Nanoparticles in Scavenging the Free Radicals

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Reactive oxygen species (ROS) play a significant role in the survival and decline of various biological systems. In liver-related metabolic disorders such as steatohepatitis, ROS can act as both a cause and a consequence. Alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) are two distinct types of steatohepatitis. There has been growing interest in using medications that target ROS formation and reduce ROS levels as a therapeutic approach for oxidative stress-related liver disorders. Mammalian systems have developed various antioxidant defenses to protect against excessive ROS generation. These defenses modulate ROS through a series of reactions, limiting their potential impact.

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1. Introduction

Numerous studies have been conducted on natural, synthetic, and nanoparticle antioxidants and their potential in a wide range of applications. It includes gene delivery [1], theranostics for cardiovascular and neurodegenerative diseases [2][3], biomedical applications, and treatment for various toxicities caused by various environmental pollutants.

2. Role of Metal Nanoparticles as Antioxidants

2.1. Silver Nanoparticles

The oxidant characteristics of silver nanoparticles that can prevent cell growth by interfering with membrane proteins or signaling pathways were covered in a previous section. Additionally, how silver nanoparticles can interact with protein sulfur groups was considered, particularly on antioxidant enzymes, and how they can hinder antioxidant action. The antioxidant properties of silver nanoparticles have been the subject of a great number of papers in recent years [4]. The science of oxidative stress is increasingly focusing on the use of nanoparticles as radical scavengers, for their redox potential, or as transporters for antioxidant chemicals [5]. The antioxidant qualities of silver nanoparticles (AgNP) may vary depending on how they are made, but in most cases, plant extracts are used to make them [6]. The high antioxidant activity of these nanoparticles may be due to the quantity of phenolics and flavonoids that are produced on their surfaces as capping agents [6]. AgNPs from aerial Lavandula

stoechas parts have been shown to scavenge DPPH radicals by 75% at a concentration of 25 mg/mL through the phytochemical components of phenols, terpenoids, and flavonoids. As AgNPs demonstrate how to exhibit both pro- and anti-oxidant effects based on their size and surface modification, a research group in 2022 found the size-dependent activity of the silver nanoparticles in inflamed liver tissues. Two differently-sized AgNP were used in the treatment of LPS-contaminated liver slices alongside silymarin. The smaller-sized AgNP (10 and 75 nm) were combined with the larger-sized AgNP (250–300 nm) to achieve the desired effect. Biochemical studies revealed that both sizes of AgNP exhibited anti-inflammatory properties, but these properties were size-dependent. When compared to AgNps, large silver nanoparticles (AgNPL) considerably reduced LPS's effects on TNF- and the proinflammatory mediator NO. However, for the proinflammatory cytokine IL-6, the effects of both AgNPL and AgNps were similarly significant. These results jived with prior accounts. The size of the AgNP particles utilized in experiments explains the variation in inflammatory mediator concentrations. The increased dispersion and toxicity of Ag in AgNps compared to AgNPL is related to the faster rate at which silver ion (Ag+) dissolution occurs in AgNps due to their greater surface area to volume ratio. This explains why NO and TNF- levels are so much higher in AgNps than in AgNPL. In vivo and in vitro studies have shown that hepatocytes respond to LPS, IL-1, TNF-, and reactive oxygen intermediates, all of which are known to favorably influence COX-2 production in other cell types. However, Kupffer cells and immortalized mouse liver cells retained the ability to express COX-2 but adult hepatocytes did not, despite the administration of pro-inflammatory stimuli. The production of PGH2 from arachidonic acid is the rate-limiting step in the synthesis of prostaglandins (PGs) and thromboxane, which COX-2 catalyzes. Intriguingly, hepatic COX-2 expression protects against acute liver damage by enhancing cell cycle progression and proliferation and decreasing apoptotic pathways in hepatocytes. In response to liver damage, the production of COX-2 increases anti-apoptotic genes and activates cell survival proteins, including phospho-Akt and phospho-AMP-kinase. However, these protective effects are lost when COX-2 is inhibited. In contrast to the AgNps group, the COX-2 expression was much higher in the AgNPL group. Their research verified the results of these other investigations and highlighted the important part played by AgNPLs [7].

2.2. Iron-Oxide Nanoparticles

The Fe_2O_3 NPs' and Fe_3O_4 antioxidant properties have already been studied, and the theory behind them is based on the transfer of an electron to neutralize free radicals [8]. Nonetheless, it was effective in tailoring Fe2O3NPs using several methods, such as coating with carbon [9], carboxymethyl-inulin [10], and poly (GA), surface functionalization with natural antioxidant (GA) [11], and curcumin in magnetic–silk core-shell nanoparticles [12]. These customized Fe_2O_3NP composites displayed improved stability and dispersibility, and they were also assessed for their cytotoxicity and biocompatibility/hemocompatibility, as well as their effective antioxidant and antimicrobial properties and the ability to deliver drugs specifically to the target organs [9]. With average particle sizes of 5 and 8 nm, respectively, surface functionalized Fe_2O_3NPs with GA by in situ and post-synthesis showed 2–4-fold higher IC50 values in the DPPH antioxidant experiment than nonfunctionalized Fe_2O_3NPs. This improved free radical scavenging for Fe_2O-NP@GA is caused by the synergistic action of Fe_2O_3-NP and GA. The free radical scavenging property is most likely due to electron transfer from Fe_2O_3-NP@GA to free radicals situated at the central nitrogen atom of DPPH. The antioxidant capacity of magnetite nanoparticles coated with GA-shell (PGA@MNPs), on the other hand, was tested in Jurkat cells in the presence of H_2O_2 as ROS, along with

hemocompatibility and blood cell viability experiments. This coating was polymerized in situ at the surface of the particles in a soft and reagent-free process. Instead of showing any interaction with entire blood cells, PGA@MNPs significantly reduced the oxidative stress caused by H_2O_2. The in vitro assays showed that PGA@MNPs are both bioactive and biocompatible.

2.3. Cerium Oxide Nanoparticles

The ability of cerium oxide nanoparticles (CNPs) to scavenge ROS/RNS and act as antioxidant enzyme mimics is largely dependent on the material's inherent nanoscale physicochemical properties. In addition, it is influenced by the capacity to absorb and release oxygen and the relative thermodynamic efficiency of redox cycling between Ce^{3+} and Ce^{4+} ions on the surface of CNPs [13][14]. Moreover, CNPs have been successfully employed to treat a variety of malignancies, including the most recently targeted one, neuroblastoma, both in vitro and in vivo. However, the generation and accumulation of ROS with concurrent decreases in antioxidant enzyme levels are required for the anti-cancer properties of CNPs. The combination of CNPs with curcumin in a formulation may lead to improved physiological activity, since curcumin has anti-cancer capabilities. In a study, Kalashnikova et al. investigated the anticancer effects of curcumin-loaded nanoceria (CNP-Cur) and dextran-nanoceria (Dex-CNP-Cur) in neuroblastoma models using MYCN-amplified and non-amplified cell lines. In MYCN-amplified IMR-32 cells, Dex-CNP-Cur was found to cause significant cell death. It showed a 2-fold and 1.6-fold loss in cell viability for MYCN-upregulated and normal expressing cell lines, respectively, with little or very little toxicity in healthy cells (compared to untreated cells). Therefore, the dextran coating of CNPs not only aids in decreasing the survival of cancer cells but also aids in avoiding opsonization and phagocyte clearance of the nanoformulations from circulation. As a result, the formulation increases local curcumin concentration, stabilizes HIF-1, and upregulates caspase-dependent apoptosis, which in turn causes a long-term oxidative stress with CNP-assisted accumulation of ROS. CNP-Cur and Dex-CNP-Cur formulations cause neuroblastomas to produce more ROS and a significantly lower ratio of Bcl-2/Bax (Bax is an apoptosis-inducing gene and Bcl-2 stands for anti-apoptic factors), which leads to the release of cytochrome C and the activation of caspase 3/7 and apoptosis [14].

As a result of their antioxidant SOD- and CAT-mimetic activity, CNPs have shown that they can efficiently lower $O_2^{\bullet-}$ and H_2O_2 levels. They have also shown that they are effective scavengers of ROS such as $^{\bullet}OH$ [15][16][17][18], and of RNS such as nitric oxide radical ($^{\bullet}NO$) [19][20] and peroxynitrite (O_2NO] [21]. Das et al.'s study, which showed that CNPs were capable of removing $^{\bullet}OH$ generated from H_2O_2 in aqueous solutions, was one of the first to infer indirectly that they have inherent $^{\bullet}OH$ scavenging capability [16]. Later, based on NP size and Ce^{3+} surface levels, Xue et al. provided direct experimental proof that CNPs efficiently scavenge $^{\bullet}OH$ [17]. The CNPs became more efficient at scavenging $^{\bullet}OH$ and preventing a drop in the visible absorbance of methyl violet as the size of the CNPs decreased and as the level of Ce^{3+} on the surface of the NPs increased (higher Ce^{3+}/Ce^{4+} surface ratios), according to a straightforward photometric study carried out by these authors. Another significant conclusion was that the ROS scavenging activity of CNPs is significantly influenced by their capacity to flip reversibly from Ce^{3+} to Ce^{4+}. Based on these findings, the authors proposed the following two-step mechanism for the $^{\bullet}OH$ scavenging activity of CNPs: Ce_2O_3 + 2[$^{\bullet}OH$] $2CeO_2$ + H_2O (8) $2CeO_2$ (in presence of aqueous H^+) Ce_2O_3 + $12O_2$. The first step indicates the oxidation of Ce^{3+} by $^{\bullet}OH$ and the second step indicates the reduction of Ce^{4+}

$$Ce_2O_3 + 2[^{\bullet}OH] \rightarrow 2CeO_2 + H_2O$$

$$2CeO_2 \text{ (aqueous H+)} \rightarrow Ce_2O_3 + ½O_2$$

Two recent studies demonstrate how CNPs can shield DNA from damage brought on by $^{\bullet}OH$ attack, adding more support for the antioxidant $^{\bullet}OH$ scavenging ability of CNPs [15][18]. The excessive synthesis of RNS, such as $^{\bullet}NO$ and O_2NO, is known as nitrosative stress. Nitric oxide is not a particularly reactive chemical on its own [22]. However, when NO reacts with O_2, it can create a wide range of dangerous species that are extremely reactive. When $^{\bullet}NO$ and $O_2^{\bullet-}$ react, O_2NO is formed. O_2NO is a powerful oxidizing agent with a high potential for damage to lipids, proteins, and DNA, similar to the reactivity of $^{\bullet}OH$. In two recent investigations, CNPs were proven to be an effective scavenger of $^{\bullet}NO$ [19][20]. In both experiments, CNPs with low Ce^{3+}/Ce^{4+} surface ratios outperformed those with high Ce^{3+}/Ce^{4+} surface ratios in terms of effectiveness. The following NO scavenging mechanism for the CNPs [20] was proposed by the authors:

$$Ce^{4+} + {}^{\bullet}NO \rightarrow [Ce^{4+} + NO \leftrightarrow Ce^{3+} + NO^{+}]$$

Bernat Córdoba-Jover et al. introduced a novel approach for reducing ROS during liver regeneration through the utilization of nanoparticles. CeO_2 nanomaterials offer several advantages over conventional anti-oxidative drugs. Firstly, they exhibit minimal toxicity even in cumulative doses. Secondly, CeO_2NPs possess multi-enzyme mimetic activities that can effectively target various sources of ROS generation. Lastly, the catalytic activity of CeO_2NPs can be continuously regenerated, thereby preventing the depletion of their anti-oxidative properties. In addition to the theoretical advantages over conventional drugs, their findings indicate that the therapeutic efficacy of the treatment under investigation surpassed that of the current standard of care, N-acetylcysteine, for managing acetaminophen toxicity in patients. The present study demonstrates that the administration of CeO_2NPs is comparably efficacious in mitigating oxidative stress and tissue injury in rats subjected to APAP overdose, relative to N-acetylcysteine. Although NAC did not exhibit any impact on hepatocyte proliferation in damaged livers, CeO_2NPs demonstrated a significant increase in cell proliferation both in vivo and in vitro. Furthermore, a noteworthy reduction in the proportion of HepG2 cells treated with CeO_2NPs that underwent apoptosis was observed after 48 h of serum deprivation. This implies that the anti-apoptotic impact linked to the nanoceria treatment could potentially aid in augmenting liver regeneration. The transcription factor NF-κB is a significant contributor to the maintenance of liver homeostasis and the process of liver regeneration. As an illustration, mice with a knockout of NF-κB (p65) exhibit embryonic lethality and demonstrate extensive apoptosis of hepatocytes. Furthermore, the induction of hepatic IκB variants, which serve as inhibitors of NF-κB activity, prior to PHx, was correlated with hindered hepatic regeneration in rats. Moreover, the process of regeneration following partial hepatectomy was hindered when NF-κB was deactivated in both Kupffer cells and hepatocytes.

In a similar fashion, the activity of CeNPs were tested on rats with steatosis by Denise Oró et al. Rats treated with CCl_4 and administered CeO_2NPs exhibited distinct pathological characteristics compared to those administered with a vehicle. These include a significant reduction in liver fat accumulation and a lower incidence of portal hypertension. Hepatic fat accumulation is a consequence of heightened triglyceride synthesis within the

hepatocytes. Irrespective of the etiology of intracellular lipid buildup in the hepatic tissue, augmented influx of free fatty acids leads to a state of mitochondrial β-oxidation overload, thereby elevating the burden on the endoplasmic reticulum. Dysfunction of the endoplasmic reticulum (ER) results in the generation of ROS, which triggers oxidative stress and initiates the inflammatory pathway. Furthermore, heightened levels of oxidative stress have been linked to hepatocellular apoptosis in rats exhibiting NASH induced by a high-fat diet. This occurrence appears to be facilitated by the activation of JNK and an inequity between pro- and anti-apoptotic proteins of the Bcl-2 family. The noteworthy aspect of this situation is the decrease in gene expression of Ncf1, Ncf2, Atf3, and Hspa5 that was observed following the administration of CeO_2NPs to rats treated with CCl_4. The Ncf1 and Ncf2 genes are responsible for encoding two subunits of NADPH oxidase, which is a complex enzyme utilized by cells for the generation of superoxide anions. In contrast, it has been observed that Atf3 and Hspa5 are molecules associated with endoplasmic reticulum stress that are modulated by ROS. Atf3 belongs to the family of transcription factors known as activation transcription factor (ATF)/cAMP responsive element binding (CREB), while Hspa5 encodes a member of the heat shock protein 70 family that participates in the process of protein folding and assembly within the endoplasmic reticulum. The aforementioned data suggest that the administration of CeO_2NPs has the ability to impede oxidative and ROS-mediated ER stress in the context of liver injury induced by CCl_4. Moreover, the significant decrease in TNFα, IL-1β, iNOS, and COX-2 expression observed in the liver of CeO_2 nanoparticle-treated animals, as reported by D. Oro et al., supports the notion that the advantageous outcomes of these nanoparticles may be attributed to their potent antioxidant properties. The notion is reinforced by the restoration of PPARγ expression. It is established that the reduction in PPARγ expression prompts the activation of quiescent adipocytes, leading to complete differentiation into HSC. Additionally, PPARγ is indispensable in averting inflammation and preserving lipid and glucose homeostasis [23]. In reference to this context, the CNPs were found to be one of the top contenders as they exhibit a higher CAT activity and help in restoring the diseased liver. However, care should be taken in analyzing the complete toxicity of the nanoparticulate system.

2.4. Manganese Oxide Nanoparticles

Manganese oxide was found to exhibit excellent anti-inflammatory activities via multiple pathways. On the other hand, MnNPs were also found to have an exceptional neutrophil reverse migration ability. Adityanarayan Mohapatra et al. prepared a biomineralized MnNp system and established its efficacy in treating the gouty arthritis mice model. Here they have found a typical ability of MnNPs of clearing the existing neutrophils in the inflammatory site. They have proved the mechanism of neutrophil clearance in zebrafish model. Enough proofs were produced to showcase the nanoparticle's ability to reduce the inflammation via iNOS, COX-2, and NF-κB pathways [24]. Similarly, Shreedevi Kumar et al. worked on PEGylated MnNPs for the protection of the cartilage from deterioration via inflammation-induced oxidative stress. The chondroprotective effects of the PEG-MnO_2 NPs were determined in a cartilage explant model that mimicked OA, allowing for the detection of structural ECM degeneration and concurrent NO production, as well as in chondrocyte monolayers that were cytokine-challenged, allowing for the analysis of gene expression. Combined, these experiments enabled people to begin investigating potential free-radical scavenging NPs' interactions with the cells' overall oxidant-antioxidant systems. The results of both tests were consistent with one another in a number of respects. For instance, PEG-MnO_2 NPs treatment lowered NO generation in cytokine-challenged cartilage explants and iNOS gene expression in cytokine-challenged

chondrocytes. Furthermore, the biochemical results from the explant investigation, which showed that PEG-MnO_2 NPs dramatically lowered release of GAGs in cytokine-challenged explants, are supported by the reduced expression of MMPs and ADAMTS genes by cytokine-challenged chondrocytes when treated with PEG-MnO_2 NPs [25]. Recent research by Mengyun Peng et al. describes an effective activity of MnNPs in greater reduction of H_2O_2 via catalase mimicking activity. Their hypothesis was that hepatic hypoxia and oxidative stress stimulated HSCs continuously and chronically, making it difficult to reverse fibrosis. TGF-1 decreased CAT activity in the pro-fibrotic environment and then caused a buildup of H_2O_2. The increasing H_2O_2 in turn caused TGF-1 to rise even more, starting a vicious cycle. In order to break the circle, H_2O_2 was chosen as the target, and MnO_2 was used to simulate CAT-like activity for H_2O_2 breakdown. By lowering hypoxia and oxidative stress, MnO_2 altered the fibrotic milieu and decreased a pro-fibrotic stimulus from the source [26].

The cytokine TGF-β1 is commonly utilized to induce activation of HSCs and is considered a prototypical pro-fibrotic agent. Consequently, it has been extensively employed in the development of in vitro models of fibrosis. Previous studies have investigated the impact of TGF-β1 on CAT in airway smooth muscle cells, albeit with limited attention. A decrease in CAT activity has been documented in cases of liver and lung fibrosis for several decades. This reduction in CAT activity is believed to contribute to an imbalance in cellular redox. The findings indicate that hepatic hypoxia leads to an upregulation of TGF-β1 expression, resulting in the inhibition of CAT expression in HSCs [27]. This inhibition is achieved through the downregulation of Foxo3a and Nrf2. The fibrotic area exhibited elevated levels of H_2O_2 accumulation and stabilized HIF-1α due to the inhibition of liver CAT. Additionally, the combined action of H_2O_2 and HIF-1α was found to induce an increase in the expression of TGF-β1, thereby establishing a detrimental feedback loop that poses a significant challenge for the treatment of liver fibrosis. The proposal posits that the hypoxic and oxidative stress conditions in the liver create persistent and long-term stimuli for HSCs, leading to challenges in the recovery of fibrosis. Within a pro-fibrotic milieu, TGF-β1 was observed to attenuate CAT activity, subsequently leading to an accumulation of H_2O_2. The surplus of hydrogen peroxide subsequently induced a further elevation of transforming growth factor beta 1 (TGF-β1), thereby establishing a detrimental feedback loop. Therefore, H_2O_2 was chosen as the focal point for disrupting the cycle, and MnO_2 was utilized to emulate the catalase-like behavior for the decomposition of H_2O_2. The application of MnO_2 resulted in the modification of the fibrotic microenvironment through the mitigation of hypoxia and oxidative stress, leading to a decrease in the pro-fibrotic stimulus originating from said environment [28]. The inhibition of CYP3A457 by Ssb1 and its deglycosylated metabolite were documented to augment liver targeting. Moreover, it has been observed that Saikosaponins, specifically Ssb1, exhibit hepatoprotective effects against liver injury induced by CCl_4. As anticipated, the treatment of Ssb1 in isolation was observed to hinder the expression of α-SMA in in vitro trials. However, its efficacy in reversing liver fibrosis in Balb/c mice was limited. Conversely, MnO2@PLGA/Ssb1 demonstrated a more potent therapeutic effect in both in vitro and in vivo experiments.

3. Role of Polymeric Nanoparticles as Antioxidants

One of the most promising nanocarriers being produced are polymeric nanoparticles, which are primarily made of synthetic biodegradable polymers. An aqueous extract of Syzygium cumini (ASc) seeds was combined with one of

the well-known synthetic polymers recognized by the US-FDA, Poly (-caprolactone) (PCL), using an emulsification/evaporation solvent method. The DPPH radical scavenging ability and ferric reducing antioxidant power test (FRAP) were used to assess the ASc and PCL-ASc. According to the study, immobilization of ASc in PCL nanoparticle had no effect on antioxidant scavenging activity. Both ASc and PCL-ASc, even at a very low concentration (100 g/mL), have nearly the same and high scavenging DPPH radicals activity and reducing power in the FRAP assay [29]. Bacterial cellulose (BC), a biologically derived nanofiber-based polymer, has also attracted a lot of attention. This is mainly due to its superior film-forming capabilities, increased water-holding capacity, porosity, and—most importantly—biocompatibility. Silymarin and zein-containing spherical nanoparticles (SMN-Zein) can be adsorbed by BC, a nanocarrier. When SMN-Zein and BC films are combined, SMN-Zein/BC nanoparticles and nanofiber composites are created. SMN-Zein/BC have improved wettability, increased swelling of the BC films, increased solubility of sparingly soluble silymarin, and release from the nanocomposite films. In comparison to free SMN, SMN-Zein/BC demonstrated higher DPPH, ABTS%, and superoxide anion scavenging activity. Although BC lacked antioxidant activity, the composites' antioxidant potential was increased by the gradual release of SMN because of its presence [30].

The efficacy of nano-drug delivery system targeting HSCs was impeded to a significant extent due to the excessive accumulation of fibrosis collagen in the space of Disse, which is associated with hepatic fibrogenesis. The present investigation involved the development of a polymeric micelle (CRM) with a nanodrill-like structure. The study demonstrated the ability of the CRM to effectively penetrate the collagen barrier that is typically present in fibrotic liver and achieve optimal targeting of HSCs. The polymeric micelles were evaluated for their cellular uptake in the context of an excessive collagen I barrier. Among the four types of micelles, the nanodrill-like CRM exhibited the highest cellular uptake. This can be attributed to the proteolysis function of collagenase I and the enhanced-uptake effect of the ligand retinol that decorates the CRM. Furthermore, Confocal Laser Scanning Microscopy (CLSM) demonstrated that the Carrier-Mediated Transport (CMT) agent efficiently discharged intracellular cargo within LX-2 cells. A two-stage, non-fatal hepatic fibrosis model was established through the administration of CCl4 via intraperitoneal injection over a period of 4 or 8 weeks. This model was utilized to evaluate the liver's stage-dependent accumulation of polymeric micelles. Moreover, the utilization of immunofluorescence staining revealed that the delivery of cargos to activated HSC was more effective with the use of cell-penetrating peptides conjugated with arginine-rich motifs in comparison to cell-penetrating peptides conjugated with membrane translocation domains (CM). Furthermore, the utilization of CRM in conjunction with the antifibrotic agent NIL resulted in the most favorable antifibrotic outcomes in the nonfatal hepatic fibrosis model, which was induced by sequential intraperitoneal administration of CCl4 for a duration of 8 weeks. This approach exhibited a substantial accumulation of the drug in the liver and effective targeting of HSC. Significantly, it was demonstrated that CRM displays exceptional cell compatibility and hemocompatibility in vitro and does not manifest any acute or chronic toxicity in vivo. Based on the aforementioned results, it is suggested that utilizing CRM as a nanodrug delivery system could be a promising approach for targeting HSCs in the treatment of liver fibrosis.

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