategies, from advanced surface modification techniques to stimuli-responsive systems, provides actionable insights with specific design parameters for researchers developing next-generation nanomedicines. Finally, this review addresses contemporary challenges in regulatory frameworks and standardisation efforts with specific recommendations for clinicians, regulatory agencies, and nanomaterial designers, making it particularly relevant for translational research and clinical practice in the rapidly evolving landscape of precision oncology.

The primary aim of this narrative review is to provide a comprehensive, evidence-based synthesis of nanoparticle-mediated cardiotoxicity in cancer treatment and to evaluate current and emerging nanomedicine interventions designed to mitigate these adverse cardiovascular effects.

The specific objectives are to:

1. Systematically examine the diverse classes of nanoparticles used in oncology and characterise their physicochemical properties that influence cardiac interactions.
2. Elucidate the molecular and cellular mechanisms underlying nanoparticle-induced cardiotoxicity, including oxidative stress, mitochondrial dysfunction, immune activation, and endothelial injury.
3. Identify and analyse the key factors that modulate cardiotoxic risk, including nanoparticle characteristics (size, shape, surface chemistry), administration parameters (dose, route, duration), and patient-specific variables (age, comorbidities, genetic factors).
4. Evaluate current methodologies and emerging technologies for detecting and monitoring nanoparticle-induced cardiotoxicity, including advanced in vitro models, novel biomarkers, and imaging techniques.
5. Explore innovative nanomedicine design strategies and interventions that minimise cardiac toxicity whilst maintaining or enhancing anticancer efficacy.
6. Assess the role of artificial intelligence and computational modelling in optimising nanoparticle design, predicting toxicity, and enabling personalised cardio-oncology monitoring.

1.1. Narrative review framework

This manuscript employs a narrative review methodology, which is particularly suited to synthesising complex, multidisciplinary topics where diverse perspectives and evolving knowledge require interpretative integration rather than purely systematic quantification. The narrative review approach was selected because it allows for a comprehensive exploration of nanoparticle-mediated cardiotoxicity across multiple domains, including nanotechnology, pharmacology, cardiology, oncology, and artificial intelligence, whilst providing contextual analysis and expert interpretation of emerging trends and translational implications.

The review was conducted following an established narrative review framework with the following methodological approach: First, a comprehensive literature search was performed across major scientific databases including PubMed, Web of Science, Scopus, and Google Scholar, using relevant keywords such as 'nanoparticles,' 'nanomedicine,' 'cardiotoxicity,' 'cancer,' 'oncology,' 'cardiac safety,' 'nanotoxicology,' and 'artificial intelligence.' The search encompassed peer-reviewed original research articles, systematic reviews, meta-analyses, clinical trials, and regulatory documents published predominantly within the last decade, with selective inclusion of seminal earlier works where foundational concepts were established. Second, the selected literature was critically appraised based on scientific rigour, relevance to cardio-oncology, and contribution to understanding nanoparticle-induced cardiovascular effects. Third, the information was synthesised thematically to present a coherent narrative that progresses from fundamental mechanisms to clinical implications and future directions. Unlike systematic reviews that prioritise exhaustive inclusion based on predefined protocols, this narrative approach enables flexibility to incorporate emerging technologies, discuss controversial findings, and provide expert perspectives

on translational challenges and opportunities in the rapidly evolving field of cancer nanomedicine.

Given the growing clinical use of nanomedicine in cancer, understanding the mechanisms underlying nanoparticle-mediated cardiotoxicity is crucial. Additionally, designing nanomedicines that mitigate or avoid cardiac injury whilst preserving anticancer efficacy remains a critical challenge. This review aims to provide a comprehensive overview of the types of nanoparticles used in oncology, elucidate their cardiotoxic mechanisms, discuss factors influencing toxicity, examine current and future nano-medicine strategies to minimise cardiac adverse effects, as well as explore the transformative role of artificial intelligence in advancing safer nanoparticle design and personalised cardio-oncology care.

2. Types of nanoparticles used in oncology

Nanoparticles employed in cancer treatment vary widely in composition, size, surface chemistry, and functionalization, each with unique advantages and potential for cardiotoxicity. Understanding the characteristics of these nanoparticles is essential to appreciating their interactions with cardiac tissues. Notably, the principles governing nanoparticle delivery to solid tumours, including biological identity acquisition, organ competition for circulating nanoparticles, tumour entry mechanisms, tumour microenvironment navigation, and the influence of physicochemical properties on transport processes, directly impact both therapeutic efficacy and off-target cardiac accumulation [3]. Fig. 1 provides a schematic overview of different types of nanoparticles used in oncology.

2.1. Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers that encapsulate therapeutic agents, mostly used due to their high biocompatibility, biodegradability and bioavailability [10]. Liposomal formulations such as Doxil (liposomal doxorubicin) have demonstrated reduced systemic cardiotoxicity compared to free drugs due to altered biodistribution and prolonged circulation times [11]. However, liposome accumulation in non-target tissues including the heart can still provoke toxicity, especially at higher doses or with repeated administration. The formation of the protein corona on liposomal surfaces significantly influences their cardiac uptake, with specific plasma proteins such as apolipoproteins and immunoglobulins mediating recognition by cardiac endothelial cells and subsequent translocation into myocardial tissue.

2.2. Polymeric nanoparticles

Polymeric nanoparticles are composed of biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) or polyethylene glycol (PEG)-modified polymers. These systems offer controlled drug release and targeted delivery capabilities [12]. Their surface properties can be engineered to minimize cardiac uptake, but polymer degradation products and surface chemistry may elicit inflammatory or oxidative responses contributing to cardiotoxicity [13].

The protein corona on polymeric nanoparticles varies significantly with surface modification. PEGylated surfaces preferentially adsorb dysopsonins (albumin, clusterin, histidine-rich glycoprotein), reducing macrophage recognition called ‘stealth’ and increasing the circulatory half-life, a tool primarily used to reduce toxicity by allowing target delivery [14]. Nonetheless, repeated PEGylation triggers anti-PEG antibodies, causing accelerated clearance and potential cardiac immune complex deposition [15–17]. PLGA nanoparticles develop a biomolecular corona in vivo, often including immunoglobulins and complement proteins as part of the opsonin profile. They can also adsorb apolipoproteins, notably Apolipoprotein E (ApoE), which has been shown to mediate uptake of PLGA-PEG nanoparticles via the LDL receptor (LDLr) pathway [18]. During PLGA degradation, acidic monomers (lactic and glycolic acid) accumulate and the intraparticle microenvironment may drop to pH values as low as ~1.5–3.5, potentially causing local protein destabilisation and generation of inflammatory cues [19].

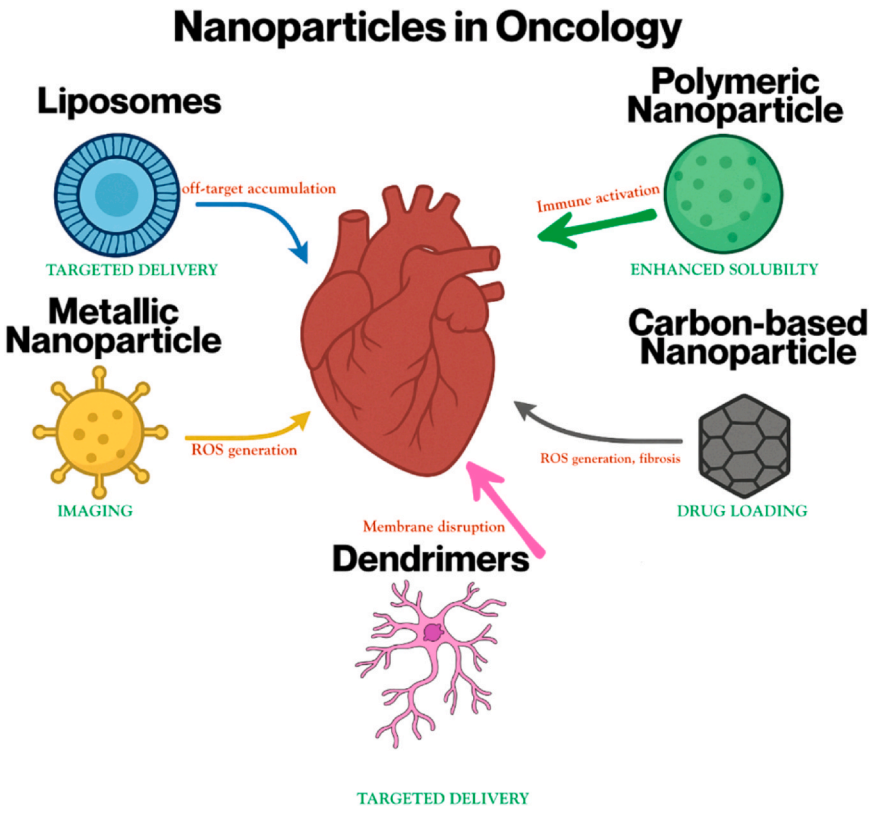

Fig. 1. Overview of nanoparticle classes and cardiac toxicity pathways. A schematic representation of major nanoparticle types employed in cancer therapy, including liposomes, polymeric nanoparticles, metallic nanoparticles, dendrimers, and carbon-based materials. The figure highlights their structural features, therapeutic advantages, and annotated cardiotoxicity risks such as oxidative stress, mitochondrial dysfunction, immune activation, endothelial injury, and off-target accumulation. Arrows and callouts illustrate key interactions and mechanistic links to cardiac tissue.

2.3. Metallic nanoparticles

Metal-based nanoparticles including gold (AuNPs), silver (AgNPs), and iron oxide nanoparticles are used for imaging, drug delivery, and photothermal therapies [20]. Metallic NPs have unique optical and magnetic properties but are prone to induce reactive oxygen species (ROS) generation and mitochondrial damage in cardiomyocytes [21,22]. Their persistence and potential bioaccumulation raise concerns about long-term cardiac safety.

Gold nanoparticles rapidly acquire coronas dominated by fibrinogen, which undergoes conformational changes exposing Mac-1 integrin binding sites that recruit inflammatory cells in the body [23]. This could potentially affect cardiac tissues. Similarly, silver nanoparticles continuously release Ag^{+} ions that cross-link corona proteins through cysteine residues, causing aggregation of NP-protein complexes [24]. superparamagnetic iron oxide nanoparticles NPs (SPION) coronas frequently include transferrin (and sometimes apolipoproteins), providing potential access to TfR1 (often upregulated after myocardial injury) and LDL-receptor family pathways in the heart [25,26]. Complement adsorption on NP coronas can activate the alternative pathway, contributing to pro-inflammatory biodistribution [27]. Together, these NP-corona-immune interactions provide biologically plausible pathways that could contribute to cardiac toxicities.

2.4. Dendrimers

Dendrimers are highly branched, monodisperse macromolecules capable of drug encapsulation or surface conjugation. Poly(amidoamine) (PAMAM) dendrimers have been explored in oncology for targeted delivery [28]. While dendrimers improve drug solubility [29], the positively charged dendrimers have been shown to induce cytotoxicity and drastic phenotypic alterations when used as nanocarriers [30].

Cationic PAMAM dendrimers, particularly higher-generation amine-terminated structures, show strong, charge-dependent binding of serum proteins and complement components (including C3 and C4b) in their protein coronas and are capable of activating complement in human plasma [31]. This complement activation provides a mechanistic basis for complement-mediated hypersensitivity responses and raises concern for complement activation-related pseudo-allergy (CARPA) and possible cardiovascular involvement, although dendrimer-specific CARPA events have not been systematically demonstrated. The highly cationic surface of PAMAM dendrimers also promotes cellular internalisation and endosomal buffering, contributing to a “proton-sponge”–type mechanism that facilitates endosomal escape. This process is linked to mitochondrial membrane potential loss, reactive oxygen species (ROS) generation, and cytotoxicity in mammalian cell models [32,33] Surface modification of PAMAM dendrimers with carboxyl groups markedly reduces complement activation, hemolytic activity and other inflammatory responses, but often also diminishes cellular uptake and endosomal escape, which may limit therapeutic efficacy for intracellular delivery [34,35].

2.5. Carbon-based nanoparticles

Carbon nanotubes (CNTs) and graphene oxide (GO) have potential in drug delivery and photothermal cancer therapies [35]. However, their biopersistence, shape, and surface chemistry can provoke inflammatory responses and endothelial damage in cardiac tissues [36].

Carbon nanotubes (CNTs) can bind serum proteins via strong π–π and hydrophobic interactions, forming dense coronas. Some studies report significant structural alteration of adsorbed fibrinogen on CNTs and related carbon-nanomaterials, and this altered fibrinogen can engage the Mac-1 (αMβ2) integrin on leukocytes, promoting inflammatory responses [37,38]. The high aspect ratio of CNTs has been implicated in “frustrated phagocytosis” by macrophages, persistent NLRP3 inflammasome activation and IL-1β release in fibrotic and lung models, suggesting a mechanistic basis for chronic inflammation, which could also be relevant in cardiac tissues [39]. Graphene oxide (GO) sheets, owing to their large planar surfaces (up to μm scale) and sharp edges, also form extensive protein coronas and can aggregate under physiological conditions; their sharp edges and large surface area may contribute to endothelial membrane disruption and microvascular clearance issues, though direct evidence in cardiac capillaries remains limited [40,41]. Both CNTs and GO exhibit considerable biopersistence in vivo, with limited biodegradation over months and possible maintenance of chronic inflammatory stimuli [41,42]. Accordingly, these nano-bio interactions provide plausible mechanistic pathways that could contribute to cardiac toxicities via endothelial injury, microvascular dysfunction, chronic inflammation and fibrosis.

Table 1 systematically catalogues common nanoparticle classes used in oncology, linking their physicochemical properties to specific molecular mechanisms of cardiotoxicity and clinically approved examples, providing a comprehensive reference for understanding structure-toxicity relationships in cancer nanomedicine. An overview of nanoparticle classes and their cardiotoxic pathways is provided in Fig. 1.

2.6. Protein corona: the critical determinant of nanoparticle biological behaviour

Upon entry into the bloodstream, nanoparticles immediately encounter a complex milieu of proteins, lipids, and biomolecules that rapidly adsorb onto their surfaces, forming what is termed the "protein corona" [3]. This protein corona, rather than the pristine nanoparticle surface, becomes the biological identity that cells and tissues recognize, profoundly influencing biodistribution, cellular uptake, and potential off-target cardiac effects [43]. The corona composition is dynamic and evolves over time, transitioning from an initial "soft corona" of loosely bound proteins to a more stable "hard corona" of tightly associated proteins [44].

The protein corona's composition is determined by multiple factors including nanoparticle size, shape, surface charge, hydrophobicity, and the biological environment encountered. For cardiac tissues, this is particularly significant because emerging data show that specific corona proteins can act as ‘molecular fingerprints’ that either enhance or attenuate cardiac uptake, with apolipoprotein-enriched coronas redirecting nanoparticles between heart and non-cardiac organs [45,46]. For instance, adsorption of opsonins such as immunoglobulins and complement proteins can enhance recognition by immune and endothelial cells, promoting inflammatory accumulation. Conversely, dysopsonins like albumin tend to reduce phagocytic uptake and prolong circulation, although albumin-rich coronas can still engage specific receptors (e.g., albumin and scavenger receptors) on endothelial and other cells and thereby modulate vascular responses [47].

The protein corona directly impacts cardiotoxicity through several mechanisms: (1) changing biodistribution and the cardiac dose of nanoparticles [48]; (2) Modulating cellular uptake in cardiomyocytes and cardiac endothelial cells [14]; (3) shielding the nanoparticle surface and preventing direct membrane damage [49]; (4) controlling metal/ion release and oxidative stress / ferroptosis in cardiovascular cells [50]; (5) driving or mitigating inflammation and immune-mediated cardiotoxicity [14,50]; (6) influencing coagulation and hemocompatibility through fibrinogen protein corona, affecting coronary perfusion [51]; (7) modulating cardiomyocyte Ca^{2+} handling and mitochondrial function (silica NP example) [52]; (8) encoding patient-specific differences in cardiotoxic response (Cisneros et al., 2024). Importantly, the protein corona can mask targeting ligands on nanoparticle surfaces, reducing tumour specificity and increasing and contributing to unintended cardiac exposure.

Surface engineering strategies to minimize problematic protein corona formation include PEGylation, zwitterionic coatings, and biomimetic cell membrane camouflaging. However, these approaches have limitations. PEGylated nanoparticles acquire distinct coronas, albeit

Table 1
Common Nanoparticle Types in Oncology and Their Cardiac Risk Profiles.

Nanoparticle Type	Composition	Key Advantages	Specific Physicochemical Properties	Cardiac Toxicity Risks	Molecular Mechanisms	Clinically Approved Examples
Liposomes [18,55,56]	Phospholipid bilayers, often PEGylated	Enhanced drug solubility; altered pharmacokinetics; improved tumor exposure via EPR effect	Size usually ~80–100 nm for pegylated liposomal doxorubicin (PLD); near-neutral or slightly negative ζ-potential; PEGylated surface forms a protein corona enriched in apolipoproteins and complement factors in vivo	Anthracycline payload–related chronic cardiomyopathy (though significantly *reduced* vs conventional doxorubicin) and acute infusion reactions with cardiopulmonary symptoms (hypotension, tachycardia, chest discomfort) due to complement activation-related pseudoallergy (CARPA)	• Anthracycline-mediated oxidative stress and mitochondrial injury in cardiomyocytes (ROS, lipid peroxidation, mtDNA damage, mitochondrial permeability transition, apoptotic signaling) • Complement activation by PEGylated liposomes with generation of C3a, C5a and sC5b-9, driving vasodilation, hypotension, tachycardia and cardiopulmonary distress in susceptible patients (CARPA) • Protein corona composition (e.g., high apolipoprotein content) modulates opsonization, complement activation and biodistribution, thereby indirectly affecting cardiac exposure	Doxil (liposomal doxorubicin), DaunoXome
Polymeric Nanoparticles / Depots [57–59]	Biodegradable polymers (PLGA, PEG)	Controlled release, targeted delivery	Size: 10–300 nm; Surface: Modifiable charge; Degradation: composition / pH-dependent	Cardiac toxicity is generally low in approved PLGA/PEG systems; clinical risk is dominated by the encapsulated drug (e.g., endocrine therapy-related metabolic/ cardiovascular effects or asparaginase-related thrombotic risk). Experimental nano-DOX PLGA systems often reduce cardiotoxicity vs free DOX in vivo by altering biodistribution and cardiac exposure	Many PLGA-based NPs are cardioprotective, ROS generation may occur through NADPH oxidase activation; NF-κB and PGC1α/PPARα pathway activation; mitochondrial membrane potential disruption; inflammatory cytokine cascade (IL-1β, IL-8)	Eligard (leuprolide acetate PLGA depot), Oncaspar (pegaspargase)
Metallic / metal-oxide Nanoparticles [50,60]	Gold (Au), silver (Ag), iron oxide (Fe_3O_4/γ-Fe_2O_3) and other metals	Imaging contrast and theranostics (MRI, CT, optical); photothermal and radiosensitizing effects; magnetic hyperthermia	Small cores (often 1–30 nm) with high surface-to-volume ratio; catalytic surfaces; variable coatings (dextran, PEG, silica, aminosilane, etc.) that strongly affect protein corona, complement activation and vascular interactions	Dose- and surface-chemistry–dependent cardiovascular toxicity in preclinical models: endothelial dysfunction, oxidative stress, mitochondrial injury and cardiomyocyte apoptosis; in humans, some formulations (e.g., IV iron) carry risk of hypotension, arrhythmia and cardiac arrest as part of severe hypersensitivity reactions	Fenton and Fenton-like reactions generating hydroxyl radicals (·OH); Mitochondrial dysfunction causing altered membrane potential, impaired oxidative phosphorylation and cytochrome-c–mediated apoptosis after gold NPs in cardiac or excitable cells; Endothelial dysfunction and autophagy dysregulation and hypersensitivity reaction to iron	Ferumoxytol (Feraheme®), Iron-oxide magnetic hyperthermia formulations (e.g., NanoTherm®)
Dendrimers [61]	Branched polymers (PAMAM) with defined generations and many terminal groups	High and precise drug loading; multivalency for targeting; high water solubility	Small (typically 1–10 nm depending on generation); monodisperse; surface often strongly cationic unless modified (e.g., acetylation, PEGylation)	Cationic dendrimers show notable intrinsic cytotoxicity, and experimental data indicate they can impair mitochondrial oxidation and contractile function in cardiac tissue at sufficient concentrations; toxicity increases with positive charge density and higher generation	Electrostatic interaction with negatively charged plasma membranes, causing membrane thinning, nanopore formation and cell lysis; mitochondrial membrane permeabilization; lysosomal destabilization; direct DNA binding and genotoxicity; Genotoxicity (DNA damage and chromatin interaction)	No dendrimer nanomedicine is yet *approved specifically for oncology*. The anionic dendrimer SPL7013 (VivaGel®) has been approved/marketed for topical use in vaginal infections

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Table 1 (*continued*)

Nanoparticle Type	Composition	Key Advantages	Specific Physicochemical Properties	Cardiac Toxicity Risks	Molecular Mechanisms	Clinically Approved Examples
Carbon-Based Nanoparticles [39,62]	Carbon nanotubes (single-walled, multi-walled), graphene and graphene oxide, fullerenes, carbon dots	Very high aspect ratio and photothermal properties (CNTs, graphene); large surface area for loading; potential for imaging and photothermal ablation	Size: Variable (CNTs: nm diameter, μm length); Surface: Hydrophobic; High aspect ratio	No approved clinical carbon-nanotube/graphene oncology products; cardiovascular risks are inferred from inhalation and systemic exposure models: oxidative stress, endothelial dysfunction, inflammation, promotion of atherosclerosis and possible adverse cardiac remodeling	Frustrated phagocytosis leading to chronic inflammasome (NLRP3, NF-κB) activation; prolonged oxidative stress via persistent ROS generation; endothelial tight junction disruption through VE-cadherin downregulation; pro-fibrotic TGF-β1 signaling	Currently in preclinical and early clinical development

with different compositions, indicating these strategies modulate rather than eliminate the phenomenon [53]. Advanced characterization techniques such as liquid chromatography-mass spectrometry (LC-MS) based proteomics and differential centrifugal sedimentation, now enable quantitative mapping of corona composition and improve prediction of nanoparticle–heart interactions [54]. Understanding and managing the protein corona remains a central challenge in the development of cardiovascularly safe nanomedicines, as the corona ultimately determines whether NPs reach intended tumour tissues or accumulate in off-target organs like the heart.

3. Mechanisms of nanoparticle-mediated cardiotoxicity

Nanoparticle-induced cardiotoxicity arises from multifactorial and often interrelated mechanisms that affect cardiomyocytes, endothelial cells, and the cardiac microenvironment. Understanding these pathways is critical for developing safer nanomedicines and effective cardioprotective strategies. Table 2 summarises mechanisms of nanoparticle mediated cardiotoxicity as well as their cellular targets and consequences of damage to cardiac tissues while Fig. 2 shows a pathway diagram illustrating how nanoparticles induce cardiotoxicity via oxidative stress, inflammation, endothelial damage, and fibrosis.

3.1. Influence of NPs composition and administration regimen on cardiotoxicity

The composition and administration regimen of nanoparticle-based therapies plays a decisive role in shaping cardiotoxic risk. Clinical experience with liposomal anthracyclines illustrates this point clearly. Pegylated liposomal doxorubicin (PLD; Doxil) consistently demonstrates a markedly safer cardiac profile than conventional doxorubicin, even when administered at similar cumulative doses. In a cohort receiving $\geq 500\ mg/m^2$ PLD, no clinical heart failure was observed and only a minority developed modest declines in ejection fraction [11]. A meta-analysis of randomized trials in multiple cancer types similarly found significantly lower rates of heart failure with PLD-based regimens [70]. These outcomes are tightly linked to the pharmacokinetics imposed by the liposomal carrier: by restricting distribution into cardiac tissue and moderating free-drug peaks, liposomes reduce myocardial exposure and thereby the probability of cumulative cardiac injury.

While liposomal systems illustrate how altered biodistribution can mitigate chronic cardiotoxicity, metallic nanoparticles highlight the importance of cumulative burden and dosing interval. Iron oxide nanoparticles, for example, have been shown to induce ferroptotic injury in cardiomyocytes following lysosomal degradation and release of catalytically active ferrous iron, promoting lipid peroxidation and mitochondrial dysfunction [50]. A broader review of magnetic nanoparticles notes that cardiovascular toxicity is strongly shaped by dose, exposure duration, surface chemistry, and biodegradation profile, with persistent particles posing particular concern for long-term cardiac accumulation [60]. Although human data remain limited, these experimental findings suggest that dosing schedules that allow insufficient recovery time between administrations may permit oxidative injury and inflammation to accumulate progressively.

The clinical relevance of regimen design becomes evident when comparing approved nanomedicine protocols. Standard Doxil dosing of $50\ mg/m^2$ every four weeks as a one-hour infusion contrasts sharply with bolus administration of conventional doxorubicin at $60\ mg/m^2$ every three weeks. Despite the lower per-cycle dose, liposomal schedules reach comparable cumulative exposures while preserving antitumor efficacy and substantially reducing cardiac injury [71]. Encapsulation and controlled infusion attenuate peak free-drug concentrations, limit acute hemodynamic reactions, and provide a more gradual equilibrium of the protein corona, all of which may temper acute and chronic cardiotoxicity. Other nano-formulations, such as nab-paclitaxel (Abraxane), similarly rely on weekly lower-dose

Table 2
Summary of Mechanisms of Nanoparticle-Mediated Cardiotoxicity.

Mechanism	Description	Key Cellular Targets	Consequences
Oxidative Stress and Mitochondrial Dysfunction [63,64]	ROS generation leading to DNA and lipid damage	Cardiomyocytes	Apoptosis, contractile dysfunction
Inflammatory and Immune Activation [65]	Cytokine release, complement activation	Macrophages, immune cells	Myocardial inflammation, fibrosis
Endothelial Dysfunction [66]	Damage to vascular endothelium and impaired NO production	Endothelial cells	Microvascular obstruction, ischemia
Off-Target Accumulation [67,68]	Retention of nanoparticles in cardiac tissue	Cardiomyocytes, fibroblasts	Chronic inflammation, toxicity
Extracellular Matrix Remodelling [69]	Activation of fibroblasts, promoting fibrosis	Cardiac fibroblasts	Fibrosis, impaired myocardial function

administration to reduce acute infusion-related complications [72], reinforcing the broader principle that regimen optimization is integral to the clinical tolerability of nano-enabled therapeutics. As the field advances toward increasingly complex nanostructures with diverse clearance profiles, systematic evaluation of dosing schedules rather than reliance on conventional chemotherapy paradigms will be central to preventing avoidable cardiotoxicity and ensuring therapeutic durability.

3.2. Direct cardiac cell toxicity

One of the primary mechanisms by which nanoparticles exert cardiotoxicity is through direct injury to cardiomyocytes. Nanoparticles can induce oxidative stress by generating reactive oxygen species (ROS), overwhelming the cell's antioxidant defenses. Specifically, nanoparticles trigger ROS generation through multiple molecular cascades: (1) NADPH oxidase (NOX) activation, particularly NOX2 and NOX4 isoforms highly expressed in cardiomyocytes; (2) disruption of the mitochondrial electron transport chain at Complex I (NADH dehydrogenase) and Complex III (cytochrome bc1 complex), causing electron leakage and superoxide (O_2^-) formation; (3) depletion of endogenous antioxidants including glutathione (GSH), superoxide dismutase (SOD), and catalase; and (4) Fenton and Fenton-like reactions catalyzed by metallic nanoparticles generating highly reactive hydroxyl radicals (·OH) from hydrogen peroxide. ROS accumulation causes lipid peroxidation producing toxic aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), DNA damage including 8-hydroxydeoxyguanosine (8-OHdG) formation, and protein oxidation affecting critical contractile proteins and ion channels, leading to mitochondrial dysfunction and triggering apoptosis or necrosis [63,64].

Mitochondrial damage is particularly detrimental in cardiomyocytes due to their high energy demand. Metallic nanoparticles, such as silver and gold nanoparticles, have been shown to accumulate within mitochondria, localizing to the intermembrane space and mitochondrial matrix, disrupting the electron transport chain and reducing ATP production [73]. This ATP depletion triggers AMP-activated protein kinase (AMPK) activation and downstream metabolic stress responses. Additionally, mitochondrial membrane potential ($\Delta\Psi_m$) dissipation occurs through opening of the mitochondrial permeability transition pore (mPTP), resulting in cytochrome c release into the cytosol, caspase-9 activation, and initiation of the intrinsic apoptosis pathway [74]. Mitochondrial DNA (mtDNA) is particularly vulnerable to oxidative damage due to limited repair mechanisms, and mtDNA damage further impairs oxidative phosphorylation capacity through reduced transcription of electron transport chain subunits. Furthermore, nanoparticle exposure can impair calcium handling in cardiomyocytes by disrupting calcium channels and pumps including L-type calcium channels (LTCC), ryanodine receptors (RyR2), and sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), contributing to contractile dysfunction and arrhythmogenic potential through delayed after depolarizations and triggered activity [75].

3.3. Inflammatory and immune-mediated cardiotoxicity

Nanoparticles can activate innate immune responses, leading to myocardial inflammation. Cardiac macrophages and resident immune cells recognize nanoparticles as foreign entities, initiating inflammatory cascades through multiple pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), particularly TLR4, NOD-like receptors (NLRs), and scavenger receptors such as CD34 and CD36. This recognition triggers downstream signaling through MyD88-dependent and TRIF-dependent pathways, activating nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1) transcription factors, which drive expression of pro-inflammatory genes [76].

The resulting signaling cascade involves sequential release of pro-inflammatory cytokines and chemokines such as TNF-α, IL-1β, IL-6, IL-8 and MCP-1/CCL2 are upregulated and contribute to leukocyte recruitment, myocardial injury and adverse remodelling, with IL-8 and MCP-1 in particular linked to post-infarction leukocyte infiltration and worse outcomes [77]. TNF-α promotes cardiomyocyte apoptosis and heart failure through activation of both intrinsic and extrinsic caspase pathways and induces endothelial and cardiac-cell expression of adhesion molecules (ICAM-1, VCAM-1 and E-selectin), thereby facilitating inflammatory cell recruitment to the myocardium [78]. In parallel, IL-1β produced via NLRP3-ASC-caspase-1 inflammasome activation exerts direct negative inotropic effects by inducing iNOS and excess nitric oxide with subsequent peroxynitrite formation, leading to nitrosative stress and contractile failure in experimental models of cytokine-induced myocardial dysfunction [62].

This cytokine storm can cause myocardial injury, fibrosis, and contribute to heart failure progression through persistent activation of cardiac fibroblasts via IL-6/JAK/STAT3 signaling and TNF-α/NF-κB pathways, promoting transition from acute inflammation to chronic fibrotic remodeling [79]. For example, dendrimers with cationic surface charges have been reported to induce CARPA, resulting in acute cardiac events in susceptible individuals [31]. Moreover, nanoparticle-induced systemic inflammation may exacerbate pre-existing cardiovascular conditions. Circulating inflammatory mediators increase systemic vascular resistance through endothelin-1 upregulation, reduce endothelial nitric oxide bioavailability, and destabilize atherosclerotic plaques by activating matrix metalloproteinases (particularly MMP-2 and MMP-9), increasing acute coronary syndrome risk in vulnerable patients [80].

3.4. Endothelial dysfunction and vascular toxicity

The cardiac endothelium plays a crucial role in regulating vascular tone and myocardial perfusion. Nanoparticles can injure endothelial cells through oxidative stress and inflammation, leading to endothelial dysfunction [66]. Mechanistically, nanoparticle-induced ROS production in endothelial cells has been shown to involve activation of NADPH oxidases (notably NOX4, and in some contexts NOX2) and mitochondrial perturbation, overwhelming antioxidant systems such as superoxide dismutase (SOD), catalase and glutathione peroxidase. Silver nanoparticles, for example, increase ROS generation in human umbilical vein endothelial cells (HUVECs) via NOX4 upregulation, while

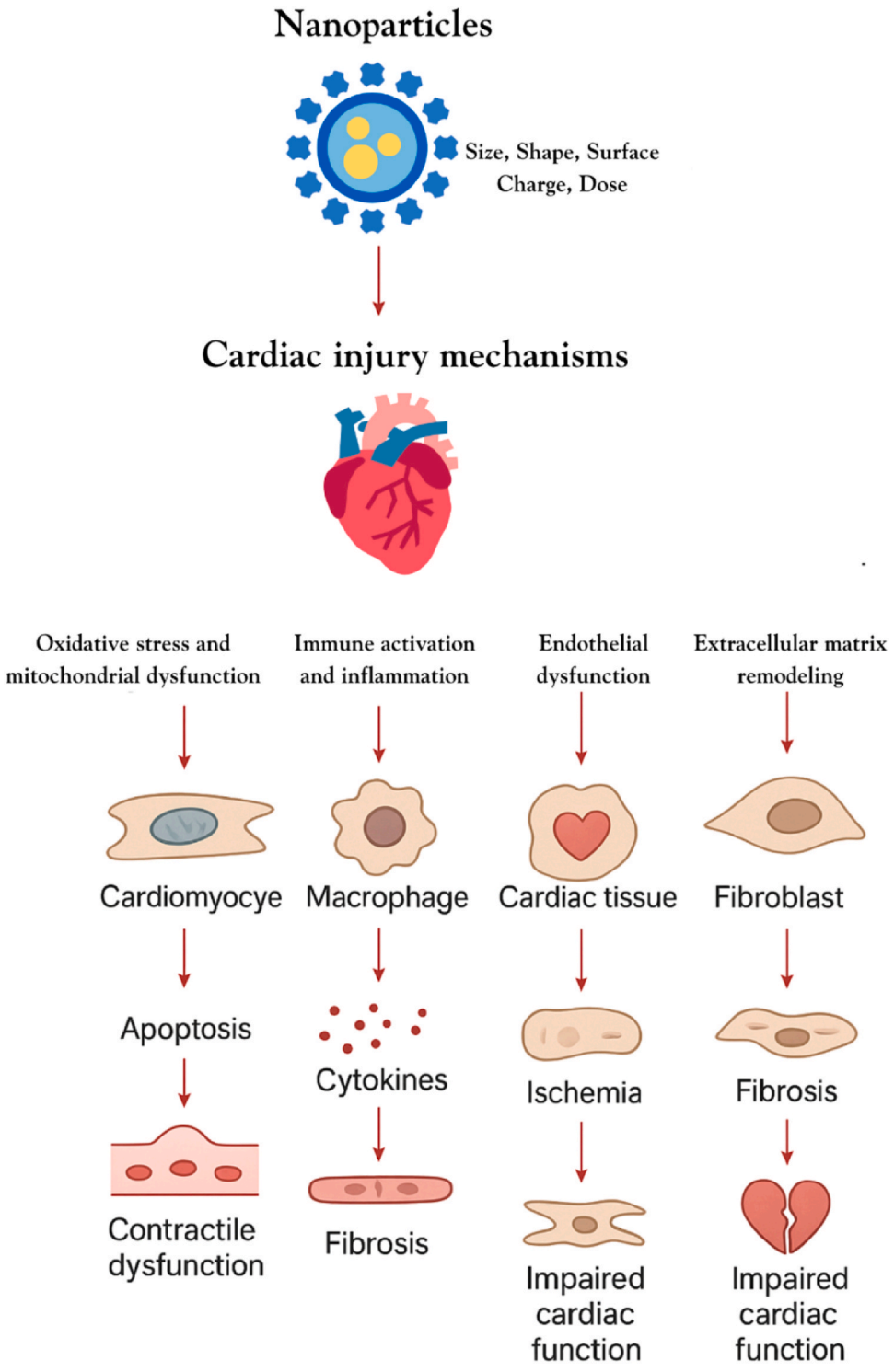

Fig. 2. Pathway diagram of nanoparticle-induced cardiotoxicity. A mechanistic pathway diagram depicting how various nanoparticles trigger cardiac injury. The infographic traces nanoparticle entry and disposition, annotates physicochemical determinants (size, shape, charge, dose), and maps injury routes including oxidative stress, inflammation, immune cell activation, endothelial dysfunction, off-target accumulation, and extracellular matrix remodeling.

impairing Nrf2-dependent antioxidant responses [81]. This oxidative stress promotes classical mechanisms of endothelial nitric oxide synthase (eNOS) dysfunction and uncoupling: oxidation of the cofactor tetrahydrobiopterin (BH_4) to BH_2, leading eNOS to generate superoxide rather than NO; altered phosphorylation of eNOS, with reduced phosphorylation at the activating Ser1177 site and increased phosphorylation at inhibitory residues under oxidative conditions; and post-translational modifications, including S-glutathionylation and nitrosylation, that further reduce enzymatic activity. Persistent oxidative stress also downregulates eNOS expression at the transcriptional level, resulting reduction in NO bioavailability diminishes endothelium-dependent vasodilation, increases basal vascular tone and favours platelet activation and aggregation [82].

In parallel, nanoparticles compromise endothelial barrier integrity. Multiple studies show that zinc oxide, gold, silver and titanium dioxide nanoparticles disrupt tight and adherens junctions, including claudins,

occludin, ZO-1 and VE-cadherin, leading to increased endothelial permeability in lung and brain microvascular beds [83]. These effects often coincide with cytoskeletal remodelling and junctional protein internalisation, consistent with activation of RhoA/ROCK signalling, a canonical pathway by which inflammatory mediators and VEGF increase endothelial permeability via actin stress fibre formation and junctional protein phosphorylation [84]. Increased permeability facilitates transendothelial migration of inflammatory cells and allows nanoparticles to extravasate into the cardiac interstitium, where they may interact directly with cardiomyocytes and resident immune cells [82].

Endothelial injury also contributes to the pro-thrombotic phenotype that underlies atherosclerotic cardiovascular disease. Endothelial activation and dysfunction shift the vascular surface from an antithrombotic to a prothrombotic state, with increased expression of adhesion molecules and pro-coagulant mediators (including tissue factor and von Willebrand factor), reduced activity of endogenous anticoagulant pathways, and impaired fibrinolysis. Silica nanoparticles, for example, trigger Weibel-Palade body exocytosis and release of ultra-large vWF multimers from endothelial cells, supporting platelet adhesion [85]. Metal oxide nanoparticles such as nano-CuO upregulate plasminogen activator inhibitor-1 (PAI-1) in microvascular endothelial cells through ROS- and p38-dependent signalling, directly suppressing the fibrinolytic system [86]. These changes favour thrombin generation, platelet adhesion and reduced clot lysis, creating a pro-coagulant microenvironment that is particularly dangerous in the coronary microcirculation, where microthrombi can contribute to no-reflow phenomena despite angiographically patent epicardial vessels.

Exposure to Nanoparticles may also trigger arrhythmias, further reducing the already lowered cardiac output or cause vasculature constriction and leading to coronary artery spasms and myocardial ischaemia. Engineered nanoparticles can promote arrhythmias through direct myocardial electrophysiology disruption and conduction uncoupling, with supportive evidence from several particle classes. Acute zinc oxide nanoparticle exposure reduced cardiomyocyte I_{Na} and I_{Ca-L}, producing atrioventricular conduction block, impaired Ca^{2+} transients, arrhythmias, and heart failure in mice, with similar Ca^{2+} disturbances reported in human iPSC-cardiomyocytes [87]. Silver nanoparticles similarly caused rapid electrophysiologic toxicity by altering transmembrane potential and suppressing I_{Na} and I_{K1}, leading to lethal bradyarrhythmias in mice [88]. Beyond ion currents, silica nanoparticles reduced gap-junction intercellular communication in H9c2 cardiomyocytes via downregulation and altered phosphorylation of connexin-43, creating a substrate for conduction slowing and re-entry [89]. In real-world exposures, epidemiologic and panel studies link particulate matter (including ultrafine/nanoparticle-rich fractions) with ventricular arrhythmias and ST-elevation myocardial infarction, and with altered autonomic control (e.g., reduced heart rate variability (HRV)), supporting clinical plausibility of particle-triggered electrical instability [90].

Coronary vasomotor instability is also biologically plausible because particle exposures can shift vascular balance toward constriction through endothelin signalling and reduced NO bioavailability. Short-term diesel exhaust (a major source of airborne NPs) exposure has been shown to elicit vasoconstriction and to increase vascular sensitivity to endothelin-1 and impair endothelin-receptor–dependent vasodilation, consistent with reduced NO buffering [91]. In animal models, particulate matter containing persistent free radicals reduced endothelium-dependent vasodilation and increased circulating endothelin-1, supporting a mechanistic link between inhaled particle exposure and systemic endothelial dysfunction that can predispose to coronary spasm/ischemia in susceptible individuals [92].

3.5. Off-target accumulation and retention

Off-target biodistribution is a major determinant of nanoparticle-associated cardiotoxicity, as only a small fraction of systemically administered nanoparticles ultimately reaches tumors, while substantial uptake occurs in non-target organs. Although tumor accumulation is often attributed to the enhanced permeability and retention (EPR) effect, quantitative analyses show that most nanoparticles are sequestered by the mononuclear phagocyte system (previously known as the reticuloendothelial system), limiting tumor delivery and increasing systemic exposure, including to the heart [93]. Cardiac accumulation is facilitated in pathological settings such as myocardial ischemia or inflammation, where increased vascular permeability permits nanoparticle extravasation; experimental studies demonstrate preferential accumulation of nanoparticles ($\approx$20–200 nm) in injured myocardium compared with healthy tissue [94]. In addition to passive leakage, endothelial uptake and transcytosis, usually modulated by nanoparticle size and protein corona composition provide further routes for nanoparticle entry into cardiac tissue [95].

Physicochemical properties strongly influence cardiac retention. Nanoparticles below the renal filtration threshold ($\sim$6–8 nm, depending on shape and coating) are rapidly cleared, whereas larger particles evade renal excretion and remain available for tissue uptake and macrophage sequestration [96,97]. Prolonged circulation, particularly with stealth surface chemistries, increases the probability of cardiac exposure in permeable or diseased myocardium. Persistent retention of non-biodegradable nanoparticles can drive chronic cardiotoxicity: iron oxide nanoparticles undergo slow lysosomal processing and incorporation into cellular iron pools over months, altering iron homeostasis and promoting oxidative stress pathways associated with cardiomyocyte injury [67]. Sub-chronic exposure to silica nanoparticles similarly induces myocardial inflammation and fibrosis in vivo, linking nanoparticle persistence to structural cardiac remodeling [68]. Together, these findings demonstrate that off-target accumulation and incomplete clearance of nanoparticles constitute central mechanisms by which repeated or sustained exposure can contribute to cardiotoxicity.

3.6. Interaction with cardiac extracellular matrix and fibrosis

Fibroblasts in the myocardium respond to injury by producing extracellular matrix proteins. Nanoparticles can stimulate fibroblast activation either directly or through inflammatory mediators, promoting cardiac fibrosis and stiffening [69]. The molecular pathway of nanoparticle-induced cardiac fibrosis involves multiple interconnected mechanisms. Accumulating evidence indicates that nanoparticle exposure can promote cardiac fibrotic remodelling, primarily through inflammation-driven fibroblast activation rather than direct fibroblast toxicity. In vivo studies demonstrate that several nanoparticle types, including silica and metal oxides, induce myocardial inflammation accompanied by increased collagen deposition and structural remodelling, linking nanoparticle persistence to fibrosis development [68]. Mechanistically, inflammatory mediators released from activated macrophages, endothelial cells, and injured cardiomyocytes, most notably transforming growth factor-β1 (TGF-β1) activate cardiac fibroblasts through the canonical TGF-β receptor–Smad2/3 pathway, driving transcription via promoting myofibroblast differentiation in cardiac cells [98]. This profibrotic shift is clinically relevant because fibrosis is not merely structural: patchy or interstitial collagen deposition can slow and fragment conduction, facilitating re-entry and triggered activity, thereby increasing arrhythmic risk even when systolic function is relatively preserved [99]. Although these pathways are well established in cardiac disease biology, the strength of evidence linking engineered NPs to clinically meaningful myocardial fibrosis remains material- and exposure-dependent, with the most direct data currently coming from toxicology-style exposure models rather than from therapeutic nanomedicine dosing scenarios.

3.7. Cardiotoxicity of clinically approved nanodrugs: translating mechanisms to patient care

While preclinical studies provide valuable mechanistic insights, understanding the cardiotoxicity profiles of clinically approved nanodrugs is essential for translating research findings into practical patient management strategies. Several nanoformulations currently used in oncology demonstrate instructive patterns linking their physicochemical properties to clinical cardiovascular outcomes.

Pegylated liposomal doxorubicin (Doxil/Caelyx) is the best-studied example: in a randomized phase III trial in metastatic breast cancer, pegylated liposomal doxorubicin (50 mg/m^2 q4 weeks) produced significantly less cardiotoxicity than conventional doxorubicin (60 mg/m^2 q3 weeks) while maintaining comparable efficacy [71]. Consistent with this, the Doxil prescribing information warns that cardiomyopathy risk rises with increasing cumulative anthracycline exposure and recommends baseline and ongoing LVEF assessment, while also documenting infusion-related reactions and explicitly stating it should not be given as a bolus [100]. These data support reduced but not absent cardiac risk, with residual toxicity arising from anthracycline class effects at higher cumulative doses and from infusion-related reactions.

Albumin-bound paclitaxel (nab-paclitaxel; Abraxane) has a different cardiovascular signature. Its albumin carrier is reported to exploit gp60-mediated, caveolin-1–associated transcytosis (a physiological albumin transport pathway), providing a mechanistic basis for altered tissue distribution [101]. Clinically, the FDA label reports hypotension during infusion (5 %), bradycardia (< 1 %), "severe cardiovascular events" in ~3 % of patients (including ischemia/infarction and cardiac arrest), and rare reports of heart failure, left ventricular dysfunction and AV block indicating that cardiovascular monitoring is most relevant in higher-risk patients and during early dosing [102].

For liposomal irinotecan (Onivyde), direct cardiotoxicity is not a dominant labeled concern compared with hematologic and gastrointestinal toxicity; however, its labeling and professional guidance emphasize atropine for early diarrhea, consistent with irinotecan's cholinergic syndrome physiology, and specifies standard infusion scheduling (e.g., 90-minute infusion q2 weeks). Reported adverse outcome includes pancytopenia and thromboembolic events like stroke and pulmonary embolism, which are clinically relevant to cardiovascular risk surveillance in susceptible patients receiving complex regimens [103].

Vincristine sulfate liposome injection (Marqibo) underscores that nanoformulation can modify exposure while preserving class toxicities. The FDA label highlights cumulative neurotoxicity and explicitly notes that orthostatic hypotension may occur, aligning with vincristine's autonomic neuropathy potential [104]. Rare documented cardiac-related adverse effect includes sinus tachycardiac, pericardial effusion, cardiac arrest especially with increase dose [104,105].

Ferumoxytol (Feraheme), while indicated for iron deficiency anemia rather than oncology, provides a clinically instructive example of metallic nanoparticle risk: its boxed warning describes fatal and serious hypersensitivity reactions with initial symptoms that may include hypotension, syncope, and cardiac/cardiorespiratory arrest, and specifies administration as an infusion over ≥ 15 min with post-infusion monitoring. Reported serious hypersensitivity reactions in clinical studies are on the order of ~0.2 %, reinforcing why infusion rate and immediate resuscitation readiness are integral to safe delivery of some nanoparticle products [106].

Translating these clinical observations into actionable patient management strategies requires: (1) comprehensive baseline cardiovascular assessment including history, physical examination, ECG, echocardiography, and biomarkers; (2) risk stratification incorporating patient age, pre-existing cardiovascular disease, previous cardiotoxic therapies, and genetic predisposition; (3) individualized monitoring protocols with more frequent assessments for high-risk patients; (4) early intervention with cardioprotective medications (ACE inhibitors, beta-blockers, statins) when subclinical changes emerge; (5) multidisciplinary cardio-oncology team involvement for patients with significant risk factors; and (6) consideration of alternative less cardiotoxic regimens when cardiac risk exceeds benefit. Future nanodrug development should incorporate these clinical lessons, prioritizing formulations that minimize cardiac protein corona formation, reduce cardiomyocyte uptake, and enable real-time biodistribution monitoring to optimize the therapeutic window between antitumor efficacy and cardiovascular safety.

4. Factors influencing nanoparticle cardiotoxicity

The cardiotoxic potential of nanoparticles is highly dependent on their physicochemical properties, administration parameters, and patient-specific factors. A nuanced understanding of these variables is essential for designing safer nanomedicines and optimizing their clinical use. Table 3 summarises how these NP characteristics and patient specific factors influence cardiotoxicity.

4.1. Physicochemical properties

4.1.1. Size

Nanoparticle size is a critical determinant of biodistribution, cellular uptake, and toxicity. Smaller nanoparticles (~120 nm) tend to have greater tissue penetration but may also more easily cross biological barriers, increasing the risk of off-target cardiac exposure. Conversely, larger NPs (> 200 nm) may be cleared rapidly by the mononuclear phagocyte system [107], but could cause embolic microvascular obstruction if aggregated.

4.1.2. Shape

Particle shape influences cellular internalization and circulation time. Rod-shaped or elongated NPs exhibit different interactions with cardiomyocytes and endothelial cells compared to spherical particles, potentially altering toxicity profiles. For example, Xu et al. [108] compared large (rod-like) carbon nanotubes and a short (cotton candy-like) carbon nanotubes to prove a hypothesis that the shape of carbon nanotubes contributes to its toxicity. The Rod-like tubes show greater pro-inflammatory effects.

Table 3
Influence of Nanoparticle Characteristics and Patient Factors on Cardiotoxicity.

Factor	Effect on Cardiotoxicity	Highlights
Size	Smaller NPs penetrate tissues more but may increase toxicity	Optimal size balancing efficacy and safety is critical
Shape	Rod-like shapes induce more inflammation	Spherical shapes generally less toxic
Surface charge	Positive charge increases membrane disruption	PEGylation reduces immunogenicity
Dose	Higher doses increase accumulation and toxicity	Dose optimization needed
Route of administration	Systemic exposure increases cardiac risk	Local delivery may reduce risk
Patient genetics	Influences oxidative stress and immune responses	Personalized approaches recommended
Comorbidities	Pre-existing heart disease increases vulnerability	Requires careful monitoring
Concomitant therapies	Synergistic cardiotoxicity with other cancer drugs	Combination therapy needs caution

4.1.3. Surface charge and chemistry

Surface charge affects nanoparticle interaction with cellular membranes and serum proteins. Positively charged nanoparticles generally exhibit higher cellular uptake but can disrupt negatively charged cell membranes, leading to increased cytotoxicity [109]. Surface functionalization with polyethylene glycol (PEGylation) often reduces immunogenicity and improves biocompatibility but may not eliminate cardiotoxic risks entirely [110].

4.2. Dose and route of administration

Nanoparticle dose directly correlates with toxicity risk. High or repeated dosing can lead to accumulation in cardiac tissue and increased oxidative or inflammatory injury [38]. Nanoparticle pharmacokinetics are often non-linear because clearance by the mononuclear phagocyte system becomes saturated at higher doses, prolonging circulation time and increasing cardiac exposure [111]. This is particularly relevant for non-biodegradable metallic nanoparticles; iron oxide nanoparticles undergo slow intracellular processing and tissue retention, with cumulative exposure rather than peak concentration determining long-term burden and toxicity [67].

Route and infusion rate further modify cardiovascular risk. Intravenous administration confers the greatest acute cardiac exposure, and rapid bolus injection can trigger CARPA, resulting in hypotension, arrhythmias, and cardiopulmonary distress, whereas slower infusions markedly reduce these events [112]. Alternative routes, including local or intra-tumoral delivery, reduce systemic exposure but are anatomically constrained, while inhalational nanoparticle exposure primarily studied in environmental contexts induces cardiovascular effects indirectly via neuronal related or pulmonary inflammation and oxidative stress [113]. Collectively, these findings indicate that dose intensity, cumulative exposure, and administration route are central determinants of nanoparticle-associated cardiotoxicity.

4.3. Patient-specific factors

Inter-individual susceptibility to NP cardiotoxicity is shaped by baseline cardiovascular risk and by host determinants that modify NP biodistribution and immune responses. Contemporary cardio-oncology guidance recommends risk stratification using clinical factors (age, prior cardiovascular disease, baseline cardiac function, and cumulative exposure to cardiotoxic therapies) because these variables predict a higher probability of cancer therapy-related cardiac dysfunction and guide intensified surveillance [114]. Ageing further increases vulnerability through reduced physiological reserve and the chronic low-grade inflammatory state termed “inflammaging,” which amplifies oxidative and cytokine-mediated injury pathways relevant to both drug- and NP-triggered cardiotoxicity [115]. Comorbidities that alter plasma composition (e.g., diabetes, dyslipidaemia, chronic inflammation) are also mechanistically relevant because the protein corona varies between individuals and disease states, producing “personalized” coronas that can change NP pharmacokinetics, biodistribution, and toxicity [38]. Genetic variability can further contribute to heterogeneity in cardiac risk, particularly in pathways governing antioxidant defenses and drug handling. For example, polymorphisms in oxidative stress-related genes (including SOD2/GST/CAT pathways) have been associated with late anthracycline-related cardiac damage, providing a plausible template for interpatient differences when cardiotoxic agents are delivered in nanoformulations, even though direct NP-specific pharmacogenetic evidence remains limited [116].

5. Challenges in detection and evaluation of nanoparticle-mediated cardiotoxicity

The identification and monitoring of cardiotoxic effects induced by nanoparticle (NP)-based therapies remain a complex and evolving field. Several challenges limit the early detection and accurate assessment of NP-related cardiac injury, which hampers timely intervention and risk mitigation.

5.1. Lack of standardized toxicity assessment protocols

Currently, there is no universally accepted protocol specifically designed to evaluate cardiotoxicity from nanoparticles. Traditional cardiotoxicity testing methods developed for small-molecule chemotherapeutics (e.g., echocardiography, cardiac biomarkers) may not capture subtle or unique NP-induced effects. There are no harmonized guidelines for evaluating nanoparticle cardiotoxicity and current methods, both in vitro and in vivo are fragmented and they often fail to capture the full spectrum of nanoparticle induced effects. Hence, there is a need for standardized and validated protocols to ensure safe clinical translation.

5.2. Sensitivity of conventional cardiac monitoring

Conventional surveillance tools (standard echocardiographic LVEF, ECG, and routine biomarkers) can miss early cardiotoxicity because functional deterioration is often detected after myocardial injury has already developed. LVEF is particularly limited by measurement variability that frequently exceeds clinically meaningful change thresholds, complicating detection of subclinical decline [117]. Myocardial deformation imaging improves sensitivity: multiple studies and professional guidance show that reductions in global longitudinal strain (GLS) precede LVEF decline, and a relative GLS decrease $> 15\,\%$ is widely used to flag early/subclinical dysfunction during cardiotoxic therapy [118].

Biomarkers provide complementary information but have important constraints. High-sensitivity troponin can identify early myocardial injury and, in some cohorts, predicts later LV dysfunction; however, results across studies are inconsistent and depend strongly on timing, assay, and treatment context [119,120]. Natriuretic peptides (BNP/NT-proBNP) primarily reflect haemodynamic wall stress, and several studies report limited value for predicting later LVEF decline compared with strain and troponin-based approaches [119]. ECG is useful for overt rhythm/QT abnormalities but performs poorly as an early screening tool for impending injury in chemotherapy settings [121]. Cardiac MRI offers superior tissue characterization (e.g., fibrosis and diffuse interstitial change via LGE and T1/ECV mapping), but its cost and logistics constrain routine serial monitoring [122].

Applied to nanoparticle cardiotoxicity, these limitations imply that relying on LVEF or late biomarkers alone may underestimate early NP-mediated injury, supporting the use of GLS and appropriately timed high-sensitivity troponin (where feasible) and reserving cardiac MRI for problem-solving or high-risk phenotypes.

5.3. Difficulty in differentiating NP effects from chemotherapy toxicity

Attributing cardiotoxicity specifically to nanoparticle formulations remains challenging because nanomedicines are typically administered alongside conventional chemotherapy, radiotherapy, or targeted agents. Many of these modalities share overlapping cardiac injury mechanisms, including oxidative stress, mitochondrial dysfunction, and inflammatory signaling, which complicates mechanistic attribution in the absence of NP-specific biomarkers. Temporal overlap obscures causality because NP-associated cardiac injury can develop after repeated exposures over weeks in preclinical models [123], while anthracycline cardiotoxicity and radiation-induced cardiac disease have well-recognized delayed presentations that may arise months to years after treatment, creating overlapping windows of cardiac events [124,125]. In addition, nanoparticle carriers can modify drug biodistribution and exposure, potentially altering the magnitude or pattern of cardiotoxicity relative to free drug, thereby confounding dose–response

relationships [111]. Clinical trial designs rarely include nanoparticle-free control arms once efficacy is established, limiting direct comparisons, while inter-patient variability in baseline cardiovascular risk and prior cardiotoxic exposure further complicates signal detection. Together, these factors underscore the need for temporal pharmacovigilance, serial cardiac assessment, and development of mechanism-informed biomarkers to better distinguish nanoparticle-related cardiac effects from those of co-administered anticancer therapies.

5.4. Regulatory and translational barriers

The rapid expansion of nanomedicine development continues to challenge existing regulatory frameworks, which were largely designed for small-molecule drugs and biologics rather than particulate systems. Regulatory agencies, including the OECD, FDA and EMA, acknowledge that NP-specific properties, such as size-dependent biodistribution, protein corona formation, surface chemistry, and biopersistence can substantially alter pharmacokinetics and toxicity profiles, yet these features are not uniformly addressed in current cardiotoxicity testing guidelines [126,127,128]. Inconsistent requirements for physicochemical characterization and limited guidance on assessing cumulative toxicity of non-biodegradable nanoparticles further complicate evaluation of long-term cardiovascular risk. Post-marketing surveillance systems also remain poorly equipped to detect late-onset cardiac effects, which may manifest years after exposure, a limitation already recognized in cardio-oncology for conventional therapies.

Translation from preclinical models to humans is additionally constrained by species-specific differences in nanoparticle behavior. Protein corona composition differs markedly between human and animal plasma, altering cellular uptake and immune recognition [129]. Clearance mechanisms also diverge, as rodents exhibit more rapid elimination activity than humans, leading to shorter circulation times and different tissue exposure patterns [130]. Cardiovascular physiology further limits extrapolation, as mice operate under markedly different haemodynamic conditions (e.g., much higher heart rate and substantially higher endothelial wall shear stress than humans), which can alter nanoparticle-endothelium interactions and downstream electrophysiological responses [131]. Immune differences are especially important for infusion reactions: CARPA shows species-dependent sensitivity and symptom patterns, and reviews emphasize that available assays/animal models only partially predict human risk [132]. Together, these factors explain why conventional allometric scaling often fails for nanoparticles and underscore the need for human-relevant models, standardized characterization, and early-phase clinical studies to better anticipate cardiotoxic risk before large-scale trials.

6. Emerging approaches to overcome challenges

As the application of nanotechnology in oncology accelerates, so does the imperative to evaluate and mitigate the unintended cardiotoxic effects of NP-based therapies. Traditional approaches to cardiotoxicity assessment relying heavily on echocardiography, serum biomarkers like troponin, and animal models are increasingly recognized as inadequate for capturing the early, subtle, and often mechanism-specific toxicities induced by nanoparticles. To address this, innovative platforms that aim to provide more predictive, mechanistic, and human-relevant data now exist. These include advanced in vitro modelling, molecular imaging, biomarker discovery, and computational simulations. Each of these tools brings unique strengths, as well as important limitations that must be acknowledged.

One of the most promising advances is the development of physiologically relevant in vitro models, particularly cardiac organoids and heart-on-a-chip platforms. Unlike traditional two-dimensional cardiomyocyte cultures, which oversimplify myocardial biology, these three-dimensional systems more accurately recapitulate the multicellular architecture, electromechanical dynamics, and microenvironment of the human heart. Cardiac organoids, composed of cardiomyocytes, endothelial cells, and supporting stromal elements, can model complex toxic effects such as mitochondrial dysfunction, contractile impairment, and arrhythmogenesis [133]. Microfluidic heart-on-a-chip devices go a step further by incorporating dynamic fluid flow and real-time measurement of contractile function and electrical activity in response to NP exposure Despite these advantages, such systems are often technically complex, costly, and not yet widely standardized across laboratories, which can limit their accessibility and reproducibility. Moreover, the lack of vascular and immune system components in most current models continues to limit their full translational relevance.

In parallel, non-invasive molecular imaging is emerging as a valuable modality for detecting early cardiac injury in vivo [134]. While standard cardiac imaging modalities focus on anatomical and functional endpoints, newer techniques leverage radiolabelled probes to visualize molecular processes such as oxidative stress, inflammation, or apoptosis in cardiac tissue. For example, PET imaging with tracers that detect reactive oxygen species or matrix metalloproteinases can reveal myocardial stress long before functional deterioration is evident [135]. These technologies offer the significant advantage of enabling longitudinal monitoring in preclinical or clinical settings, but they are not without limitations. Imaging costs, exposure to ionizing radiation, and the specificity of molecular tracers, many of which are still in development, pose practical and interpretative challenges.

Another promising avenue involves the discovery of circulating biomarkers that reflect NP-induced cardiotoxicity at early or subclinical stages. While troponins and natriuretic peptides are well-established, they often reflect advanced injury and lack specificity for nanoparticle-related mechanisms. In contrast, microRNAs (miRNAs) such as miR-1, miR-208a, and miR-499, which are released during myocardial stress, offer a more dynamic and mechanism-based readout [136]. Similarly, extracellular vesicles (EVs) and exosomes membrane-bound particles carrying molecular cargo from injured cells can provide insight into intercellular communication and tissue stress. Advances in transcriptomics, proteomics, and metabolomics are further enabling the identification of comprehensive molecular signatures associated with NP exposure [137]. However, validation of these biomarkers across diverse populations, standardization of sample processing, and differentiation from confounding systemic effects remain major hurdles to clinical implementation.

Finally, computational approaches, particularly physiologically based pharmacokinetic (PBPK) modelling and AI-driven toxicity prediction, are playing an increasingly important role in the rational design of safer nanomedicines. PBPK models simulate the biodistribution of nanoparticles by integrating data on size, surface chemistry, protein corona formation, and physiological variables [138]. These models can predict cardiac exposure levels under different dosing regimens and patient conditions, helping guide preclinical safety assessment and nanoparticle optimization. When combined with machine learning techniques and quantitative structure (activity relationship (QSAR) models), it becomes possible to screen vast libraries of nanomaterials for cardiotoxic risk before synthesis or in vivo testing [139]. Yet, these computational models are only as good as the data they are trained on. A lack of standardized, high-quality input data, especially for novel nanoparticle formulations remains a barrier, as does the limited acceptance of in silico methods by regulatory agencies.

Collectively, these emerging approaches offer complementary insights and, when integrated, can form a robust framework for next-generation cardiotoxicity assessment. A strategic combination of in vitro functional testing, non-invasive molecular imaging, biomarker profiling, and computational modelling may significantly improve our ability to predict, detect, and prevent NP-induced cardiac injury, particularly in the context of complex, multimodal cancer therapies. Such an integrated strategy aligns with the goals of precision medicine and is essential for ensuring that nanomedicine advances do not come at the expense of cardiovascular safety. Table 4 summarises various

Table 4
Critical Appraisal of Emerging Approaches in NP-Mediated Cardiotoxicity Evaluation.

Approach	Advantages	Limitations	Outlook
Cardiac Organoids / Heart-on-a-Chip [133]	Human-relevant, real-time functional data	Technical complexity, low throughput	High translational potential for early-stage screening
Molecular Imaging [134,135]	Visualizes early oxidative/inflammatory events in vivo	Cost, limited access, probe specificity issues	Valuable for mechanistic and diagnostic use
Biomarkers (miRNA, EVs) [136]	Non-invasive, scalable, mechanism-linked	Specificity, validation hurdles	Promising tool for personalized monitoring
Computational Modelling [138]	Predictive simulation of NP behaviour and toxicity	Requires accurate data; limited regulatory uptake	Essential for screening and NP design

approaches, their pros and cons in preventing NP-mediated cardiotoxicity.

7. Nanomedicine strategies to mitigate cardiotoxicity

While NPs hold great promise for targeted cancer therapy, the risk of cardiotoxicity necessitates innovative approaches to minimize cardiac damage without compromising therapeutic efficacy. Recent advances in nanomedicine design and cardioprotective strategies aim to reduce off-target cardiac exposure and attenuate toxic mechanisms.

7.1. Design of safer nanoparticles

7.1.1. Surface modification and targeting ligands

Surface modifications and ligand targeting are foundational to safer nanoparticle design especially for clinical applications in drug delivery and nanomedicine. Surface functionalization with hydrophilic polymers such as polyethylene glycol (PEG) reduces opsonization and recognition by the immune system, prolonging circulation time and decreasing non-specific uptake by cardiac tissue. Abdelkawi et al. [140] further highlights how modification strategies such as polymer coatings, functional group attachment and bioconjugation with targeting ligands improve target specificity, reducing systemic toxicity and enhanced therapeutic efficacy.

7.1.2. Biodegradable nanoparticles

Employing biodegradable materials such as poly (lactic-co-glycolic acid) (PLGA), liposomes, or dendrimers that degrade into non-toxic metabolites provides biocompatibility, long term stability, high mechanical strength and low toxicity. Controlled release formulations can minimize peak plasma concentrations, decreasing acute cardiotoxicity risk.

7.2. Co-delivery of cardio-protective agents

Encapsulating antioxidants (e.g., curcumin, resveratrol), anti-inflammatory agents, or mitochondrial protectants within NPs can simultaneously enhance anticancer efficacy and shield cardiac cells from oxidative and inflammatory damage [58]. For example, Radeva et al. [141] developed a lipid-polymer hybrid nanoparticle system that co-encapsulates Doxorubicin (a potent chemotherapeutic with known cardiotoxicity) with Resveratrol (a cardioprotective antioxidant). This was shown to preserve the anticancer efficacy, alleviate the cardiotoxicity and neurotoxicity related to doxorubicin and improved overall safety profile.

7.3. Biomimetic nanoparticles

Biomimetic NPs have emerged as a strategy to improve biocompatibility and reduce immune-mediated toxicity by cloaking synthetic cores with cell-derived membranes, thereby presenting a controlled biological interface. Red blood cell membrane coating is the most established approach and confers prolonged circulation by transferring CD47, which engages SIRPα on macrophages to inhibit phagocytic clearance [142]. By limiting rapid recognition and clearance by phagocytes, cell-membrane cloaking (e.g., RBC membrane coating) prolongs nanoparticle circulation and alters early blood–particle interactions, which is relevant to cardiotoxicity because complement activation is a major trigger of acute infusion reactions (CARPA) to several nanomedicines**.** Complement activation by nanoparticles can drive inflammatory mediator release (e.g., C3a/C5a-associated cytokine responses in human whole blood), creating a plausible pathway for acute cardiopulmonary stress in susceptible patients [143]. While preclinical studies consistently show reduced immune clearance and improved targeting relative to uncoated NPs, translational challenges remain, including membrane sourcing and standardization, preservation of protein orientation and function, and regulatory evaluation of complex bio-synthetic hybrids.

7.4. Personalized nanomedicine approaches

Personalizing nano-enabled therapy requires integrating baseline cardiovascular risk, early injury markers, and exposure modelling to minimize cardiotoxicity while preserving efficacy. The 2022 ESC cardio-oncology guidelines endorse structured baseline risk assessment (e.g., HFA-ICOS) and risk-adapted surveillance using cardiac imaging and biomarkers, supporting individualized monitoring intensity rather than uniform schedules [114]. Pharmacogenomic variation can further stratify susceptibility to cardiotoxic injury. For example, the GSTM1 null genotype was associated with increased odds of anthracycline-related cardiomyopathy in childhood cancer survivors, illustrating how inherited differences in detoxification/oxidative-stress pathways can identify higher-risk subgroups who may benefit from modified regimens and closer follow-up [144].

Mechanistically informed modeling is also relevant for nanoparticles because exposure is governed by size/surface-dependent uptake and mononuclear phagocyte system sequestration rather than simple linear kinetics. Recent work highlights the expanding role of PBPK models for nanomaterials, including explicit representation of phagocytosis as a dominant determinant of organ exposure, and PBPK frameworks have been calibrated to reproduce multi-organ nanoparticle biodistribution in vivo [138]. Together, these approaches support a pragmatic “personalized” pathway in which (i) baseline clinical risk and prior cardiotoxic exposure determine monitoring intensity and preventive therapy, and (ii) nanoparticle-specific PBPK modelling is used to anticipate patient-level cardiac exposure and optimize dose/schedule before escalation to large trials.

Table 5 summarises six key nanomedicine strategies to mitigate cardiotoxicity, including surface modification, biodegradable materials, co-delivery of cardioprotectants, stimuli-responsive release systems, biomimetic coatings, and personalised nanomedicine approaches, each offering distinct mechanisms for enhancing cardiac safety whilst maintaining therapeutic efficacy.

Table 5
Nanomedicine Strategies to Mitigate Cardiotoxicity.

Strategy	Description	Examples	Benefits
Surface modification and targeting [140]	PEGylation,ligand conjugation	PEGylated liposomes, antibody-targeted NPs	Reduced immune clearance, enhanced tumor specificity
Biodegradable materials [145]	Use of PLGA, liposomes, dendrimers	PLGA-based NPs, liposomal doxorubicin	Reduced long-term toxicity, controlled release
Co-delivery of cardioprotectants [146]	Encapsulation of antioxidants, anti-inflammatory agents	Liposomes with dexrazoxane and doxorubicin	Dual action: tumor killing and cardioprotection
Stimuli-responsive release [147]	pH/redox/enzyme-triggered drug release	pH-sensitive polymeric NPs	Minimized systemic exposure
Biomimetic coatings [148]	Cell membrane cloaking	Platelet membrane-coated NPs	Immune evasion, decreased inflammation
Personalized nanomedicine [149]	Risk-adapted design and dosing	Patient-specific modelling and biomarker use	Optimized efficacy and safety

8. Future directions and conclusions

8.1. Future directions

The convergence of nanotechnology, cardio-oncology, and precision medicine presents unprecedented opportunities to develop safer, more effective cancer therapies. However, realizing this potential requires coordinated efforts across multiple interconnected domains. Table 6 provides a strategic framework mapping key research priority, specific actions, responsible stakeholders, expected timelines, and measurable outcomes.

8.1.1. Development of Predictive Models and Biomarkers

Advancing predictive in vitro and in vivo models that closely replicate human cardiac physiology and nanoparticle interactions is crucial. Integration of multi-omics approaches, such as genomics, proteomics, metabolomics and artificial intelligence can facilitate discovery of sensitive and specific biomarkers for early NP-induced cardiotoxicity [137,138].

8.1.2. Personalized nanomedicine and precision cardio-oncology

Leveraging patient-specific data, including genetic predispositions, existing cardiac function, and comorbidities, will allow for customized nanoparticle design and dosing. Real-time monitoring via wearable technologies and biomarker panels may enable dynamic risk assessment and intervention.

8.1.3. Engineering safer nanoparticles

Future nanomedicine design should prioritize biodegradable and biomimetic materials that minimize immunogenicity and off-target effects. Multifunctional NPs capable of delivering therapeutic agents alongside cardioprotective molecules and responsive to tumor-specific stimuli hold great promise [146].

8.1.4. Regulatory and collaborative frameworks

There is a need for harmonized regulatory guidelines specifically addressing nanoparticle cardiotoxicity. Enhanced collaboration among oncologists, cardiologists, toxicologists, material scientists, and regulatory bodies will accelerate safe translation from bench to bedside.

8.2. Role of artificial intelligence in predicting and managing nanoparticle cardiotoxicity

8.2.1. Predictive modelling of cardiotoxicity

Computational modelling, including machine learning (ML) and artificial intelligence (AI), is increasingly applied to predict NP toxicity using physicochemical descriptors (e.g., size, surface charge, composition), pharmacokinetic behavior, and preclinical toxicity data. ML and read-across/QSAR approaches are increasingly used to predict NP hazard from physicochemical descriptors (e.g., size, surface chemistry, ζ-potential) and experimental biointeraction/toxicity data, providing an evidence base for prioritising materials before extensive in vivo testing. A representative open model family is Nano-Lazar, which performs read-across toxicity predictions using calculated and measured nanoparticle properties [152]. A recent systematic review of AI tools for nanoparticle toxicity similarly reports frequent use of Random Forest and support vector machines across published studies, supporting feasibility of ML-based prediction (though most models are not endpoint-specific to the heart) [153].

In parallel, risk-prediction models integrating clinical variables, including baseline cardiovascular disease, prior exposure to cardiotoxic therapies, and cardiac biomarkers are already established in cardio-oncology and outperform reliance on left ventricular ejection fraction alone for early detection of therapy-related cardiac dysfunction [154]. Although, external validation is still limited. Nonetheless, extending these approaches to nanomedicine by combining clinical risk stratification with NP-specific ML models represents a plausible pathway for anticipating cardiotoxic risk.

8.2.2. AI-enhanced imaging and monitoring

High-dimensional cardio-oncology data from echocardiography, ECG and cardiac MRI (CMR) can be analysed with machine-learning and deep-learning methods to detect or predict cardiotoxicity beyond conventional visual interpretation. A recent systematic review of AI in cardio-oncology imaging (echocardiography and CMR) concluded that published studies consistently report improved discrimination of cancer therapy-related cardiotoxicity risk, while also noting the evidence base is still small and heterogeneous [155].

In echocardiography, interpretable ML using radiomics features extracted from baseline studies has been used to predict later chemotherapy-related EF decline (a cardiotoxicity definition) in clinical cohorts [156]. In parallel, AI models applied to baseline ECG have been shown to predict future cancer therapy-related cardiac dysfunction in patients receiving cardiotoxic chemotherapy, indicating that algorithms can capture latent risk not evident on routine interpretation [157]. For CMR, deep-learning tools can automate segmentation and analysis of T1/T2 mapping (parametric tissue characterization) with performance comparable to expert delineation, enabling more scalable monitoring of subtle myocardial changes where manual workflows are limiting [158]. Overall, the strongest current evidence supports AI as a way to standardize and sensitize detection of early cardiotoxicity signals (particularly when combined with established surveillance markers such as strain, troponin, and CMR mapping), but widespread clinical deployment still depends on external validation and demonstration of benefit across diverse scanners, sites, and treatment regimens.

8.2.3. Integration with 'Digital Twin' platforms

The concept of a digital twin, a virtual replica of a patient integrating omics data, imaging, NP pharmacology, and real-time monitoring, is being explored in cardio-oncology [159]. Such platforms could simulate patient responses to different NP-based therapies, enabling adaptive treatment planning and improved cardiac safety.

Table 6
Strategic Framework for Future Nanomedicine Cardiotoxicity Research and Translation.

Research Priority	Specific Actions	Key Stakeholders	Timeline	Expected Outcomes	Key Interdependencies
Predictive Models & Biomarkers [136,138]	• Develop PBPK frameworks for nanoparticles that explicitly model saturable phagocytosis and organ sequestration • Validate human cardiac organoid/microtissue platforms for cardiotoxicity screening, including particle/toxin responses • Develop circulating miRNA/EV biomarker pipelines for early/late cardiotoxicity (anthracycline examples)	Academia, Industry, Regulatory agencies	2–5 years	• More human-relevant early signals • Improved mechanistic attribution • Better trial enrichment	Requires standardized NP characterization + curated datasets
Personalized Nanomedicine & Precision Cardio-Oncology [114,136,138]	• Implement risk-adapted surveillance pathways (imaging/ biomarkers) consistent with cardio-oncology guidance • Combine with NP-specific PBPK simulations to anticipate organ exposure variability • Use EV/miRNA and other biomarker dynamics to trigger early intervention in high-risk groups (proof-of-concept in doxorubicin settings)	Clinicians, Bioinformaticians, Industry	3–7 years	• Risk-stratified monitoring • earlier injury detection • individualized dose/ schedule exploration	Depends on validated biomarkers + interoperable data systems
Next-Generation Safe Nanoparticle Design [142,150]	• Advance “bio-interface control” strategies (e.g., cell-membrane cloaking) that alter blood interactions and immune recognition • Develop biodegradation/biotransformation-informed designs and test in human-relevant cardiac systems	Materials scientists, pharma, synthetic biologists	5–10 years	• Lower off-target toxicity risk • Improved therapeutic index • Clearer structure-toxicity relationships	Requires harmonized characterization + translation models
Regulatory Harmonization & Standardization [126,127,128]	• Expand NP-specific quality/characterization expectations in line with regulatory guidance: physicochemical characterization and PK/BE expectations for complex nanosystems • Support measurement standardization (e.g., nanoparticle size distribution methods)	FDA, EMA, OECD, Industry consortia	2–4 years	• More consistent submissions • Clearer comparability expectations • better post-market interpretability	Foundation for translation + comparability assessments
Clinical Implementation & Infrastructure [151]	• Build multidisciplinary cardio-oncology care pathways and registries suitable for tracking cardiac outcomes in modern therapies	Health systems, societies, payers	3–6 years	• Standardized surveillance • Improved access and consistency • Real-world signal capture	Requires validated tests + reimbursement + data infrastructure

Large initiatives such as the Living Heart Project are advancing patient-configurable virtual heart models intended to support testing and decision-making in cardiovascular applications (including regulatory-facing virtual evidence), providing a technical foundation that could be adapted for cardio-oncology safety questions [160]. In parallel, digital-twin approaches are already being deployed for continuous monitoring use-cases: the EU-funded ARCHANGEL "Checkpoint Cardio" program explicitly describes building a personalised digital twin using advanced wearables for real-time detection of deterioration, a model that is conceptually relevant for early identification of cardiotoxic trajectories during treatment [161]. Beyond cardiovascular disease, EU projects such as CERTAINTY are developing "virtual twins" for personalised cancer immunotherapies, underscoring translational momentum for twin-style decision support in oncology settings even though cardiotoxicity-specific validation remains limited [162].

For NPs cardiotoxicity specifically, the key translational barrier is that most "digital twin" work is still at the level of platform development or early deployment claims rather than prospective trials demonstrating improved cardiac outcomes in nanomedicine-treated cohorts. This makes rigorous external validation, transparent model governance, and regulatory clarity essential before twin-based dosing or monitoring recommendations can be relied upon in routine cardio-oncology practice.

9. Conclusion

Nanoparticle-based therapies have revolutionized cancer treatment by enabling targeted drug delivery, reducing systemic toxicity, and improving therapeutic outcomes. However, growing evidence suggests that these nanomedicines may exert unintended cardiotoxic effects through complex mechanisms involving oxidative stress, inflammation, mitochondrial dysfunction, protein corona-mediated biological identity transformation, and electrophysiological disruption. As cancer survival improves, the long-term cardiovascular safety of oncologic treatments, including nanotherapeutics, becomes an urgent priority.

This review has outlined the current understanding of nanoparticle-mediated cardiotoxicity, highlighting key mechanistic insights, including the critical role of the protein corona in determining biodistribution and cellular interactions, the influence of nanoparticle physicochemical properties and administration regimens, and patient-specific vulnerabilities. We have specifically examined cardiotoxicity profiles of clinically approved nanodrugs, linking mechanistic insights directly to patient care strategies. We have discussed the limitations of conventional cardiotoxicity assessment tools and emphasized the importance of emerging solutions, including advanced imaging, in vitro modelling, and biomarker discovery.

Critically, advances in nanotechnology also offer opportunities to mitigate these risks. Strategies such as covalent surface engineering, biodegradable materials, biomimetic coatings, co-delivery of cardioprotective agents, and stimuli-responsive systems represent promising approaches to enhance safety profiles. Furthermore, the integration of artificial intelligence into nanoparticle design, toxicity prediction, and patient monitoring has demonstrated measurable clinical successes, including validated predictive models, AI-enhanced imaging systems detecting subclinical toxicity, rationally designed safer nanoformulations, and functional digital twin platforms enabling personalized treatment optimization, collectively transforming the potential for personalized, risk-adapted cardio-oncology care.

Moving forward, we provide the following actionable recommendations for key stakeholders:

For Clinicians:

- Implement comprehensive baseline cardiovascular assessment for all patients receiving nanotherapies
- Adopt validated biomarker panels (troponin, NT-proBNP, miRNAs) for early toxicity detection
- Utilize AI-enhanced imaging interpretation when available to identify subclinical dysfunction
- Consider prophylactic cardioprotection (ACE inhibitors, beta-blockers) for high-risk patients
- Engage multidisciplinary cardio-oncology teams for complex cases

For Regulatory Agencies:

- Establish harmonized international guidelines for nanoparticle cardiotoxicity testing
- Mandate standardized characterization of protein corona composition in nanodrug submissions
- Require administration regimen optimization studies during clinical development
- Create regulatory pathways for AI-based prediction and monitoring tools
- Implement post-market surveillance systems tracking long-term cardiovascular outcomes

For Nanomaterial Designers and Industry:

- Prioritize surface engineering strategies minimizing problematic protein corona formation
- Incorporate cardiotoxicity prediction using validated in silico and in vitro models early in development
- Design biodegradable or rapidly-cleared nanoformulations to prevent cardiac accumulation
- Engineer stimuli-responsive systems limiting off-target cardiac exposure
- Conduct comparative studies with clinically approved nanodrugs to benchmark safety profiles
- Integrate AI-driven design optimization to explore safer nanoparticle architectures

For Researchers:

- Develop and validate standardized cardiac organoid and heart-on-a-chip screening platforms
- Discover and validate mechanism-specific biomarkers beyond troponin
- Create comprehensive databases linking nanoparticle properties to cardiac outcomes
- Establish protein corona composition-toxicity relationships
- Advance digital twin technologies for personalized risk assessment
- Conduct clinical studies evaluating cardioprotective co-delivery strategies

Only by aligning innovation with safety through coordinated multidisciplinary collaboration, rigorous standardization, and integration of cutting-edge technologies can we fully harness the therapeutic potential of nanomedicine while protecting cardiovascular health in cancer patients. The framework, examples, and recommendations provided in this review offer a roadmap for achieving this critical goal, ultimately ensuring that advances in nanotechnology translate into improved cancer survival without compromising cardiovascular outcomes.

CRediT authorship contribution statement

Emmanuel O. Oisakede: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Olawunmi O. Oyedeji:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Olabanke Florence Olawuyi:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation. **John Oluwatosin Alabi:** Writing – review & editing, Writing – original draft,

Methodology, Investigation. **Raphael Igbarumah Ayo Daniel:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **David B. Olawade:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Project administration.

Ethics statement

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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