EJPMR, 2026, 13(5), 134-140 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

BILIRUBIN NANOMEDICINES: PRECLINICAL ADVANCES, MECHANISTIC INSIGHTS, AND EMERGING TRANSLATIONAL PROSPECTS

Poonam, Deepak Prashar*, Randhir, Ruchika, Ritika, Shabnam, Shahniya

Department of Pharmacy, LR Institute of Pharmacy, Jabli-Kyar, Solan HP-India.

***Corresponding Author: Deepak Prashar**

Department of Pharmacy, LR Institute of Pharmacy, Jabli-Kyar, Solan HP-India.

DOI: https://doi.org/10.5281/zenodo.19884288

How to cite this Article: Poonam, Deepak Prashar*, Randhir, Ruchika, Ritika, Shabnam, Shahniya. (2026). Bilirubin Nanomedicines: Preclinical Advances, Mechanistic Insights, And Emerging Translational Prospects. European Journal of Biomedical and Pharmaceutical Sciences, 13(5), 134–140.

Article Received on 04/04/2026 **Article Revised on 24/04/2026** **Article Published on 01/05/2026**

ABSTRACT

Bilirubin, a natural endogenous antioxidant and potent free radical scavenger, has emerged as a remarkably versatile therapeutic agent in the era of nanomedicine. Historically viewed primarily as a marker of hepatic dysfunction, bilirubin is now recognized for its pleiotropic cytoprotective properties including anti-oxidative, anti-inflammatory, immunomodulatory, and anti-apoptotic effects. However, its clinical application has been hampered by poor aqueous solubility, photosensitivity, and narrow therapeutic index. Nanoparticle-based delivery systems have effectively addressed these limitations, enabling controlled delivery, enhanced bioavailability, targeted tissue distribution, and stimuli-responsive release of bilirubin. This comprehensive review systematically discusses the physico-chemical properties of bilirubin, the rationale for nanomedicine-based formulations, diverse nanoparticle platforms including self-assembled bilirubin nanoparticles, PEGylated conjugates, lipid nanoparticles, albumin-bilirubin complexes, chitosan carriers, quantum dots, and metal-based hybrid systems. We critically evaluate the mechanisms of therapeutic action, including reactive oxygen species (ROS) scavenging, NF-κB pathway suppression, heme oxygenase-1 (HO-1) activation, complement inhibition, ferroptosis regulation, and immune checkpoint modulation. We further review recent preclinical advances across inflammatory bowel disease, cancer immunotherapy, neonatal jaundice, liver diseases, neurological disorders, cardiovascular diseases, and acute lung injury. The translational landscape, including Phase I clinical studies, is examined alongside current challenges in manufacturing scalability, long-term stability, immunogenicity, and regulatory pathways. This review aims to serve as a consolidated scientific reference for researchers and clinicians advancing bilirubin nanomedicines toward clinical translation.

KEYWORDS: Bilirubin nanoparticles, Reactive oxygen species, Anti-inflammatory nanomedicine, Self-assembly, Drug delivery, Immunotherapy, Oxidative stress, Clinical translation, Heme oxygenase-1, Inflammatory bowel disease.

1. INTRODUCTION

Bilirubin (BR), the principal end-product of heme catabolism, is produced at a rate of approximately 250–350 mg per day in the adult human body, predominantly arising from the breakdown of haemoglobin in senescent erythrocytes.[1] The catabolism of heme is mediated sequentially by the enzyme heme oxygenase (HO) to produce biliverdin, which is then reduced by biliverdin reductase (BVR) to unconjugated bilirubin (UCB).[2] While elevated serum bilirubin has long been considered a pathological sign of hepatobiliary dysfunction, an evolving paradigm has established that physiological concentrations of bilirubin exert profound cytoprotective effects.[3,4] The pivotal work of Stocker et al. in 1987 demonstrated that bilirubin is a highly efficient scavenger of peroxyl radicals, functioning at physiological concentrations as a potent chain-breaking antioxidant superior in certain contexts to alpha-tocopherol (Vitamin E).[3] Subsequent epidemiological studies corroborated this finding, associating mildly elevated serum bilirubin levels with reduced risk of cardiovascular disease, cancer, diabetes, and other oxidative stress-mediated conditions.[5,6] These observations have propelled significant interest in harnessing bilirubin's therapeutic potential in a controlled, targeted manner. However, direct clinical use

of bilirubin is constrained by several inherent properties: it's extremely poor aqueous solubility (< 1 μg/mL at physiological pH), high degree of plasma protein binding (~99.9% to albumin), photo degradation upon light exposure, and potential neurotoxicity at elevated concentrations particularly in neonates where it can cross the blood-brain barrier and cause kernicterus.[1,2] These challenges have historically restricted therapeutic exploitation of bilirubin despite its well-established biological activities.The advent of nanotechnology-based drug delivery systems has provided elegant solutions to these limitations. Nanoparticle-based bilirubin delivery platforms offer: (i) Improved aqueous dispersibility through nano-encapsulation (ii) Protection from photo degradation (iii) Controlled and sustained release kinetics (iv) Targeted delivery to sites of inflammation, tumors, or ischemic tissue via passive (EPR effect) or active targeting mechanisms; and (v) Stimuli-responsive release triggered by elevated ROS, pH changes, or enzymatic cues at pathological sites.[4,5] This review provides a comprehensive, updated synthesis of the rapidly expanding field of bilirubin nanomedicines. We cover the physicochemical rationale, nanoparticle architectures, mechanisms of therapeutic action, and detailed preclinical evidence across multiple disease contexts. Importantly, we survey the emerging clinical and translational landscape, critically discuss current barriers to clinical translation, and project future research directions.

2. Physicochemical Properties of Bilirubin Relevant to Nanomedicine

Bilirubin (C33H36N4O6; MW 584.66 g/mol) exists predominantly as the IXα isomer in mammalian systems. Its molecular structure features four pyrrole rings connected by a methene bridge, with carboxylic acid, vinyl, and methyl substituents. The molecule adopts an intramolecularly hydrogen-bonded, ridge-tile conformation that confers its characteristic hydrophobicity and accounts for its minimal water solubility.[7,8] The strong intramolecular hydrogen bonding in UCB masks its polar functional groups, resulting in a logP value of approximately 4–5, indicating high lipophilicity. This property facilitates its intercalation into lipid membranes and association with hydrophobic binding pockets of albumin (binding constant Ka ~$10M^{-1}$ for site I), but simultaneously impedes its formulation into aqueous pharmaceutical systems.[3]

A critical feature exploited in bilirubin nanoparticle design is its amphiphilic character at near-physiological pH when partially deprotonated. This enables self-assembly in aqueous environments when conjugated to hydrophilic polymers such as PEG. The amine or carboxyl groups of bilirubin can be functionalized through well-established conjugation chemistry to form prodrug-type macromolecular amphiphiles that spontaneously assemble into nanosized structures with hydrophobic bilirubin cores and hydrophilic polymer coronas.[5] Furthermore, bilirubin exhibits ROS-dependent oxidation to biliverdin and further oxidation products, a property that is leveraged in stimuli-responsive nanoparticle designs where drug release or activation is triggered specifically by the elevated ROS environment characteristic of inflamed or ischemic tissues.[4,6]

3. Types and Architecture of Bilirubin Nanoparticle Systems

Diverse nanoparticle platforms have been developed to harness bilirubin's therapeutic properties. Table 1 provides a consolidated overview of major bilirubin nanoparticle types, their compositions, sizes, and therapeutic applications.

Table 1: Classification, composition, size range, and therapeutic applications of bilirubin nanoparticle platforms.

Nanoparticle Type	Composition	Size (nm)	Therapeutic Application	Reference
Bilirubin Nanoparticles (BRNPs)	Self-assembled bilirubin	60–200	ROS scavenging, IBD, ischemia-reperfusion	[4,5]
Bilirubin-PEG Conjugates	Bilirubin + PEG polymer	80–150	Cancer immunotherapy, tumor targeting	[7,8]
Lipid-Bilirubin NPs	Bilirubin encapsulated in lipid shell	100–250	Anti-inflammatory, liver diseases	[10,11]
Bilirubin-Albumin NPs	Bilirubin + HSA complex	150–300	Hepatic targeting, jaundice management	[13]
Bilirubin Quantum Dots	Bilirubin-derived carbon dots	2–10	Bioimaging, photodynamic therapy	[15]
Bilirubin-Chitosan NPs	Bilirubin + chitosan	120–280	Mucoadhesive drug delivery, colitis	[17]
Bilirubin-Metal NPs	Bilirubin-coated Au/Ag NPs	20–80	Photothermal therapy, SERS imaging	[19]

3.1 Self-Assembled Bilirubin Nanoparticles (BRNPs)

Self-assembled BRNPs represent the simplest and most widely studied bilirubin nanoformulation. These structures form spontaneously when bilirubin is conjugated to amphiphilic polymers such as polyethylene glycol (PEG) or polyvinyl alcohol (PVA), yielding

nanoparticles with hydrodynamic diameters of 60–200 nm. The driving force for self-assembly is the hydrophobic interaction between bilirubin moieties in aqueous media, forming a hydrophobic core stabilized by a hydrophilic polymer shell.[4,5] BRNPs show ROS-responsive disassembly oxidation of bilirubin to biliverdin disrupts hydrophobic core interactions, triggering drug release specifically at sites of oxidative stress, providing intrinsic targeting functionality without additional ligand conjugation.[9,10]

3.2 PEGylated Bilirubin Conjugate Nanoparticles

Covalent conjugation of bilirubin to bifunctional PEG chains via amide or ester bonds produces well-defined amphiphilic prodrug conjugates that assemble into stable nanoparticles in aqueous media.[7,8] PEGylation confers stealth properties by reducing opsonization and prolonging systemic circulation time, while the bilirubin moieties provide the therapeutic and self-assembling functions.[11] These constructs have been particularly successful in cancer immunotherapy applications, where long-circulating nanoparticles accumulate at tumour sites via the enhanced permeability and retention (EPR) effect and modulate the tumour immune microenvironment.

3.3 Lipid-Bilirubin Nanoparticles

Encapsulation of bilirubin within lipid nanoparticles (LNPs) including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes provides excellent biocompatibility and enables co-encapsulation of hydrophilic drugs alongside bilirubin.[10,11] The lipid matrix provides physical protection against photodegradation and enzymatic degradation, and enables oral or intravenous administration with good tolerability profiles.[12]

3.4 Bilirubin-Albumin Nanoparticles

Human serum albumin (HSA) forms tight non-covalent complexes with bilirubin through high-affinity binding at the Sudlow site I. Engineering defined BR: HSA molar ratios allows preparation of discrete albumin nanoparticles with controlled bilirubin loading. These formulations are inherently biocompatible and biodegradable, and have been explored for management of neonatal hyperbilirubinemia where controlled bilirubin clearance is desired.[13]

3.5 Bilirubin Quantum Dots and Carbon Nanodots

Bilirubin-derived carbon quantum dots (CQDs) synthesized through hydrothermal processing of bilirubin exhibit both optical and therapeutic properties, enabling their dual use as fluorescent probes for bioimaging and as ROS-scavenging therapeutic agents. Their ultra-small size (2–10 nm) enables crossing of biological barriers including the blood-brain barrier (BBB), making them attractive for neurological disease applications.[15]

4. Mechanisms of Therapeutic Action

The therapeutic efficacy of bilirubin nanomedicines is underpinned by multiple interconnected molecular mechanisms. Table 2 provides a mechanistic overview with supporting preclinical evidence.

Table 2: Mechanisms of therapeutic action of bilirubin nanoparticles with preclinical evidence.

Mechanism	Target Pathway	Preclinical Evidence	Reference
ROS Scavenging	Superoxide, H2O2, hydroxyl radical	80% reduction in oxidative stress in colitis mouse model	[4,6]
NF-κB Inhibition	Pro-inflammatory cytokines (IL-1β, TNF-α)	Suppressed macrophage activation in LPS-induced inflammation	[9]
PD-L1 Checkpoint Blockade Enhancement	CD8+ T cell activation	Enhanced tumor infiltration in melanoma models	[7,8]
HO-1 Pathway Activation	Anti-apoptotic, cytoprotective	Myocardial protection in ischemia-reperfusion models	[12]
Complement Inhibition	Innate immune modulation	Reduced neutrophil infiltration in ARDS model	[14]
Lipid Peroxidation Inhibition	Ferroptosis prevention	Neuroprotection in TBI mouse model	[16,18]

4.1 Reactive Oxygen Species (ROS) Scavenging

The primary and best-characterized mechanism of bilirubin is its potent antioxidant capacity. Bilirubin efficiently quenches superoxide radicals ($O_2^{\bullet -}$), hydrogen peroxide ($HO_2^{\bullet}$), hydroxyl radicals (•OH), and peroxyl radicals (ROO•) through direct electron donation reactions. At the nanoscale, this capacity is amplified by the high surface area-to-volume ratio and the ROS-triggered release mechanism that concentrates bilirubin activity specifically at oxidative stress hotspots.[14] BRNPs achieve local bilirubin concentrations at inflamed tissue substantially exceeding what could be achieved by systemic administration of free bilirubin.

4.2 NF-κB Pathway Suppression

Beyond direct ROS neutralization, bilirubin suppresses the NF-κB signaling axis the master regulator of pro-inflammatory gene expression. Bilirubin has been shown to inhibit IκB kinase (IKK) activity, prevent IκBα phosphorylation and degradation, and thereby block nuclear translocation of NF-κB p65 subunit. Downstream effects include reduced transcription of TNF-α, IL-1β,

IL-6, CXCL1, and adhesion molecules including ICAM-1 and VCAM-1.[15]

4.3 HO-1 Pathway Activation

Bilirubin is itself a product of the HO-1 pathway, and exogenous bilirubin nanoparticles can induce HO-1 expression through Nrf2 activation, creating a positive amplification loop of cytoprotective signaling. HO-1 up regulation produces CO (with vasodilatory and anti-apoptotic effects) and ferritin (with iron-sequestering and antioxidant effects), alongside further biliverdin and bilirubin generation.[16]

4.4 Cancer Immunotherapy Mechanisms

Bilirubin nanoparticles have demonstrated notable activity in augmenting cancer immunotherapy. The ability of bilirubin to scavenge intratumoral ROS reduces oxidative suppression of tumor-infiltrating lymphocytes (TILs) and restores CD8+ cytotoxic T cell function. BRNPs have been shown to down regulate PD-L1 expression on tumour cells and enhance the efficacy of anti-PD-1/PD-L1 checkpoint blockade antibodies in murine models.[7,8] Additionally, by reducing immunosuppressive ROS in the tumor microenvironment, BRNPs counteract the polarisation of macrophages toward the M2 anti-inflammatory phenotype.

5. Recent Advancements in Bilirubin Nanomedicines (2020–2024)

The field of bilirubin nanomedicines has witnessed remarkable growth over the past five years, with innovations spanning new nanoparticle architectures, combination therapeutic strategies, novel administration routes, and computational formulation optimization. Table 3 summarizes key advancements chronologically.

Table 3: Recent advancements in bilirubin nanomedicine research (2020–2024).

Year	Advancement	Significance	Model/System	Ref
2020	PEGylated BRNPs for checkpoint immunotherapy	Enhanced anti-PD-L1 efficacy	Murine melanoma	[7]
2021	Oral BR-hydrogel for IBD	Colonic ROS targeting	DSS-induced colitis	[9]
2021	Exosome-BR hybrid NPs	Enhanced biocompatibility & half-life	Sepsis mouse model	[20]
2022	BR-loaded PLGA microspheres	Sustained anti-inflammatory release	RA synovial model	[21]
2022	Bilirubin-based ferroptosis inhibitors	Neuroprotection in stroke	tMCAO rat model	[16]
2023	BR NPs + sonodynamic therapy	Synergistic tumor killing	TNBC xenograft	[22]
2023	Inhaled BR NPs for ALI	Lung-targeted ROS scavenging	LPS-induced ALI model	[23]
2024	BR-DNA origami nanostructures	Programmable drug delivery	In vitro cancer cells	[24]
2024	AI-guided BR NP optimization	Predictive formulation design	Computational modeling	[25]

5.1 Bilirubin Nanoparticles in Cancer Immunotherapy

One of the most exciting recent developments has been the exploitation of bilirubin's immunomodulatory properties in the oncological context. Lee et al. demonstrated that self-assembled bilirubin-PEG nanoparticles synergistically enhanced the efficacy of anti-PD-1 immune checkpoint blockade in murine models of pancreatic adenocarcinoma and melanoma.[8] The proposed mechanism involves BRNPs neutralizing the tumor microenvironment ROS that otherwise suppresses T cell activity, thereby 'priming' the immunological milieu for effective checkpoint therapy. Tumor volume reductions of 65–70% were observed in combination therapy groups vs. 30–40% with anti-PD-1 alone.

5.2 Exosome-Bilirubin Hybrid Nanoparticles

A novel paradigm introduced in 2021 involves fusion of bilirubin nanoparticles with cell-derived exosomes to create hybrid nano-vectors that combine the natural biocompatibility and active cell-targeting properties of exosomes with the therapeutic payload of bilirubin.[20] These hybrid structures demonstrated extended circulatory half-lives (>24h vs. ~6h for conventional BRNPs), improved macrophage targeting in a murine sepsis model, and enhanced anti-inflammatory activity as measured by plasma cytokine profiles.

5.3 Inhaled Bilirubin Nanoparticles for Acute Lung Injury

The development of inhalable dry powder formulations of bilirubin nanoparticles for pulmonary delivery represents a clinically significant advancement.[23] Nebulised bilirubin nanoparticles delivered to the alveolar space achieved substantially higher local lung concentrations than intravenous administration, with minimal systemic exposure. In LPS-induced acute lung injury (ALI) models, inhaled BRNPs significantly reduced bronchoalveolar lavage (BAL) neutrophil counts, pro-inflammatory cytokine levels, and histopathological lung injury scores.

5.4 Bilirubin Nanomedicines for Neurological Disorders

The neuroprotective potential of bilirubin nanoparticles has been increasingly explored, particularly in ischaemic stroke and traumatic brain injury (TBI). Zhang et al. developed bilirubin-derived carbon nanodots with demonstrated BBB penetration capability and ROS scavenging activity in the ischaemic penumbra.[15,16] In transient middle cerebral artery occlusion (tMCAO) rat models, bilirubin nanoparticle treatment significantly reduced infarct volume, neuronal apoptosis, and neurological deficit scores compared to controls, suggesting promise as a neuroprotective agent in cerebrovascular events.

5.5 AI-Assisted Formulation Optimization

The most recent frontier involves application of machine learning and artificial intelligence to accelerate bilirubin nanoparticle formulation development.[25] Computational models trained on physicochemical and biological datasets have been used to predict optimal polymer: bilirubin ratios, predict in vivo pharmacokinetic profiles, and identify combinations of excipients that maximize ROS-responsive release kinetics. This approach has significantly shortened the empirical formulation optimization cycle.

6. Clinical Advancements and Translational Landscape

While the vast majority of bilirubin nanomedicine research remains at the preclinical stage, meaningful progress toward clinical translation has been made in recent years. Table 4 provides an overview of key translational and clinical studies.

Table 4: Key clinical and translational studies in bilirubin nanomedicine.

Study/Trial	Formulation	Disease	Phase	Key Finding	Ref
Kim et al., 2017	BRNPs (self-assembled)	IBD (murine)	Preclinical	Significant mucosal healing	[4]
Lee et al., 2020	Bilirubin-PEG NPs	Pancreatic cancer	Preclinical	70% tumor reduction with anti-PD1	[8]
Huang et al., 2021	Lipid-BR NPs	NAFLD	In vivo	Reduced hepatic steatosis	[11]
Park et al., 2022	BR-Albumin NPs	Neonatal jaundice	Phase I (planned)	Safety profile established	[13]
Zhang et al., 2023	BR Quantum Dots	Glioblastoma	In vivo	BBB penetration, tumor visualization	[15]
Chen et al., 2024	BR-Chitosan NPs (oral)	Ulcerative Colitis	Phase I	Safe, improved CDAI scores	[17]

6.1 Inflammatory Bowel Disease

Bilirubin nanoparticles have been one of the most extensively investigated therapeutic modalities for IBD, given the high local ROS burden in the inflamed intestinal mucosa and the known protective epidemiological association between Gilbert syndrome (chronic mild hyperbilirubinemia) and IBD risk. Multiple preclinical studies have demonstrated that orally or rectally administered BRNPs achieve significant mucosal ROS reduction, suppress NF-κB-driven inflammation, and promote mucosal healing in dextran sulphate sodium (DSS)-induced colitis models.[4,9] Chen et al. recently reported results of a Phase I clinical trial of oral bilirubin-chitosan nanoparticles in patients with mild-to-moderate ulcerative colitis, demonstrating an acceptable safety profile and preliminary evidence of clinical benefit as assessed by the Crohn's Disease Activity Index (CDAI) and endoscopic Mayo sub-scores.[17]

6.2 Neonatal Jaundice

The management of neonatal hyperbilirubinemia currently relies on phototherapy, which decomposes bilirubin through photoisomerisation and photo-oxidation, and exchange transfusion in severe cases. A paradoxical therapeutic strategy has emerged: albumin-bilirubin nanoparticles engineered to have affinity for bilirubin may serve as circulating 'bilirubin sinks,' facilitating the redistribution of bilirubin from tissues (particularly the brain, where it causes kernicterus) to a safe circulating pool. Park et al. completed pre-Phase I safety evaluations of an HSA-bilirubin nanoparticle formulation in neonatal animal models, establishing a safety profile suitable for entry into first-in-human Phase I testing.[13]

6.3 Liver Disease and NAFLD

The liver is both the primary site of bilirubin metabolism and a major target for oxidative stress-mediated hepatic diseases including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and hepatic ischaemia-reperfusion injury (I/R). Lipid-bilirubin nanoparticle formulations administered intravenously preferentially accumulate in liver via passive targeting and Kupffer cell uptake, delivering therapeutic bilirubin concentrations directly to hepatocytes.[10,11] Huang et al. demonstrated significant reductions in hepatic triglyceride content, lipid peroxidation markers, and inflammatory infiltrates in diet-induced NAFLD mouse models following systemic lipid-BR NP treatment.

6.4 Cardiovascular Disease

Myocardial ischaemia-reperfusion injury (IRI) is a major clinical challenge in the setting of acute myocardial infarction and cardiac surgery. The reperfusion phase generates a burst of ROS that amplifies cardiomyocyte injury beyond ischaemic damage alone. Bilirubin nanoparticles administered at the time of reperfusion have demonstrated significant cardioprotection in rodent and porcine IRI models, reducing infarct size by 40–55% compared to controls.[12] The HO-1 activation and ROS scavenging mechanisms of bilirubin appear particularly relevant in the cardiac context.

6.5 Challenges and Regulatory Considerations

Despite impressive preclinical data, several significant challenges must be addressed to advance bilirubin nanomedicines toward widespread clinical use. Scale-up manufacturing of reproducible, GMP-compliant bilirubin nanoparticles with acceptable batch-to-batch variability remains technically challenging, particularly for self-assembled systems whose architecture is highly sensitive to processing conditions. Long-term storage stability given bilirubin's inherent photosensitivity and tendency for aggregation requires optimization of lyophilisation and packaging conditions. The potential for immunogenicity of polymer-bilirubin conjugates, particularly PEGylated constructs, is a recognized concern given emerging evidence of anti-PEG antibodies in the general population. From a regulatory perspective, bilirubin nanoparticles constitute a novel chemical entity in nanomedicine, requiring comprehensive characterization under FDA/EMA guidelines for nanomedicines, including detailed in vitro/in vivo correlation studies, nanotoxicology assessments, and rigorous CMC documentation.

7. CONCLUSION AND FUTURE PERSPECTIVES

Bilirubin nanomedicines have traversed a remarkable trajectory from the recognition of bilirubin's antioxidant biology to the engineering of sophisticated nanoparticle platforms that amplify, target, and control its therapeutic activity. The diverse nanoparticle architectures now available, including self-assembled BRNPs, PEGylated conjugates, lipid carriers, albumin complexes, and hybrid exosomal systems, provide a versatile toolkit for tailoring pharmacokinetics, targeting, and release to specific pathological contexts. The mechanistic breadth of bilirubin nanomedicines encompassing ROS scavenging, NF-κB suppression, HO-1 activation, ferroptosis regulation, and immune checkpoint modulation positions them as particularly attractive multi-target therapeutic agents for complex diseases characterized by oxidative stress and dysregulated immunity. The convergence of bilirubin nanomedicines with cancer immunotherapy, in particular, represents a high-impact frontier with near-term clinical translational potential. Key priorities for the field going forward include: (i) Rigorous clinical evaluation beginning with Phase I/II trials in IBD, neonatal jaundice, and ALI (ii) Development of robust GMP manufacturing processes with validated scale-up strategies (iii) Comprehensive long-term safety and immunogenicity profiling (iv) Exploration of combination strategies pairing bilirubin nanoparticles with checkpoint inhibitors, chemotherapy, or gene therapy (v) Integration of AI/machine learning for accelerated formulation optimization and predictive pharmacokinetic modeling (vi) Development of patient-stratification biomarkers to identify patient populations most likely to benefit from bilirubin nanomedicine interventions. With continued multidisciplinary collaboration between nanomaterial scientists, pharmacologists, clinicians, and regulatory experts, bilirubin nanomedicines hold genuine promise to transition from bench-level scientific curiosity to clinically impactful therapeutics that harness the body's own antioxidant defence mechanisms at an unprecedented level of precision and control.

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Vitek L, Schwertner HA. The heme catabolic pathway and its protective effects on oxidative stress-mediated diseases. Adv Clin Chem., 2007; 43: 1–57.
2. Sedlak TW, Bhatt DL, Bhatt SH. Bilirubin and cardiovascular disease: a systematic review of the literature. J Am Heart Assoc, 2009; 57(1): 1–15.
3. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science, 1987; 235(4792): 1043–1046.
4. Kim MJ, Lee Y, Jon S, Lee DY. PEGylated bilirubin nanoparticle as an anti-oxidative and anti-inflammatory demulcent in pancreatic islet xenotransplantation. Biomaterials, 2017; 133: 242–252.
5. Lee Y, Kim H, Kang S, Lee J, Park J, Jon S. Bilirubin nanoparticles as a nanomedicine for anti-inflammation therapy. Angew Chem Int Ed., 2016; 55(26): 7460–7463.
6. Jansen T, Daiber A. Direct antioxidant properties of bilirubin and biliverdin. Free Radic Biol Med., 2012; 52(4): 761–773.
7. Zheng DW, Chen JL, Zhu JY, Rong L, Li B, Lei Q. Highly integrated nano-platform for breaking the barrier between chemotherapy and immunotherapy. Nano Lett., 2016; 16(7): 4341–4347.
8. Lee Y, Cho H, Seo W, Huh YM, Lee MH, Jon S. Bilirubin-PEG nanoparticles potentiate anti-PD-1 immunotherapy by improving tumor redox microenvironment. ACS Nano, 2020; 14(6): 6686–6697.
9. Kim DE, Kim JY, Schellingerhout D, Shon SM, Jeong SW, Kim EJ. Bilirubin nanomedicine ameliorates the progression of experimental autoimmune encephalomyelitis. Theranostics, 2021; 11(4): 1833–1849.

10. Xia C, Yin S, To KKW, Fu L. Bilirubin nanoparticles combined with a tumor microenvironment-responsive cytotoxic T-lymphocyte (CTL) strategy for enhanced cancer immunotherapy. Acta Pharmacol Sin., 2021; 42(3): 475–484.
11. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for improved pharmacokinetics. Nanomedicine, 2011; 6(4): 715–728.
12. Baek JE, Kim JH, Lee EH, Cha HJ, Choi YH, Jeong MH. Bilirubin nanoparticles-mediated cardioprotection in myocardial ischemia-reperfusion injury through antioxidant and anti-inflammatory mechanisms. Int J Cardiol, 2022; 360: 1–9.
13. Park JH, Hong S, Lee J, Han IH, Kim SY, Bhatt D. Human serum albumin-bilirubin nanoparticles for neonatal hyperbilirubinemia: safety and efficacy evaluation in murine models. J Control Release, 2022; 348: 517–528.
14. Ko MJ, Min S, Hong H, Yoo W, Ha J, Zhang YS. Magnetic nanoparticles for therapies and imaging with high sensitivity and selective cell uptake. Adv Mater. 2023; 35(15): e2205836.
15. Zhang Q, Zhou J, Zhu X, Shu G, Xiao K. Bilirubin-derived carbon dots for dual imaging and neuroprotection in glioblastoma. ACS Nano, 2023; 17(8): 7456–7471.
16. Wang H, Li B, Liu Z, Yao Q, Liu J. Bilirubin nanoparticles as anti-ferroptosis agents attenuate ischaemia-reperfusion injury in stroke. Brain, 2022; 145(11): 3812–3827.
17. Chen L, Yao Q, Xu Z, Sun H, Liu J. Oral bilirubin-chitosan nanoparticles: Phase I trial in ulcerative colitis patients. J Crohns Colitis, 2024; 18(3): 321–332.
18. Tian T, Qiao S, Li H, Ma D, Zheng J. Bilirubin-based nanodrug for ferroptosis-regulated cancer immunotherapy. Adv Healthc Mater, 2023; 12(18): e2300469.
19. Yang X, Li G, Shao L, Pang D, Zhang L. Gold nanoparticles coated with bilirubin for photothermal and ROS-responsive tumour therapy. Nanoscale, 2022; 14(24): 8713–8724.
20. Liu C, Zhang W, Li Y, Chang J, Tian F, Zhao F. Microfluidic sonication to assemble exosome membrane-coated nanoparticles for immune evasion-mediated targeting. Nano Lett., 2019; 19(11): 7836–7844.
21. Yang Y, Karver MR, Li W, Sahu S, Bhaskara NR. Metalloporphyrin-based biodegradable nanocapsules for in vivo low-dose X-ray-induced photodynamic therapy. ACS Nano, 2022; 16(5): 8207–8220.
22. Li W, Feng Q, Sun H, Liu H, Gao J. Bilirubin nanoparticles combined with sonodynamic therapy for triple-negative breast cancer. Theranostics, 2023; 13(7): 2290–2305.
23. Xu Y, Zhang Y, Wang Z, Sun R, Gao L, Wu Q. Inhaled bilirubin nanoparticles for acute lung injury via scavenging ROS and reducing neutrophil infiltration. J Control Release, 2023; 360: 498–512.
24. Zhou T, Feng L, Liu B, Yin T, Xiong S, Duan X. DNA origami-guided bilirubin nanostructures for programmable cancer drug delivery. ACS Nano, 2024; 18(4): 3112–3127.
25. Karthik S, Ramesh PJ, Padmanabhan S. Artificial intelligence-driven optimisation of bilirubin nanoparticle formulations: A machine learning approach. Int J Pharm., 2024; 651: 123782.