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The applications of cerium oxide nanoform and its ecotoxicity in the aquatic environment: an updated insight

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Abstract – The widespread usage of nanotechnology in many essential products has raised concerns about the possible release of nanoparticles (NPs) into aquatic habitats. Cerium dioxide (CeO_2) has gained the most interest in the worldwide nanotechnology industry of all types of Ce minerals owing to its beneficial uses in a wide range of industry practices such as catalysts, sunscreens, fuel additives, fuel cells, and biomedicine. Besides, it was realized that CeO_2 nanoparticles (n-CeO_2) have multi-enzyme synthesized properties that create various biological impacts, such as effectively antioxidant towards almost all irritant intracellular reactive oxygen species. Lately, it was discovered that a large amount of n-CeO_2 from untreated industrial waste could be released into the aquatic environment and affect all living organisms. In addition, the physical/chemical characteristics, fate, and bioavailability of nanomaterials in the aquatic environment were discovered to be related to the synthesis technique. Thus, there are intended needs in identifying the optimal technique of synthesized CeO_2 nanoparticles in order to assess their beneficial use or their potential ecotoxicological impacts on aquatic organisms and humans. Therefore, this review sheds light on the possible threats of n-CeO_2 to aquatic creatures as well as its synthesized techniques. Also, it discusses the possible mechanism of n-CeO_2 toxicity as well as their potential benefits in the aquaculture industry.

Keywords: Nanotechnology / n-CeO_2 / aquatic environment / toxicity

1 Introduction

Nanoparticles (NPs) are unparalleled compounds due to their tiny size (≤ than 100 nm), and size-dependent characteristics (length, width, height, volume, and mass) (Zhang et al., 2016). Currently, the production of engineered NPs, especially metal oxide nanomaterials (NMs) were extensively increased due to the numerous and widely used commercial applications worldwide. They can be utilized in several products such as human consumption products, agriculture, construction materials, biomedical and pharmaceutical industries, and information technologies (Hoecke et al., 2009). There is numerous metal oxide NMs that have been used for many industrial purposes, but their unhygienic disposal in large quantities in the aquatic environment will

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cause toxicity signs to the exposed fish, bivalve mollusks, and other living organisms (Abdel-Latif et al., 2021a).

One of the most important and expansively used metal oxide NMs is the cerium oxide NPs (*n*-CeO_2) (Perullini et al., 2013). Cerium (Ce) is one of the most abundant trace elements (Abdelnour et al., 2019). Ce exists in two primary oxidation liquid forms (Ce^{3+} and Ce^{4+}) (Sun et al., 2012). The worldwide produced *n*-CeO_2 compounds at a rate of ten thousand tons per year (Keller et al., 2013). They have numerous industrial uses, for example, in biomedical applications (Reed et al., 2014), several paint coatings, polishing powder, catalysts (Zhao et al., 2012), and personal care products, particularly the broad-spectrum inorganic sunscreen (Patil et al., 2002). In the human medical industry, *n*-CeO_2 has various medical importance, such as cancer treatment, neuroprotective effects (Das et al., 2007), and wound healing. Also, *n*-CeO_2 can protect the host cells from the oxidative damage induced by the overproduction of free radicals (Li et al., 2016; Nelson et al., 2016a). Besides, the scavenger activity of *n*-CeO_2 against the generated free radicals (Xia et al., 2008) depends on its ability to activate the entire cell enzymatic production, such as superoxide dismutase (SOD) and catalase (CAT) (Das et al., 2007). Furthermore, *n*-CeO_2 exhibited potent antibacterial effects against a wide variety of pathogenic bacteria (Thill et al., 2006).

Several studies have revealed several ways to synthesize *n*-CeO_2 for various uses. The final product is affected by the changes in synthesis processes (Wu et al., 2019; Nyoka et al., 2020). Also, it suggests that the generated nanostructures will have various physical/morphological and chemical characteristics, influencing their function (Abd El-Naby et al., 2019; Huang et al., 2019). Thus, it is critical choosing the synthesis technique that creates the nanostructure that fulfilled the desired application (Mehana et al., 2020). In the medical application, for example, it is essential to choose the synthesis technique that generates the final characteristics of the nanostructures that can interact with living cells to cause the necessary biological activity (Al-Gabri et al., 2021; Rozhin et al., 2021).

The toxicity and protective effects of *n*-CeO_2 depend on the preparation method, particle size, cell type, and exposure route. In fish, dietary *n*-CeO_2 has been reported to promote growth, attenuate ammonia nitrogen stress, and boost immunity in a Chinese mitten crab (*Eriocheir sinensis*) (Qin et al., 2019). Moreover, it can alleviate the amine-coated Ag-NPs toxicological effects in rohu (*Labeo rohita*) (Khan et al., 2018). However, their widespread production and their varieties of uses, *n*-CeO_2 have been reported to induce severe toxicological impacts in the exposed aquatic organisms. For instance, *n*-CeO_2 elicited genotoxic effects in *Daphnia magna* (García et al., 2011), and growth-inhibitory impacts in *Pseudokirchneriella subcapitata* (Rodea-Palomares et al., 2010). Besides, its oxidative stress effects in *Corophium volutator* (Dogra et al., 2016), mild cytotoxic and cardiac toxicity in the white sucker fish (*Catostomus commersonii*) (Rundle et al., 2016) and immunotoxicity with a high mortality rate of rainbow trout (*Oncorhynchus mykiss*) (Correia et al., 2019) had been reported.

Indeed, toxicity research in *n*-CeO_2 provides inconsistent findings, indicating harmful effects in some studies, protective ones in others, and sometimes no impact at all. This review summarizes the available rare studies from the literature and focuses mainly on the synthesis, behavior, and fate of *n*-CeO_2 in aquatic environments. Moreover, a detailed discussion of their toxicological effects on several species of finfish, shellfish, algae, and other aquatic organisms. This review also spotlights their biomedical role and expected beneficial effects on fish.

2 *n*-CeO_2 characteristics

Cerium (Ce) is a chemical element with atomic number 58. It can be found in many minerals, the most prevalent of which are bastnaesite and monazite. Moreover, heating bastnaesite ore and treating it with hydrochloric acid generates cerium oxide (Ismael et al., 2021). In addition, in the liquid form, Ce can be found in two oxidation states (Ce^{3+} and Ce^{4+}) rather than most of the other trace elements, which showed one state of oxidation in the liquid form ($^{(+3)}$) (Abdelnour et al., 2019). The presence of Ce^{3+}/Ce^{4+} redox couples creates reactions dependent on existing oxygen that allows metabolic, catalytic, and biological reactivity (Caputo et al., 2017). While, physicochemical structures of *n*-CeO_2 as their specific surface area, zeta potential, small size, and lower dissolution rate, increase its opportunities to distribute and generate nano-bio interfaces with sugars, lipids, proteins, cells, membranes, cellular organelles and DNA (Teske and Detweiler, 2015). Also, the internalization of *n*-CeO_2 and release of Ce^{+3} could be responsible for a toxic influence on live cells.

The scavenger ability of *n*-CeO_2 was related to the inherent physicochemical properties of nanoscale materials. *n*-CeO_2 contains a mixture of both Ce^{4+} and Ce^{3+} on its surface (Nelson et al., 2016b). Thus, as oxygen atoms are lost from the *n*-CeO_2 surface, there is a reduction in the oxidation state of Ce ($Ce^{4+} \rightarrow Ce^{3+}$) and an increase in the number of oxygen vacancies (defect sites) on the *n*-CeO_2 surface (Deshpande et al., 2005). The ratio of Ce^{3+}/Ce^{4+} sites on the surface is strongly correlated with the antioxidant/enzyme-mimetic activity of the *n*-CeO_2. Furthermore, the small size of *n*-CeO_2 (20 nm to 2 nm) increases the number of Ce^{3+} sites on its surface that bind or release oxygen atoms (Dogra et al., 2016). Also, it was determined that by reducing the nanoparticle size to 12 nm, *n*-CeO_2-loaded liposomes preserved the colloidal stability and antioxidant capabilities (Grillone et al., 2017).

3 Synthesis of *n*-CeO_2

Several recent studies have proved the beneficial and therapeutic effects of *n*-CeO_2, while other studies have documented that *n*-CeO_2 might induce harmful and toxic effects on cells (Huang et al., 2019). Also, there are several investigations indicated that the therapeutic properties or toxicological effects of *n*-CeO_2 are mainly relient on synthesis conditions (temperature or pH) as well as the synthesis method, which affect the physicochemical properties of the synthezined *n*-CeO_2 molecules (such as particle size, shape, specific surface area, and surface charge) (Nyoka et al., 2020). Thus, understanding these synthesis-related features may contribute to the creation of safer nanoparticles and determine their overall potential toxicity.

3.1 Chemical method

There are several chemical methods for n-CeO_2 syntheses, such as, co-precipitation (Farahmandjou et al., 2016), precipitation (Ketzial and Nesaraj, 2011; Babitha et al., 2015), microwave diversion processing (Shirke et al., 2011; Soren et al., 2015), sonochemistry (Yin et al., 2002; Pinjari and Pandit, 2011), reverse-co-precipitation (Jalilpour and Fathalilou, 2012), and a combination of microwave and hydrothermal method (Gao et al., 2006).

Apoferritin, a cage-shaped protein, is used in a novel approach for the synthesis of n-CeO_2. This protein was used as a biotemplate and resulted in a two and three-D array formation. The chemical reaction happened in the cavity (Naiel et al., 2020). Trivalent Ce ions were oxidized and resulted in n-CeO_2 formation, as perceived in the formation of iron oxide. The particles were definite to be n-CeO_2 (average size, 5.0 ± 0.7 nm). The ferritins, wherein each apoferritin contains NPs and multivalent Ce ions, display salt bridge forms. Effective salt bridge formation results in a 2-D array of n-CeO_2 that contains ferritin and 3-D arrays with two various resulting morphology, i.e., prism structured or octahedral (Okuda et al., 2011).

3.2 Green method

Researchers have lately developed a safe, less poisonous method called "green synthesis". Furthermore, synthesis NPs by the green method is preferable to other approaches since it is simple and clear, cost-effective, and generally controllable, and it often results in more stable materials (Maqbool et al., 2016). The green synthesis process is based on using biological substances such as plants, microorganisms, and any other biological component (Aseyd Nezhad et al., 2020). In addition, plant extracts are high in phytochemicals such as asketones, amine group, enzymes, and phenol compounds, which are thought to be responsible for the stability and reduction of bulk salts into nanoparticles (Nadeem et al., 2020). Therefore, *Gloriosa superba* L. leaf extract could be used to generate n-CeO_2 and XRD confirmed that NPs had been formed, and they were spherical in shape (Arumugam et al., 2015). Another alternative study showed that n-CeO_2 synthesis could be done by *Curvularia lunata* culture filtrate. This study found that NPs have a spherical shape and range from 5 to 20 nm (Munusamy et al., 2014). These synthesized NPs displayed potent antibacterial actions against a wide range of bacterial species. On the other hand, it was determined that the NPs could not pierce the bacterial cell walls (Maqbool et al., 2016). Also, synthesized n-CeO_2 by green method demonstrated higher antibacterial properties via promoting the formation of an excess of free oxygen radical species in cells (Rajeshkumar and Naik, 2018). Other additional studies verified the use of leaf extracts of *Acalypha indica* and *Aloe vera* plant in n-CeO_2 synthesis (Priya et al., 2014), where these extracts are considered as coating agents through the synthesis process. Moreover, the extract of *Hibiscus sabdariffa* flower also was used as a chelating agent in the n-CeO_2 synthesis. The size of the resulting n-CeO_2 was about 3.9 nm in diameter (Thovhogi et al., 2015). Figure 1 is a proposed schematic diagram for the synthesis of n-CeO_2 by using *Gloriosa superba*-based method.

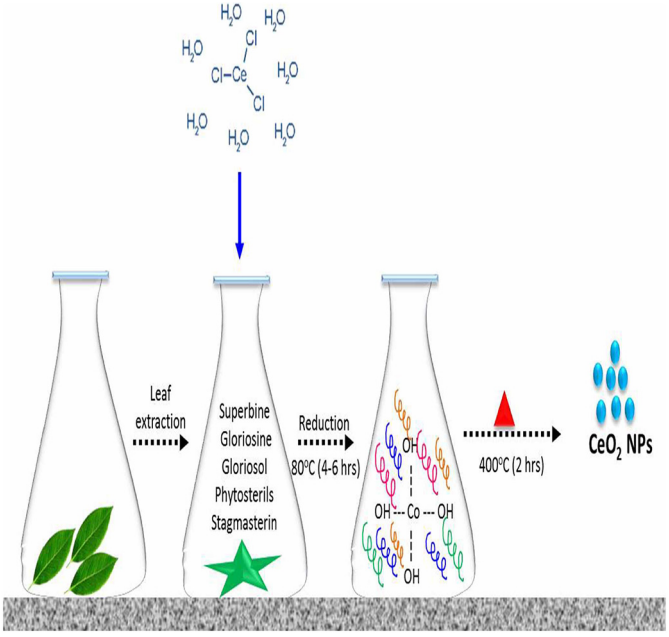

Fig. 1. A proposed schematic diagram for cerium oxide nanoparticle synthesis by using *Gloriosa superba*-based method.

3.3 Synthesis from nutrients

Todate, green synthesis is broadly believed as a dependable and safe ecological process. Numerous studies have proposed n-CeO_2 synthesis using different nutrients, such as the protein of egg white (Kargar et al., 2015). Lysozyme and ovalbumin are two proteins present in egg white that can act as stabilizing agents for the n-CeO_2 synthesis. The mechanism of n-CeO_2 synthesis could be elucidated by the electrostatic interaction arising between protein and Ce ions (Ce^{3+}) a per the opposite charge, which promotes small, stable, isotropic nanoparticle formation (Singh et al., 2005). Another research suggested that n-CeO_2 could be formed by using honey, whereas the enzymes, carbohydrates and vitamins in the honey matrix possess amine and hydroxyl groups. So, honey was used as a coating and stabilizing agent for the n-CeO_2 along with Ce species that repressed their crystal development (Darroudi et al., 2014).

4 n-CeO_2 prevalence and transformation pathways in the aquatic environment

It was recently revealed that up to 6% of CeO_2 might escape from waste treatment stations, eventually reaching wastewater and being dissolved in natural water streams (Keller et al., 2013). Thus, the excessive production of n-CeO_2 into natural water resources may have a severe impact on human health and the environment, raising concerns about the toxicological dangers of these chemicals (Yao et al., 2014). In addition, the discharge of NPs directly or indirectly into the aquatic ecosystems may be dangerous to the aquatic fauna and the living organisms (Weinberg et al., 2011). At present, n-CeO_2 concentrations in freshwaters are estimated using modeling studies only (to be ranged between 0.6 and 100 ng L^{-1}), due to the difficulty in

measuring the concentrations of *n*-CeO_2 in this dissolved media. Limited studies have been revealed to model the *n*-CeO_2 concentration in aquatic environments; however, they elucidate values with the range of ng or μg per liter (Gottschalk et al., 2015). It was reported that the expected limit of CeO_2 in water must be less than 0.0001 μg L^{-1} (Boxall et al., 2008). Other studies showed the extensive use of *n*-CeO_2 in diesel fuel, which can reach levels of 0.02–300 ng L^{-1}, leading to an increase in the environmental levels of *n*-CeO_2 in water (Johnson and Park, 2012; Sun et al., 2014). This directed to change in the estimation of probable effect concentrations which become 1 μg L^{-1} in surface waters. However, the projected environmental levels are somewhat small and under the pg L^{-1} in marine water (Giese et al., 2018).

Several articles have reported that once released in the water, the chemical and physical properties of *n*-CeO_2, such as the dissolution and aggregation tendency, would be greatly modified (Quik et al., 2010; Auffan et al., 2014; Booth et al., 2015; Tella et al., 2015). These modifications are likely to alter the NPs distribution in diverse locations and change the bioavailability results and increase the toxic probabilities in the aquatic ecosystems (Garaud et al., 2016). Several investigations cleared that the *n*-CeO_2 coating influences the higher stability in water, which leads to additional modulation of the biological activities to exposed organisms. For instance, citrate-coated *n*-CeO_2 presented dissimilar stabilization of the exposure systems in freshwater in comparison to non-coated *n*-CeO_2 (Tella et al., 2015).

In the same context, recent ecological studies have proven that *n*-CeO_2 undergoes partial dissolution under specific conditions (temperature, pH and dissolved oxygen) (Grulke et al., 2014). It was found that the release of Ce was three times greater for the large NPs than for small NPs under unstable levels of pH (Dahle et al., 2015). Thus, Plakhova et al. (2016) proposed that the pH-dependence of Ce anti- and pro-oxidant activity is connected to the dissolution of *n*-CeO_2 in aqueous environments. While, under unsuitable environmental conditions, the *n*-CeO_2 at low levels could be highly toxic to aquatic creatures.

5 The toxicological aspects of *n*-CeO_2

The ability of *n*-CeO_2 to form aggregates (Ramirez et al., 2019) allows these particles to settle in the aquatic environment (Quik et al., 2014). Under high polluted environment, the increment of accumulation of *n*-CeO_2 within fish tissues depends on the low water solubility and sedimentation properties (Cross et al., 2019). The main uptake method of *n*-CeO_2 into living organisms is through ingestion (Cross et al., 2019). However, *n*-CeO_2 may enter into the body cavity through the gills or skin through direct contact with the water as incase of zebrafish as contrasting to many dissolved compounds (Hwang and Chou, 2013). The summary of toxicological aspects of *n*-CeO_2 in several aquatic organisms is presented in Table 1.

The biodegradation of *n*-CeO_2 and its toxicological effects in the aquatic ecosystem depends on physicochemical features of these NPs (shape, surface chemistry, size, molecular weight, etc.) and water chemical properties (ionic strength, pH, colloids and the content of natural organic matter (NOM)) (Zhang et al., 2018). In natural waters, the composition and concentration of NOM vary considerably and change the NPs behavior (Wang et al., 2011). There were two types of acids (fulvic and humic acids) existing in NOM structure. These acids could make *n*-CeO_2 more stable in algae growth media and natural waters, either by steric or electrostatic repulsion (Quik et al., 2010). Moreover, the adsorption capacity *n*-CeO_2 is significantly affected by water pH, consequently influencing the size of *n*-CeO_2 aggregation (Keller et al., 2010). Besides, *n*-CeO_2 tend to agglomerate under ecotoxicological conditions in freshwater which may influence the toxicity and bioavailability properties (Rodea-Palomares et al., 2010; Röhder et al., 2014).

Also, *n*-CeO_2 might suffer various alteration processes in aquatic environments, such as dissolution, sedimentation, and homo-aggregation (Quik, 2013). Collaboration with other compounds already present or contaminates in the water (hetero aggregation) can direct the aggregation process or help in stabilization of NPs dispersed (Khan et al., 2019). In addition, the behavior of absorption or aggregation process can have a substantial on the toxicological NPs effects (Dahle et al., 2015). Furthermore, Quik et al. (2012) stated that the foremost deletion mechanisms of *n*-CeO_2 behavior in different water aqueous was hetero-aggregation.

The aforementioned pathways described the toxicological impact of *n*-CeO_2 on the aquatic environment and organisms. Furthermore, the dangers of *n*-CeO_2 in certain aquatic organisms is discussed in further depth below.

5.1 Finfish species

The toxicological effects of *n*-CeO_2 were investigated in a wide variety of finfish species. For instance, Gaiser et al. (2009) and Gaiser et al. (2012) detected that sensitivity pattern was highest at cerium oxide nano forms (*n*-CeO_2) compared with micro forms in common carp, *Cyprinus carpio*. At the same context, Arnold et al. (2013) stated that CeO_2 showed more toxic effects at NPs form in compared with equimolar bulk form in zebrafish (*Danio rerio*). The toxicological effects of CeO_2 depended on the NPs particle size, element type, exposure time, fish species and age and NPs concentration. Conversely, Hoecke et al. (2009) reported that acute exposure of *D. rerio* embryos to *n*-CeO_2 for 24 h to a concentration of 5000 mg L^{-1} (14, 20, and 29 nm CeO_2 particles) showed no toxic effects. While, Krysanov and Demidova (2012) investigated that low concentrations of pure *n*-CeO_2 and pure doxorubicin showed no significant effects on the development of zebrafish embryos. However, the treatment of zebrafish eggs with a mixture of nanoparticles and doxorubicin led to a significant increase in the incidence of embryo malformations. Thus, the probable toxicity mechanisms may be due to the synergistic toxicological effects of both *n*-CeO_2 and doxorubicin.

The cytotoxic influences of CeO_2 depends on the pH value of the cell components, where it helps to internalize the high level of particles (Augustine et al., 2020; Abdel-Latif et al., 2021b). Hence, *n*-CeO_2 could exhibit a strong difference in cytotoxicity depending on the exposed cell type and its ability to absorb these NPs inside cell to induce its biological activity. Furthermore, fish may exhibit different physiological

Table 1. Summary of the toxicological studies of *n*-CeO_2 in several aquatic species.

Aquatic species	Characters of *n*-CeO_2 and exposure conditions			Target tissue	Uptake	Toxicological effects	References
	Particle size (nm)	**Concentration and exposure method**	**Exposure**				
1. Finfish						↑Plasma cortisol and glucose levels	
C.commersonii	227	1.0 mg/L	25 h	Heart Gills	Gills	↑ MDA levels.Did not altered RBCs counts.	Rundle et al. (2016)
C. auratus	20 to 40	160 up to 320 mg/L	N/A	Brain, gills, and liver	Gills	↓AChE,SOD and Na+/K +-ATPase activites. ↓ CAT level.	Jun et al. (2013)
O. mykiss	<25	10 μg/L	96 h	Gills, liver	Gills	↑ $nCeO_2$ accumulation ↑ mortality rate	Correia et al. (2019)
	<50	0.1, 0.01, and 0.001 μg/L	28 d	Gills, brain, liver, eyes	N/A	↑ GST activity in gills ↑ CAT activity in livers ↓ AChE in fish eyes Induced Histopathological alteration in gills and liver	Bour et al. (2015)
D. rerio	10.2±0.78	500 and 5000 μg/L	21 d	Gill, liver, skin, brain, gut, blood and kidney	liver	↑ *n*-CeO_2 accumulation	Felix et al. (2013)
D. rerio embryos	10.2±0.78	500 and 5000 μg/L	7 d	brain, gills, skin and liver	Liver	↑accumulation in brain, gills and skin	Jemec et al. (2015)
	53.3±3.12	7.5 x 10^{-7} mg	96 h	N/A	N/A	↓ gross developmental	Jemec et al. (2012)
	<25 nm	0.001, 0.01, 0.1, and 1 mg/L	96 h	N/A	N/A	↓Embryo malformations	Khan et al. (2018)
	10–30	20, 50, and 100 mg/L	5 dpf	Digestive system	N/A	↑ 5-HT level	Özel et al. (2013)
	10–15	1, 10, 50 and 100 mg/L	4 dpf	N/A	N/A	↓ larvae growth	Felix et al. (2013)
2. Crustacea							
D. magna neonates	6.5	0.011- 0.015 mg/ml	48 h	N/A	N/A	LC50 = 0.012 mg/mL	Gaiser et al. (2012)
D. similis D. pulex	3±1	1, 10 and 100 mg/L	48 h	N/A	N/A	*D. similis* 350 times more sensitive ↓ Swimming velocities to 30% and 40% at 1 mg/L in *D. pulex* and *D. similis*	Jemec et al. (2012)
D. magna neonates	<25	0-10 μg/ml	96 h	N/A	N/A	↓ tissue accumuation No significant mortalities	Auffan et al. (2013)
	<25	0 to 10 mg/L 0, 0.1, 1, 3 & 10 mg/L	96 h 21 d	N/A	N/A	100% mortality at 10 mg/L (after 7 d) 30% mortality at 3 mg/L (over 21 d)	
3. Bivalves	24±3	1 mg/l to 10 mg/L	24, 48, 72, and 96 h	soft tissues	Pseudo feces	↑accumulation (62 μg/g)	García et al. (2011)
	15-30	1, 5, 10 μg/mL	from 30 min to 4 h	Hemocytes	N/A	↓ Total extracellular oxyradical production Induced mitochondrial damage, cardiolipin oxidation	Lee et al. (2009)
M. galloprovincialis	67±8 × 8±31	1, 2, or 3 mg/L	35 days	Soft tissues	Pseudo feces	Not affect Ce accumulation in mussel tissue ↑ Clearance rate	Auguste et al. (2019)
	26 ± 16. 9 ± 4	1, 10 and 50 mg/L	from 30 min to 4 h	Hemocytes	blood	Negative impacts on hemocytes	Montes et al. (2012)
	20–25	100 μg/L	96 h		blood		Sendra et al. (2018)

Table 1. (continued).

Aquatic species	Characters of n-CeO_2 and exposure conditions			Target tissue	Uptake	Toxicological effects	References
	Particle size (nm)	Concentration and exposure method	Exposure				
				Gills, digestive gland Hemocytes		↑ ROS production and serum LYZ activity ↑ CAT in gills and digestive gland ↑ GST in digesive gland ↓ lysosomal lipofuscin accumulation ↑ Embryotoxicity	
D.polymorpha	3–4	(Citrate-coated n-CeO_2)1 mg/L	21 d	Digestive gland	Digestive gland	↑ Removal of n-CeO_2 from the water ↓ Bioaccumulation in mussels	Garaud et al. (2016)
C. fluminea	20–25	10 and 100 µg/L	6 days	Digestive gland	Digestive gland	↑ DNA damage ↑ T-AOC, CAT, GST, caspase-3 No differences in Ce bioaccumulation	Koehlé-Divo et al. (2018)

Abbreviations: T-AOC: Total antioxidant capacity, CAT: Catalase, GST: Glutathione-S-transferase, LYZ: Lysozyme, ROS: Reactive oxygen species, AChE: Acetyl choline esterase, SOD: Superoxide dismutase, RBCs: Red blood cells, MDA: Malondialdehyde, Ce: cerium.
↑ = means increase and ↓ = means decrease while N/A = means not indicated in the current investigation.

responses to the harmful effects of n-CeO_2. In addition, the various physiological responses to nano cerium were discovered to be associated with fish species, fish age, water pH, and exposure rate and dosage. In the same issue, Özel et al. (2013) investigated that exposure zebrafish embryos more than three days to n-CeO_2 (20 and 50 ppm) increases the intestinal 5-HT quantity in live embryos. These results propose that the particles of n-CeO_2 can concentrate 5-HT at the accumulation site of nanoparticle and deplete it from the tissues. Besides, Jun et al. (2013) investigated that contaminated *Carassius auratus* rearing water with n-CeO_2 remarkably inhibited brain-acetylcholinesterase (AChE) and liver SOD and CAT biomarker activities at high levels (≥160 mg L^{-1}).

Additionally, Rundle et al. (2016) demonstrated that acute exposure to n-CeO_2 increased plasma cortisol levels though there was no indication of osmoregulatory stress signs in *Catostomus commersonii*. Also, Felix et al. (2013) found that contaminated zebrafish environment with ≥800 mg L^{-1} CeO_2 under low pH values inhibited embryo hatching process. On another study, Jemec et al. (2015) investigated no toxic effects of n-CeO_2 up to 100 mg L^{-1} on the early stages of zebrafish.

However, long-term exposure of target tissue to n-CeO_2 may cause a variety of toxicological effects in these organs. For example, Rosenkranz et al. (2012) demonstrated that n-CeO_2 induced cytotoxic effects on rainbow trout gonadal cell lines (RTG2 cell lines). Also, Gaiser et al. (2009) investigated that n-CeO_2 induced hepatotoxic effects on early stages of trout fish. While, Gagnon et al. (2018) represented that contaminated surface water with n-CeO_2 showed immunotoxicity signs and accumulation in high levels at rainbow trout gills. Moreover, Correia et al. (2019) investigated that exposed rainbow trout to the highest levels of n-CeO_2 (0.1 µg L^{-1}) for 28 days significantly increase the liver CAT activity as well as caused marked histopathological alters in the hepatocytes cells (e.g. pyknotic nucleus, hepatocyte vacuolization, hyperemia and enlargement of sinusoids) and gills (e.g. hyperplasia epithelial, intercellular edema, lifting, aneurysms, secondary lamella fusion and lamellar hypertrophy). In vitro investigations indicate that the capability of n-CeO_2 to promote ROS production was implicated in the cytotoxicity mechanisms.

5.2 In bivalve mollusks

Many bivalve species serve significant roles in aquatic and marine ecosystems by purifying water and providing habitat and food for a wide range of ocean creatures (Abdel-Latif et al., 2020). As suspension-feeders, bivalve mollusks have greatly grown processes for cellular internalization of NPs (endo- and phagocytosis), integral to key physiological functions such as non-specific immunity and intra-cellular digestion (Canesi et al., 2012). Several kinds of bivalve mollusks are abundant in marine and freshwater ecosystems, where they are commonly used in biomonitoring of ecosystem perturbations.

Several studies evaluated the toxicological effects of n-CeO_2 in a wide range of bivalve mollusks. Bustamante and Miramand (2005) informed that the digestive glands of the scallop, *Chlamys varia*, could accumulate up to 3.17 µg g^{-1} from 10.85 µg g^{-1} CeO_2 contaminated sites in the Bay of Biscay. Also, Montes et al. (2012) illustrated that the blue mussel, *Mytilus galloprovincialis* can accumulate Ce in its

tissues was very low (1–3%) which indicated by their mass balance and approximately all the introduced *n*-CeO_2 were down in the pseudo-feces. In a similar way, it was demonstrated that the directly fed *M. galloprovincialis* with *n*-CeO_2 contaminated phytoplankton revealed that almost 99% of the CeO_2 levels was uptaken and expelled in pseudo-feces (Sendra et al., 2019). The highest accumulation of CeO_2 levels declined the lysosomal membrane stability and increased the production of total extracellular oxyradical (Ciacci et al., 2012). Sendra et al. (2018) found that the differences in zeta potential, biocorona formation, and shape of NPs appeared to be responsible for a diverse effect on *M. galloprovincialis* hemocytes. The physico-chemical properties of NPs, such as spherical shape and the negative charge of *n*-CeO_2, induced ROS and phagocytosis reactivity and reduced biomarker indicating stress.

Exposed the freshwater bivalve, *Corbicula fluminea*, to high *n*-CeO_2 concentrations (100 μg L^{-1}) for six days significantly enhanced glutathione-S-transferase (GST), caspase-3, lactate dehydrogenase (LDH), total antioxidant capacity (T-AOC) and CAT activities (Koehlé-Divo et al., 2018). Moreover, DNA degradation in other aquatic organisms such as *Chironomus riparius* and *Daphnia magna* was induced by *n*-CeO_2 toxicity at a concentration of 1 mg L^{-1} for 24 h exposure (Lee et al., 2009). Besides, Garaud et al. (2015) demonstrated that the sublethal *n*-CeO_2 exposure suppressed CAT activity, lipoperoxidation in the digestive glands of the bivalve mussel, *D. polymorpha*. The toxicological effects and accumulation level of *n*-CeO_2 depends on its concentration and exposure period (Rosenkranz et al., 2012). At the same trend, Garaud et al. (2016) revealed that bioaccumulation of citrate-coated *n*-CeO_2 in the *D. polymorpha* mussels was three times more than bare *n*-CeO_2, perhaps because of the long-time of exposure (three weeks) or the *n*-CeO_2 form.

5.3 Planktonic and other aquatic species

The toxicity of *n*-CeO_2 to planktonic and algae species is induced by adsorption to cell surfaces and disruption of membrane transport (Heinrichs et al., 2020). Whereas, the higher organisms can directly ingest *n*-CeO_2 (Sterner 2009), and within the food web, both aquatic and terrestrial organisms can accumulate nanoparticles (Lasley-Rasher et al., 2016). It is remarkable that the exposed plankton especially zooplankton to toxins and environmental contaminants often induced unfavorable behavioral responses, then it will affect negatively on the organisms consuming them (Michalec et al., 2013a). Furthermore, responses may depend on dosage and time of exposure (Michalec et al., 2013b).

Several investigations have been designed to examine the toxicological effects of *n*-CeO_2 on aquatic planktons and other organisms. Lee et al. (2009) described a genotoxic adverse impact of *n*-CeO_2 with elevated DNA strand breaks in *Daphnia magna* at a level of 1 mg L^{-1}. Besides, García et al. (2011) illustrated that the LC50 was 0.012 mg ml^{-1}. In contrast, Hoecke et al. (2009) indicated that no acute toxicity signs was observed in *D. magna* and *Thamnocephalus platyurus* exposed to a high level of *n*-CeO_2 (5 mg L^{-1}) for 24 hr. Otherwise, the chronic exposure of *D. magna* to 10-100 mg L^{-1} *n*-CeO_2 for 21 days resulted in significant adverse effects on their reproduction process.

The acute and chronic toxicity of *n*-CeO_2 (up to 1000 mg L^{-1}) on growth and reproduction capability of *Ceriodaphnia dubia*, *D. magna*, *and Pseudokirchneriella subcapitata* significantly influenced by EC50 values (11.9 and 25.3 mg L^{-1}) with or without humic acids addition (Manier et al., 2011). Also, Artells et al. (2013) found that the acute toxicity impacts of *n*-CeO_2 on the capability of swimming of *D. similis* is 350 times extra than *D. pulex*, under EC50 of 0.26 mg L^{-1} and 91.79 mg L^{-1}, respectively for 48 h. In addition, it was found that ingestion of contaminated algae through the food chain was the main pathway *n*-CeO_2 uptake by *D. pulex* (Auffan et al., 2013). Moreover, the toxicity effects may be depends on the *n*-CeO_2 form in the environment. Tella et al. (2015) investigated that bare and citrate-coated *n*-CeO_2 showed various colloidal and chemical behaviors in the aquatic ecosystem. The coated *n*-CeO_2 dissolved in water faster than any other forms because of surface complex formation with citrate that led to the freeing of Ce that dissolved into the column of water. Also, the *n*-CeO_2 absorption by planktonic filter feeders (*Eudiaptomus vulgaris*) and benthic grazers (*Planorbarius corneus*) is affected by its forms, exposure duration, level, and aggregate concentration in aqueous sediment. For instance, the sediment-dwelling amphipod, *Corophium volutator* develop in marine sediments contaminated with 12.5 mg L^{-1} *n*-CeO_2 showed a remarkable elevation in oxidative damage (increases in superoxide dismutase (SOD) activity, lipid peroxidation and single-strand DNA breaks) in comparison to those matured in sediments without NPs and those holding huge-sized CeO_2 particles despite of there was no influence on survival rate (Dogra et al., 2016).

The experimental induction of sub-lethal reproductive toxicosis of *n*-CeO_2 was studied in daphnids (Manier et al., 2011) and nematodes (Roh et al., 2010). Also, the malformations and inhibition of growth was noted in fish intoxicated with 10 mg L^{-1} *n*-CeO_2 (Jemec et al., 2012), while genotoxicity was noted in chironomids and daphnids (Lee et al., 2009) and amphibian species (Bour et al., 2015). Additionally, many researchers investigate the behavior of *n*-CeO_2 in various aquatic ecosystem; they reported that NPs can quickly aggregate and settle (Keller et al., 2010; Quik et al., 2010), and end in the sediment/water interface or at the sediment.

In another toxicity study on the unicellular green alga, *Pseudokirchneriella subcapitata*, it was found that the acute exposure to *n*-CeO_2 for 24 h to a concentration of 5000 mg L^{-1} (14, 20, and 29 nm CeO_2 particles), showed 12, 10 and 7% mortality rate, respectively (Hoecke et al., 2009). Besides, Rogers et al. (2010) fixed a 50% effect concentration (EC50) for preventing the growth of 10.3 mg L^{-1} for *P. subcapitata*, while Van Hoecke et al. (2011) established an EC10 of 2.6–5.4 mg L^{-1} and Rodea-Palomares et al. (2010) an EC50 of 2.4–29.6 mg L^{-1} for the same species. *n*-CeO_2 were internalized as intracellular vesicles within *C. reinhardtii*, but there is no remarkable impact on the growth of algal within any intense exposure (Taylor et al., 2016).

Moreover, Zhang et al. (2011) clarified that the environmental relevant exposure concentrations (approximately 140–14000 ng L^{-1}) remarkably reduced the mean life span of could and nematodes prompt the collection of ROS and oxidative damage in *Caenorhabditis elegans*. NPs were observed to accumulate and gather in the sediment. Thus, Bour et al. (2016) investigated suppressed with bacterial communities in the third week of NPs (1 mg L^{-1}) pollution. The interaction between

microorganism and *n*-CeO_2, or NPs concentration, dissolution and the structural complexity of the biological environment could be indirectly responsible for the toxicity observed on *Pleurodeles* (Bour et al., 2016). Furthermore, LC50 values of *n*-CeO_2 exhibited a negative relationship to the ratio of surface-to-volume toward 14 ciliated protist species, indicated that *n*-CeO_2 surface adsorption could participate in the reported toxicity. The possible *n*-CeO_2 toxicity mechanisms toward ciliated protists include induction of DNA damage, cellular necrosis, and oxidative injury because of size and surface chemistry of NPs and heavy metals leaching from the colloidal form (Zhao et al., 2012).

6 Expected beneficial effects of using *n*-CeO_2 in aquaculture

6.1 Antioxidant and therapeutic properties

Because of its numerous medicinal uses, such as antibacterial, antioxidant, and anticancer activity, drug delivery applications, anti-diabetic properties, and tissue engineering processes, *n*-CeO_2 has lately gained a lot of interest (Thakur et al., 2019). Many researches pointed out that *n*-CeO_2 considered as a potent scavenger for free radicals to promotes a protective cellular response (Xia et al., 2008), as well as it could display as an effective antioxidant agent (Korsvik et al., 2007; Li et al., 2016; Nelson et al., 2016a). The antioxidant features of *n*-CeO_2 can protect biological tissues from oxidative stress resulted from the overproduction of ROS because of its physicochemical properties (Karakoti et al., 2008). Particular, *n*-CeO_2 antioxidant properties might occur from oxygen vacancies in the surface of crystal lattice due to the existence of Ce in the trivalent state, which could give reaction sites trapping ROS (Korsvik et al., 2007; Xue et al., 2011; Ciofani et al., 2014).

A wide-ranging result of toxicological researches using *n*-CeO_2 proved the ROS ability of *n*-CeO_2 which acts as a regulator agent based on the intracellular pH (Alili et al., 2011; Amin et al., 2011). Therefore, *n*-CeO_2 is of a great help in the treatment of tumor and act as neuroprotective agent (Colon et al., 2010; Alili et al., 2011), as well as stimulation and regulation of angiogenesis process (Das et al., 2012), and healing of wound (Chigurupati et al., 2013). Moreover, due to the protective characteristic against some biological and chemical hazards, *n*-CeO_2 was studied as a scavenger for free radical and recently applied in nanomedicine to augment the generation of free radicals (Telek et al., 1999; Ciofani et al., 2014). Possibility of *n*-CeO_2 molecular mechanisms that occur in the antioxidant properties has confirmed by SOD and CAT attributed the immune regulated role of *n*-CeO_2 in the live cell (Das et al., 2007; Korsvik et al., 2007; Pirmohamed et al., 2010). Also, the mRNA expression have investigated the ROS trapping characteristics of *n*-CeO_2 (Ciofani et al., 2014). Exactly, *n*-CeO_2 are recognized to catalyze the ROS decomposition, such as hydrogen peroxide and superoxide radicals due to their CAT-like and SOD-like upregulated activities (Baldim et al., 2018).

The antioxidant ability of *n*-CeO_2 allows it to act as an immune enhancer (Caputo et al., 2015). Specifically, the transformed and recycled ability of *n*-CeO_2 might be responsible for this biological activity. For instance, Ce^{4+} can be reduced to Ce^{3+} at the nanoscale, to stabilize surface oxygen defects (Eriksson et al., 2018). While, the reduction form of CeO_2 is a long half-life free radical scavenger, which protects the integrity of proteins and DNA, reduces the possible free radicals as well as reduced cell injury and catalyzes the decomposition of excessive free radicals (Amin et al., 2011; Nelson et al., 2016a). Also, *n*-CeO_2 enhances natural killer cells activity immune marker expression by protecting hematopoiesis and enhancing the body immune activity. For instance, Qin et al. (2019) found that the dietary inclusion of *n*-CeO_2 (0.8 mg kg^{-1}) promoted growth in crabs (*Eriocheir sinensis*) and decreased the mortality rate as well as reduced ammonia nitrogen stress relief, and enhanced immunity status. Moreover, the pre-treatment with *n*-CeO_2 simulated the activities of GST, SOD, CAT, and SOD enzymes and alleviated hepatopancreatic damaged induced by the ROS reaction. The possible beneficial application of *n*-CeO_2 were summarized in Figure 2.

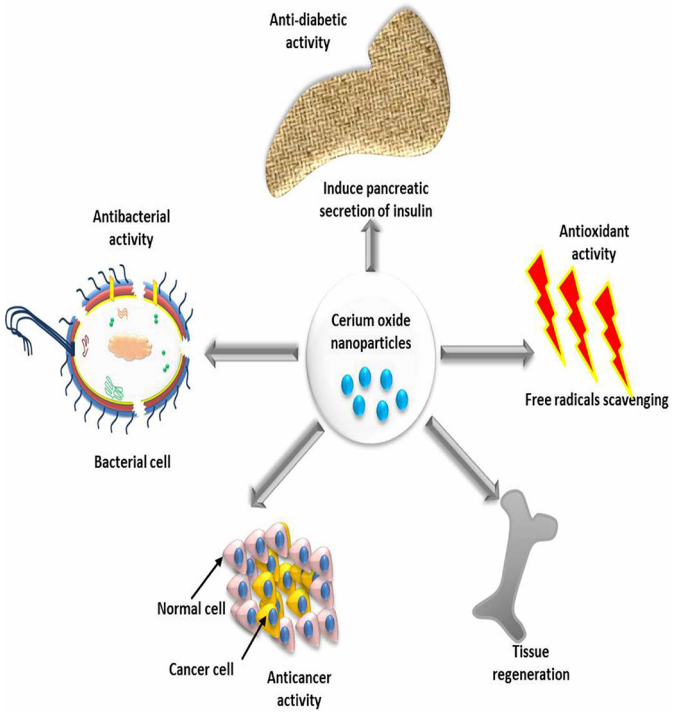

Fig. 2. the expected beneficial applications of *n*-CeO_2. *n*-CeO_2 can act as **a** pro-oxidant in acidic conditions and an antioxidant in a neutral environment. These properties make *n*-CeO_2 an ideal therapeutic that is toxic to cancer cells without damaging normal cells. In addition, *n*-CeO_2 showed antiapoptotic effects while increasing insulin secretion.

6.2 Antimicrobial properties

n-CeO_2 is a more efficient antibacterial agent because of its minimal cytotoxicity to normal cells and its novel antibacterial mechanism based on the reversible conversion between two valence states of Ce (III)/Ce (IV).

Also, *n*-CeO_2 showed higher toxic properties against wide range of microbial strains. For example, it was found that a decreased size (<7 nm) of *n*-CeO_2 was adequate to induce a

cytotoxic effect against *Escherichia coli*, via simple diffusion throughout the cell membrane (Thill et al., 2006). In addition, several in vitro studies proved antibacterial activity of *n*-CeO_2 against *Pseudomonas aeruginosa*. Specifically, Ravishankar et al. (2015) investigated that the increasing of an inhibition zone in the *P. aeruginosa* (NCIM-2242) related with the high levels of *n*-CeO_2 (500, 750, and 1000 μg L^{-1} per well). Moreover, dos Santos et al. (2014) stated under low temperature conditions, the antibacterial role of *n*-CeO_2 enhances against *E. coli*, *Bacillus subtilis*, and *Shewanella oneidensis*. The possible mechanisms that cause this reaction was due to the scavenge role of *n*-CeO_2 against ROS. Also, the green synthesized *n*-CeO_2 (spherical, average size, 17 nm) exhibit a high antimicrobial activity against *S.aureus, E.coli, P. aeruginosa, C. albicans, and A. fumigatus* in the range of 15–31 mm zone inhibition (Putri et al., 2021).

The antibacterial activity of *n*-CeO_2 is related to its photocatalytic characteristics. Specifically, ROS entering bacterial cells and bends with cellular constituents such as the mesosome, cytoplasm, protein, and nucleoid, causing serious damage to the cell components, weakening the cells, and finally leading to cell death (Putri et al., 2021). Thus, this is an interesting research area focusing on the therapeutic use of *n*-CeO_2 as antioxidants.

3 Conclusions and perspectives

The increasing production of *n*-CeO_2 and its wide utilization in numerous industrial products are growing very rapidly and their disposal into the aquatic environment would pose drastic and serious risks to the exposed aquatic organisms and subsequently health of human beings. This review highlights the possible fate of *n*-CeO_2 in aquatic ecosystems and modes of toxicological effects in species of finfish, shellfish, algae, and other aquatic organisms. Among the available approaches, green synthesis has recently received a lot of attention from researchers in order to synthesized *n*-CeO_2 that employ high stable compounds and induce low toxic impacts. The literature indicates the urgent need for the future development of different standard protocols to test the toxicological impacts of *n*-CeO_2 in the exposed aquatic organisms, their fate in aquatic environments, and potential interaction with various environmental contaminants. Furthermore, to eliminate *n*-CeO_2 dissolution to hazardous ions, it could be suggested to (1) produce coated NPs, (2) generate the NPs molecules using a method that produced a low NPs surface area and thus dissolution, or a chelating agent can be applied to the NPs surface. Moreover, with regard to the serious effects of these environmental pollutants, it is recommended to give great concern to general human health and to develop strategies to reduce and inhibit their release to aquatic ecosystems.

Authors contributions

Naiel M.A.E. Conceptualization, Writing - original draft & collected literature; Abdel-Latif H.M.R., helped in Conceptualization & Investigation; Khafaga A.F., Abd El-Hack M.E. & Elhady H.A., Supervision & Writing - original draft; Dawood M. A.O. & Alkazmi L., Investigation; Conte-Junior C.A.& Elnesr S. S., Supervision & Writing - original draft; Alagawany M. & Batiha G.E., Investigation & Writing - original draft.

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Availability of data and materials

This is a review article with no original research data.

Conflicts of interest

The authors declare no conflict of interest.

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