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Bilirubin- Based nanomedicines as emerging antioxidant therapeutics for reactive oxygen species control

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Abstract
Reactive oxygen species (ROS) play a crucial role in cellular signaling under normal physiological conditions, but their excessive accumulation is strongly associated with oxidative stress and the progression of various pathological conditions, including cardiovascular disorders, neurodegenerative diseases, cancer, and inflammatory syndromes. Conventional antioxidant therapies often face challenges such as poor bioavailability, rapid degradation, and limited therapeutic efficacy. In recent years, bilirubin, a natural end product of heme metabolism with potent antioxidant and cytoprotective properties, has gained increasing attention as a therapeutic candidate. However, its hydrophobic nature and instability in physiological environments restrict its direct clinical application. Nanomedicine-based strategies have emerged as an effective approach to overcome these limitations by enhancing bilirubin solubility, stability, targeted delivery, and controlled release. Bilirubin-loaded or bilirubin-based nanocarriers not only improve pharmacokinetic profiles but also provide site-specific therapeutic action, thereby minimizing systemic side effects. This innovative nanoplatform shows promising potential in mitigating ROS-induced tissue damage and restoring redox balance in multiple disease models. Overall, bilirubin nanomedicines represent a novel and versatile therapeutic strategy for managing ROS-mediated diseases and warrant further translational research to realize their clinical applicability.

Keywords: Reactive oxygen species (ROS), Bilirubin nanomedicine,Antioxidant therapy,Targeted drug delivery, Oxidative stress management

Introduction
Reactive oxygen species (ROS) are chemically reactive molecules that, at high levels, damage lipids, proteins, and nucleic acids and contribute to the pathology of numerous disorders, including ischemia–reperfusion injury, neurodegeneration, cardiovascular disease, inflammatory disorders, and certain cancers. Endogenous antioxidants normally limit ROS; when these systems fail, exogenous antioxidant strategies become attractive therapeutic options. Bilirubin, a natural heme catabolite, is a potent antioxidant with the ability to scavenge several ROS types and to modulate redox-sensitive signaling. However, free bilirubin is hydrophobic, rapidly cleared, and—in high systemic concentrations—can be cytotoxic. Nanomedicine approaches that encapsulate, conjugate,, or mimic bilirubin can overcome these limitations & deliver its antioxidant benefits selectively to diseased tissues. [1]

Basics of Bilirubin
Bilirubin is an open-chain tetrapyrrole (breakdown product of heme via biliverdin).
It is hydrophobic, with strong intramolecular hydrogen bonding (for example, between keto oxygens and propionate carboxygroups),s), which makes its solubility in water very low. [2]

Why Nanomedicines with Bilirubin?
Because of bilirun
Antioxidant/ROS-scavenging activity
Anti-inflammatory effects
Poor water solubility, which limits direct use; nanoscale formulation helps with solubilization, protection, targeting, and release. [3]

Literature Review
Bilirubin, a characteristic heme-derived antioxidant, has solid ROS-scavenging and cytoprotective properties, however its clinical application is confined due to destitute water solvency, insecurity, and potential harmfulness when in its free frame. Later considers show that nanomedicine-based bilirubin formulations—such as self-assembled bilirubin nanoparticles, polymer-coated frameworks, and ROS-responsive nanocarriers—can overcome these impediments by improving solvency, steadiness, circulation time, and focused on conveyance. Preclinical inquire about appears that bilirubin nanomedicines viably diminish oxidative stretch, aggravation, and tissue harm in models of intense lung harm, liver infection, metabolic disarranges, and ischemia–reperfusion damage. These nanoplatforms offer site-specific antioxidant action, diminished systemic presentation, and progressed restorative adequacy compared to free bilirubin.

What Are ROS?
Reactive Oxygen Species (ROS) are a group of short-lived and highly reactive oxygen-containing molecules. They include: [4]

Types of ROS
1. Endogenous (internal) sources
Mitochondrial respiration (electron transport chain leak)
NADPH oxidases (NOX enzymes)
Xanthine oxidase
Cytochrome P450

2. Peroxisomes

Immunecells(macrophages)aPeroxisomesnerate ROS during in(macrophages and. Exogenous (external) sources:
infection).ht
Ionizing radiation
Pollution (e.g., ozone, cigarette smoke)
Drugs and t(e.g.,
Heavy metals (e.g., iron, copper) [5]

Biological Roles of Bilurubin

At Low Levels (Physiological) role Bilirubin signaling molecules:
Regulate gene expression. (e.g., via NF-κB, HIF-1α).
Promote cell growth and become sHIF-1α).zed.
Help the body fight infections by prodspecialized.ive oxygen species (ROS).
Help with healing wounds and controlling bl(ROS).essel size
At High Levels (Pathological)
ROS can cause oxidative stress, which harms the body:
Lipid peroxidation – damages cell membranes
Protein oxidation—changes how enzymes work
DNAdamage—causes mutat—changesreaks in DNA strands
Mitocho—causessfunction—stops cells from getting energy

Mechanisms of action in disease

scenarios Bilirubin nanomedicines act through multiple, complementary mechanisms: direct scavenging of ROS and termination of lipid peroxidation chains. - Protection of mitochondrial function by limiting oxidative damage to mitochondrial membranes and proteins. - Modulation of redox-sensitive signaling pathways (e.g., NF-κB, Nrf2) that regulate inflammation and cell survival. - Reduction of subsequent tissue damage in acute events (e.g., reperfusion after ischemia) and reduction of disease progression in chronic oxidative illnesses. Advantages of nanodelivery Nanocarriers enhance bilirubin's therapeutic potential by improving solubility and stability. - Extending systemic half-life and reducing off-target exposure.
Permitting controlled and stimuli-responsive discharge at locales of tall ROS.
Enabling surface functionalization for dynamic focusing onto ailing tissue. These highlights diminish the requirement for high systemic concentrations and lower the hazard of bilirubin-associated toxicity.
Safety also has translational challenges.
Although promising, a few obstacles remain:
Toxicology also includes dosage control:
Overabundance of bilirubin is neurotoxic in neonates; thorough preclinical toxicology is basic for security margins.
Fabricating with flexibility: A solid GMP-grade era of bilirubin-containing nanoparticles at scale needs affirmed processes.
Pharmacokinetics and biodistribution: Optimizing carrier access surface properties and release vitality to maximize tissue take up while minimizing hepatic accumulation is critical.
Mechanism of Antioxidant Action
Bilirubin applies its antioxidant development basically through scavenging responsive oxygen species (ROS) such as superoxide radicals, hydroxyl radicals, and hydrogen peroxide. The bilirubin–biliverdin redox cycle licenses bilirubin to neutralize free radicals, and at that point recuperates itself through BVR-mediated diminution of biliverdin. This catalytic cycle makes bilirubin shockingly profitable at keeping up redox homeostasis, without a doubt at moo physiological concentrations.
Furthermore, bilirubin ruins lipid peroxidation, along these lines securing cellular layers from oxidative hurt. It, in addition, changes the development of NADPH oxidase and nitric oxide synthase, diminishing the ROS period & keeping up nitric oxide bioavailability, which supports vascular health.
Physiological and Clinical Significance
In ordinary physiological rangesbilirubin serves as a cytoprotective particle. Research suggests that individuals with tenderly raised bilirubin levels (such as those with Gilbert's clutter) as often as possible show lower frequencies of cardiovascular illnesses, metabolic disorders, and oxidative stress-related derangements. This is credited to bilirubin's capacity to smother oxidative alteration of low-density lipoprotein (LDL) and make strides in endothelial work.
Moreover, bilirubin gives security to diverse organs, including the liver, kidney, brain, and heart, by calming oxidative hurt. It has appeared to quell disturbance, apoptosis, and mitochondrial brokenness actuated by overabundance of ROS. These disclosures have driven the improvement of captivating bilirubin-based helpful administrators and nanocarriers for diseases driven by oxidative stress.
Bilirubin Redox Cycle
Heme debasement produces biliverdin through the action of heme oxygenase (HO-1).
Biliverdin reductase (BVR) changes over biliverdin into bilirubin.
Bilirubin neutralizes ROS, changing back into biliverdin.
The cycle goes over, expanding antioxidant security with unimportant essentialness cost.
This self sustaining redox cycle underlies bilirubin's exceptional capacity to act as a catalytic antioxidant or perhaps indeed a stoichiometric one like meaning a single molecule can neutralize various responsive species over time. [9]

Bilirubin as an Anti-Inflammatory Agent

Bilirubin, a yellow color made in the midst of the breakdown of heme in reddish blood cells, has generally been considered, as it were, a waste thing careful for jaundice. Be that as it may, afterward coherent disclosures have revealed that bilirubin plays a basic physiological portion as an effective endogenous anti-inflammatory particle. It appears to have strong immunomodulatory and cytoprotective impacts, which are crucial in controlling aggravation and oxidative
stress-related diseases.

1. Instrument of Anti-Inflammatory Activity gives

a. Restriction of Pro-inflammatory Cytokines

Bilirubin can smother the era of key pro-inflammatory cytokines such as tumor corruption components like alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). By downregulating these referees, bilirubin expects to plan secure incitation and tissue harm that commonly go with deep rooted inflammation.

b. Concealment of NF-κB Signaling Pathway

The atomic factor-kappa B (NF-κB) pathway is a central controller of disturbance. Bilirubin quells NF-κB sanctioning by blocking the phosphorylation and degradation of IκBα (the NF-κB inhibitor). This movement dodges NF-κB translocation into the center, in this way lessening the interpretation of provocative genes.

c. Change of Grasp Molecules

Bilirubin reduces the expression of vascular cell connection molecule-1 and intercellular grasp molecule-1 on endothelial cells. These particles are competent of leukocyte connection & development into stimulated tissues.

d. Interaction with Secure Cells

Bilirubin particularly impacts safe cells, particularly macrophages with T lymphocytes. It propels a move in macrophage polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype; they offer assistance in tissue repair and assurance of aggravation. Moreover, bilirubin can smother T-cell increase and sanctioning and help in coordinating safe reactions.

Regulatory considerations

As bilirubin is endogenous but utilized in a novel definition gives clear regulatory strategies and well designed clinical trials will be required.

Bilirubin as an Antioxidant

Bilirubin is a yellow bile shade conveyed in the midst of the catabolism of heme which was verifiably regarded as a harmful misuse thing reliable for jaundice. Be that as it may, present-day research has revealed that bilirubin plays an urgent role as a solid endogenous organic system. It is molded when biliverdin is lessened by the protein biliverdin reductase (BVR), and this reversible redox cycle between bilirubin and biliverdin contributes basically to cellular defense components against oxidative stress. [8]

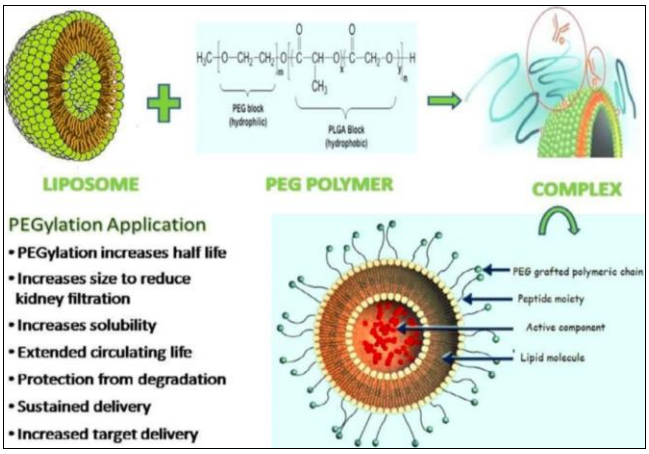
Challenges in Nanomedicine

Regulatory complexity (FDA/EMA approval is strict)
High production cost
Long-term safety/toxicity is unknown in some cases.
Scaling up from lab to industry can be difficult.Fundamental Essential Models of Nanomedicines

Here's a rundown of the most commonly utilized nanomedicine models, with charts (ASCII-style) and brief explanations:

1. Polymeric Nanoparticles (PNPs)

Utilized for: hydrophobic or hydrophilic sedated delivery
Structure: solid atom made of biodegradable polymers (e.g., PLGA, PEG, PLA)
Hydrophilic Shell
| ● ● ● ● ● | ← Calm, scattered, or encapsulated
| ● POLYMER ● | ← Biodegradable polymer system (e.g., PLGA)
| ● ● ● ● ● |_____|
The sedate is epitomized or scattered in the polymer matrix.
Degradation of the grid controls the calm release



2. Liposome
3. Micelles

Hydrophobic pharmaceutical stacked in the center [12]

4. Dendrimers

Utilized for: correct, steady movement and quality delivery
Structure: branched, tree-like polymers with surface utilitarian groups

Functional Bunches (Centering on / Drug)
o o o o
| | |[Center]/ | | |
Drugs can be exemplified interiorly or conjugated to the surface.
Highly tunable and uniform

5. Inorganic Nanoparticles

Utilized for: imaging + treatment (theranostics)
Structure: metal or metal oxide center (e.g., gold, silica, press oxide)
Surface Coating (PEG, ligands, etc.)
Inorganic Center (e.g., Au, Fe_3O_4)
Can be alluring, photo-responsive, and radiopaque
Functionalized for centering on or steady attachment
Examples: Gold NPs, press oxide NPs (MRI contrast)

6. Stimuli-Responsive Nanoparticles

Utilized for: quick cured release
Structure: responds to pH, ROS, warmth, chemicals, or light
Environment-Sensitive Outside Layer
| [Cure Payload Insides] | ← Calm released when triggered
↑ ↑
pH ROS
Bilirubin-based nanoparticles routinely drop into this category.
Triggered destroying in oxidative/inflammatory conditions

Applications of Nanomedicines

1. Cancer Treatment—E.g., liposomal doxorubicin targets tumors with less toxicity

Bilirubin, a normal conclusion item of heme catabolism, was long regarded just as a squander compound related to jaundice and hepatic clutters. In any case, after a long time, broad inquiryhas uncovered its noteworthy natural capacities, including antioxidant, anti-inflammatory, cytoprotective, and anticancer exercises. These advantageous impacts are fundamentally ascribed to its redox potential and its capacity to balance cellular signaling pathways included in cancer movement.

1. Antioxidant Regulation

One of the central components by which bilirubin applies anticancer action is through its antioxidant property. It can neutralize reactive oxygen species, which are major donors to oxidative stress, DNA transformations, By keeping up redox homeostasis, bilirubin secures typical cells from oxidative harm while sensitizing cancer cells to oxidative stress–induced apoptosis.

II. Anti-inflammatory Pathway Bilirubin restrains key provocative go-betweens such as NF-κB, TNF-α, and IL-6, in this manner decreasing the incendiary microenvironment that advances tumor movement. Its concealment of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) contributes to its anticancer potential.

c. Acceptance of Apoptosis

Bilirubin actuates modified cell passing in a few cancer cell lines by enacting the mitochondrial pathway. This handle specifically targets dangerous cells while saving typical tissues. [15]

III. Inhibition of Cell Multiplication and It tweaks key signaling pathways, including PI3K/Akt, MAPK/ERK, and STAT3, which are regularly overactivated in cancers. Besides, bilirubin can repress lattice metalloproteinases (MMPs), in this manner anticipating cancer cell relocation and invasion.

Result

Nanomedicines designed to modulate ROS have shown promising therapeutic outcomes across multiple preclinical models. The key results include:

1. Effective ROS Scavenging

Antioxidant-loaded nanoparticles (e.g., bilirubin, cerium oxide, polymeric antioxidants) efficiently neutralize excessive ROS such as superoxide, hydroxyl radicals, and hydrogen peroxide.

This reduces oxidative stress–related cellular injury in models of inflammation, neurodegeneration, and cancer.

2. Targeted Delivery to Diseased Tissues

Surface-functionalized nanoparticles accumulate specifically at ROS-rich sites (e.g., tumors, inflamed tissues).

This leads to higher local antioxidant concentration with lower systemic toxicity.

3. Controlled and Stimuli-Responsive Release

ROS-responsive nanocarriers break down in the presence of elevated ROS, enabling site-specific drug release.

This enhances therapeutic precision and minimizes off-target effects.

4. Improved Cellular and Mitochondrial Protection

Nanomedicines protect lipids, proteins, and DNA from oxidative damage.

They also prevent mitochondrial dysfunction by stabilizing membrane potential and reducing oxidative bursts.

5. Enhanced Anti-inflammatory and Cytoprotective Effects

By reducing ROS-triggered signaling pathways (NF-κB, MAPK), nanomedicines decrease inflammation.

This leads to improved tissue repair, reduced edema, and faster recovery in injury

Conclusion

Bilirubin has advanced from a metabolic byproduct into a promising immunotherapeutic atom and antibody adjuvant. Its capacity to tweak safe reactions, rummage free radicals, and provide biomolecules positions it as a multifunctional device in present-day immunology. Future inquiries may center on clinical interpretation, optimizing bilirubin nanocarriers for focused immunotherapy, and coordinating bilirubin into next-generation antibody stages for irresistible and immune-mediated disease.

Immunizations & Immunotherapy – mRNA antibodies (like COVID-19) utilize lipid nanoparticles.

Homegrown Nanomedicine—Upgrading conventional homegrown definitions for cutting-edge use

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