

Green Synthesis of Cerium Oxide Nanoparticles (CeO₂ NPs) and Their Antimicrobial Applications: A Review

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Abstract: During the last decade green synthesized cerium oxide nanoparticles (CeO₂ NPs) attracted remarkable interest in various fields of science and technology. This review, explores the vast array of biological resources such as plants, microbes, and other biological products being used in synthesis of CeO₂ NPs. It also discusses their biosynthetic mechanism, current understandings, and trends in the green synthesis of CeO₂ NPs. Novel therapies based on green synthesized CeO₂ NPs are illustrated, in particular their antimicrobial potential along with attempts of their mechanistic elucidation. Overall, the main objective of this review is to provide a rational insight of the major accomplishments of CeO₂ NPs as novel therapeutics agents for a wide range of microbial pathogens and combating other diseases.

Keywords: nanotechnology, green synthesis, cerium oxide, nanoparticles, antimicrobial, infections, biomedical

Introduction

Nanotechnology has got a remarkable interest in every field of science and technology and is presently considered among one of the leading research avenues. It has a multitude of applications in the field of electronics, imaging, industry, and healthcare.^{1,4} Mostly, in healthcare it has been exploited in diseases diagnostics, treatment, delivery, and formulations of novel drugs.^{1,4} It exploits nano size structures with size ranges from 1–100 nm, known as nanoparticle (NPs). These nano-scale entities have unique physicochemical properties and have been utilized in various fields of physics, biology, and chemistry.⁵

Among other NPs, Cerium Oxide (CeO₂) NPs have been mostly exploited due to their unique surface chemistry, high stability, and biocompatibility.^{6,7} It is mostly used in the fabrication of sensors, cells, catalysis, therapeutics agents, drug delivery carriers, and anti-parasitic ointments (Figure 1).^{1,6,8} Presently, CeO₂ NPs is mostly synthesized via two methods, such as physical and chemical.^{7,9} However, these methods utilize toxic reducing solvents posing several threats to the biodiversity and ecosystem. Moreover, the NPs obtained with such approaches are toxic and unstable, making them less efficient.^{9,10} Thus, recently a safe, less toxic method has been used by researchers known as Green Synthesis. This method utilizes various biological resources such as plants, microbes, or any other biological derivative.^{11,15} These biological extracts have a rich source of phytochemicals

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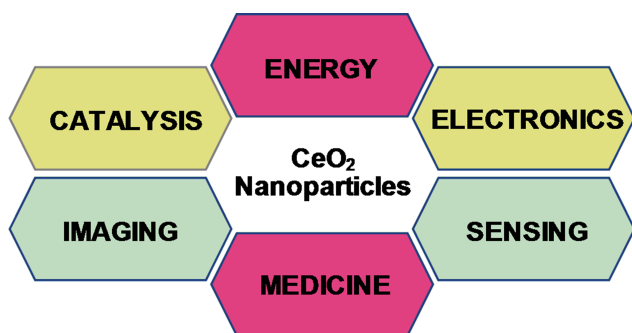


Figure 1 General applications of CeO₂ nanoparticles.

such as ketones, amines, enzymes, and phenols, which are believed to be responsible for the reduction and stabilization of bulk salts into respective nanoparticles NPs.^{16,19}

To date various applications of green synthesized CeO₂ NPs have been reported such as antimicrobial, anti-cancer, anti-larvicidal, photo-catalysis, and antioxidant therapies.^{16,20,22} Among other biomedical applications the antimicrobial potential is certainly the most exploited. Previously it has been reported that CeO₂ NPs to display their anti-microbial actions through various mechanisms.⁹ But mostly CeO₂ NPs kill microbes via triggering the production of an excess of reactive oxygen species in cells.^{9,16} However, further studies need to be conducted to fully elucidate the complete mechanism of action. Here in this review we aim to focus on the following topics. Arrays of biological resources have been exploited to date for the synthesis of CeO₂ NPs. Moreover, the synthesis mechanisms along their biomedical applications are discussed with special emphasis on the antimicrobial activity.

Synthesis of CeO₂ NPs

Nanoparticles are synthesized through various physico-chemical methods.⁵ However, both methods require toxic solvents, high temperature, and pressure, which pose threats to the environment.^{23,25} Moreover, higher cost, laborious downstream processing, lesser biocompatibility, instability, and low yield make them further inefficient.^{7,10} There is a growing need to fabricate nanostructures which have the potential to solve these problems.^{5,9} Presently, researchers have exploited the green method to overcome all these challenges.⁵ For instance, plants, microbes, and other biological products have been used as reducing and/or stabilizing agents in the fabrication of ecofriendly NPs.²⁵ CeO₂ NPs have also been synthesized using various physical, chemical, and biological methods.⁹ The

latter is extensively utilized for its biomedical, pharmacological, and food applications due to their safe and biocompatible nature.⁹ Moreover, features like high yield, everlasting stability, and better morphologies can be obtained using a greener approach.^{7,9}

Green Synthesis from Plants

Green syntheses of CeO₂ NPs have been reported using plant extracts, microbial, and other biological derivatives. Plants in this regard have been the most efficient source due to their abundance, safe nature, and rich source of reducing and stabilizing agents.^{26,29} Various parts of plants such as leaves, flower, and stem have been used for the synthesis of CeO₂ NPs.^{16,30,31} Till date the majority of green synthesis studies have been conducted on leaves extracts, as it is a rich source of metabolites.^{11,16,32,33} A broad variety of metabolites/phytochemicals in plant extracts such as ketones, carboxylic acids, phenols, and ascorbic acid are used as reduction and stabilizing agents (Figure 2). Plants based CeO₂ NPs are produced through a simple approach in which bulk metal salt is mixed with the extract and the reaction completes in minutes to a few hours in ordinary lab conditions.^{28,29,34} The metallic salt solution is reduced into respective nanoparticles via the phytochemicals whose synthesis is confirmed firstly through color change from colorless to yellowish, brownish, or whitish, and then characterized through various spectroscopic and imaging techniques.^{16,29,35}

Leaf extract of *Moringa oleifera L* was used to synthesize CeO₂ NPs with spherical morphologies and size of 100 nm. The synthesized NPs showed potential antimicrobial and wound healing properties.³⁶ *Gloriosa Superba* leaf extract was used as a reducing and stabilizing agent in synthesis of CeO₂ NPs and has shown potential antibacterial properties.³⁷ *Hibiscus sabdariffa* natural extract yielded crystalline CeO₂ with a diameter of 3.9 nm.³⁰ Spherical shaped nanoparticles of size 63.6 nm synthesized from Gel extract of medicinally important plant *Aloe Barbadosis*.³⁸ The resultant CeO₂ NPs showed high antioxidant potential. Green synthesis of CeO₂ nanoparticles was demonstrated using *Jatropha curcus* leaf extract having high photocatalytic activity and a monodispersed shape of 3–5 nm.¹⁰ Spherical shaped cerium oxide nanoparticles are synthesized using Leaf extract of *Oleo Europaea*, with a size of 24 nm having high antimicrobial activity against both gram-negative and positive strains of bacteria.¹⁶ *Origanum majorana* extracts were used to synthesize CeO₂ NPs, having pseudo

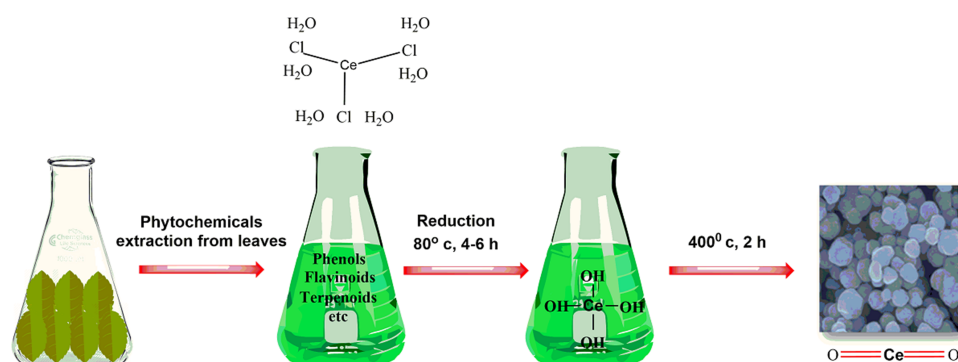


Figure 2 Biosynthesis: Reduction, stabilization and characterization of CeO₂ nanoparticles.

spherical shape (20 nm). FT-IR confirmed that the reduction is attributed to the presence of different phenolic and flavonoids compounds in the extract.¹⁸ CeO₂ was synthesized using *Rubia cordifolia* leaf fusions. Spectroscopic and microscopic analysis revealed hexagonal shaped NPs having a size of 26 nm. The biogenic CeO₂ NPs also showed excellent anti-cancer potential.³³ Nano rod size ranges from 5–55 nm CeO₂ NPs resulted when *Pedalium murex* L. was added to the aqueous solution of salt at room temperature having high antibacterial activity.³² *China rose* petal was used as a robust bio template for the facile fabrication of novel ceria Nano sheet with a size of about 7 nm.³⁹ The deviation in size and morphology noticed among the reported studies might be due to the different influence of reaction temperature, pH, time, concentration of salt precursor or plants extracts, and part of the plant being used.^{13,27,28,40} Moreover, plants based CeO₂ NP's showed excellent stability at diverse conditions. For instance, green mediated ceria NP's remain stable at liquid solution and no physiochemical changes were observed.^{13,36} Similarly, biogenic CeO₂ NP's also showed high thermal stability at high temperature and remained stable for a longer period of time, which indicates their long durability and everlasting stability.^{27,28,33,41} Until now, various plants have been used in the biogenic synthesis of CeO₂ NPs and are shown in Table 1.

Green Synthesis from Microbes

Microbes also have an intrinsic potential to synthesize nanoparticles, as they are a rich source of secondary metabolites.²³ Among other nanoparticles CeO₂ NPs with various shapes and sizes have been synthesized in recent years from microbes (Table 2). Green synthesis of CeO₂ from microbial species is a simple, reliable, cost-effective, and eco-friendly approach.⁴² Microbial metabolites such as

enzymes, proteins, and heterocyclic derivatives play a crucial role in reducing and stabilizing of CeO₂ bulk salt into respective NPs.^{42,43} Moreover, micro-biogenic CeO₂ NPs exhibited improved stability, water dispensability, and showed high fluorescent properties and were less agglomerated.⁴³

Aspergillus niger extract yielded cubic fluorite NPs with spherical morphology and an average size of 5 nm. FT-IR analysis revealed the presence of an hydroxyl group, carboxylic group, and phenol group which are supposed to be involved in the reduction of NPs.²¹ *Curvularia lunata* extract has also been used to synthesize spherical shaped CeO₂ NPs with size ranges from 5–20 nm. Color change from white to yellow brown indicated initial reaction. The NPs were tested against microbial pathogens and showed excellent antibacterial potential. Spherical shaped CeO₂ NPs of size ranges from 20–30 nm were made using *Fusarium solani* extract which showed effective growth inhibition and biofilm formation of pathogenic bacterial strains.⁴² *Shadab Ali Khan* observed the biosynthesis of spherical shaped (12–20 nm) CeO₂ NPs by using a thermophilic fungus *Humicola* capping agent.⁴³ The resultant NPs were characterized by UV, XPS, PL- Spectroscopy, TEM, FT-IR, and XRD. Moreover, these NPs showed excellent potential in treatment of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Bacterial extract has also been exploited in the fabrication of CeO₂ NPs, for instance *Bacillus subtilis* extract yielded spherical shaped NPs with an average size of 8 nm. The bacterial mediated NPs also showed excellent antioxidant potential in vitro.⁴⁴ Despite, all these applications the microbial route of synthesis has certain shortcomings, such as the high probability of pathogenicity, laborious culturing, and contamination issues. However, it offers a lot of promise in the field of nanotechnology and could become a leading avenue in

Table 1 CeO₂ Nanoparticles Made from Various Plants Species

S. NO	Plant Name	Part	Characterization	Shape	Size (nm)	FT-IR Group	Ref
1.	<i>Gloriosa superba</i>	Leaf	XRD, XPS, TEM, FT-IR & UV- vis	Spherical	5	O-H, Ce-OH, H-O-H & O-C-O	[37]
2.	<i>Hibiscus sabdariffa</i>	Flower	HRTEM, SEM, XRD, XPS, EDS, FT-IR		3.9	Ce-OH	[30]
3.	<i>Olive</i>	Leaf	SEM, XRD, FT-IR, TGA	Spherical	6	C-O, O-H & H-H	[26]
4.	<i>Oleo Europaea</i>	Leaf	XRD, SEM, TEM, UV- Vis, FT-IR, TGA	Spherical	24	O-H, C-H & N-O	[16]
5.	<i>Prosopis juliflora</i>	Leaf	UV-vis, PSA, FT-IR, XRD, XPS & HRTEM/TE	Spherical	15	O-H & Ce-O	[11]
6.	<i>Salvia macrosiphon Boiss</i>	Seed	XRD, UV-Vis, FT-IR, FESEM & TGA	Spherical	~47	Ce-O, O-Ce-O, C-H & C=O	[22]
7.	<i>Acalypha indica</i>	Leaf	XRD, SEM, TEM, EDS & FT-IR	Spherical	25–30	O-H, Ce-OH & Ce-O-Ce	[13]
8.	<i>Aloe barbadensis</i>	Leaf	XRD, TEM, FT-IR & PSA	Spherical	63.6	-C-H-, C=O, -C-H-, C-F, =C-H & C-Cl	[38]
9.	<i>Aloe vera</i>	Leaf	FT-IR, XPS, HR-TEM	Spherical	2–3	-C-H, -C-C	[19]
10.	<i>Rubia cordifolia</i>	Leaf	UV- Vis, XRD, XPS, SEM, FT-IR, EDAX	Hexagonal	26	O-H & Ce-O	[33]
11.	<i>Prosopis farcta</i>	Aerial	UV-Vis, PXRD, TEM, FESEM, FT-IR	Spherical	30	O-H, Ce-O and N=O	[58]
12.	<i>China rose</i>	Petal	FESEM, FETEM, AFM, XRD & XPS	Nano-sheet	7	-	[39]
13.	<i>Centella asiatica</i>	-	UV-vis, DLS, SEM, HRTEM & EDS	Spherical	8	-	[59]
14.	<i>Walnut</i>	Shell	XRD, SEM, TEM, EDS & FT-IR	Spherical	9–12	Ce-O and O-H	[60]
15.	<i>Azadirachta Indica</i>	Leaf	UV-Vis, XRD, XPS, FESEM, TEM, HRTEM, EDS, UV-DRS & FT-IR	Spherical	10–15	Ce-O-C, O-H, C-H	[61]
16.	<i>Euphorbia tirucalli</i>	Stem	PXRD, SEM, TEM, FT-IR & PL	Flaky	37–40	-OH, -COO- and C-H	[28]
17.	<i>Lemon grass</i>	Grass	XRD, PL, TEM & SAED	-	10–40	-	[62]
18.	<i>Leucas aspera</i>	Leaf	PXRD, SEM, UV-vis, TEM, SAED	Microsphere	4–13	-	[63]
19.	<i>Petroselinum crispum</i>		UV-vis, IR-, XRD, SEM, TEM	Spherical	50–15	-	[14]
20.	<i>Moringa oleifera</i>	Peel	UV- Vis, FT-IR, XRD & HRTEM	Spherical	45	Ce-O & Ce-O-Ce	[36]
21.	<i>Watermelon</i>	Fruit juice	PXRD, FT-IR, UV-Vis & SEM	Irregular	36	Ce-O, C=O, C-O, C-H & O-H	[64]
22.	<i>Carrageenan</i>	-	PXRD, FT-IR, FESEM, UV-Vis, and TGA/DTA	Spherical	34	-SO ₃ -, Ce-O, H-O-H & C-O	[27]

(Continued)

Table 1 (Continued).

S. NO	Plant Name	Part	Characterization	Shape	Size (nm)	FT-IR Group	Ref
23.	<i>Ceratonia siliqua</i>	Leaf	XRD, FESEM, TEM & FT-IR	Spherical	22	–	[57]
24.	<i>Stevia rebaudiana</i>	-	XRD, FESEM, EDS, VSM	Spherical	8–10	–	[65]
25.	<i>Salvadora persica</i>		PXRD, FT-IR, UV-Vis, TEM, FESEM, EDS	Spherical	10–15	O-H, C-H, C=C, Ce-O & C-O C	[20]
26.	<i>Morus nigra</i>	Fruit	TEM, XRD & UV-Vis	Irregular	~ 7.5	–	[35]
27.	<i>Annona muricata</i>	Fruit	XRD, FT-IR, UV-DRS, FESEM	–	–	–	[50]
28.	<i>Justicia adhatoda</i>	Leaf	XRD, SEM, TEM, FT-IR & UV-DRS	Stick-like	20–25	-OH, C-H, C=O, N=O, C=C, C-O & C-N-C	[17]
29.	<i>Jatropha curcus</i>	Leaf	XRD, TEM & UV-Vis	Monodispersed	3 –5	–	[10]
30.	<i>Origanum majorana</i>	Leaf	TEM, FESEM, XRD & FT-IR	Spherical	20	O-H, C-H & C=O	[18]
31.	<i>Pedaliium murex</i>	Leaf	XRD, FT-IR, UV-Vis DRS, SEM	Nano-rod	5–55	O-H, C-H, C-O, C=O, C=N, C-N & Ce-O	[32]
32.	<i>Elaeagnus angustifolia</i>	Leaf	XRD, SEM, TEM, FT-IR	Spherical	30–75	C-H & C=O	[29]
33.	<i>Euphorbia amygdaloides</i>		TEM, SEM, XRD & UV-vis	Spherical	42	–	[31]
34.	Orange	Peel	XRD, TEM, FT-IR & UV-vis	Cubic structure	20–25	C-O-H or C-O-R	[34]
35.	<i>Piper betle</i>	Leaf	XRD, FT-IR, SEM, EDS, XPS & TEM	–	-	N-H, N-O & C-N	[66]

nanomedicine, but is yet to be explored. Particularly, these microbial based NPs can be used in designing novel fertilizers, fabricating sterile surfaces, polymers, and medical

accessories. Moreover, these biogenic NPs can also be exploited in disease management, drug synthesis, and delivery.

Table 2 CeO₂ Nanoparticles Synthesized from Various Fungus Species

S. NO	Microbe Name	Characterization	Shape	Size nm	FT-IR Group	Ref
1.	<i>Curvularia lunata</i>	TG/DTA, XRD, Raman, PL, FT-IR, UV-vis and TEM	Spherical	5–20	–	[54]
3.	<i>Humicola sp.</i>	UV-Vis, XPS, PLS, TEM, FT-IR & XRD	Spherical	12–20	Ce-O & Ce-O-Ce	[43]
4.	<i>Fusarium solani</i>	FT-IR, PL, TG/DTA, FESEM, XRD, EDAX, TEM, XPS, SAED & CLSM	Spherical	20–30	-OH, C-N & -C-O-C	[42]
5.	<i>Aspergillus niger</i>	UV-Vis, FT-IR, XPS, XRD, TG/DTA, PL & TEM	Spherical	5–20	H-O-H, O-C-O & Ce-O	[21]

Green Synthesis from Biological Products

Apart from the synthesis of nanomaterial from eukaryotes and prokaryotes organisms, NPs have also synthesized from biological derivatives.²³ They also play a crucial role in the reduction and stabilization of NPs.^{23,25} In contrast to plants and the microbial approach, bio-product based CeO₂ are much safer, scalable, and have shown excellent biocompatibility.^{45,47} For instance, egg white protein was used in order to synthesize CeO₂ NPs having size ranges from 8–17 nm with spherical morphologies.⁴⁸ These NPs were characterized and confirmed by UV's, FT-IR, TGA/DTA, and PXRD. FT-IR analysis revealed that the phenol, ether, hydroxyl, and amide groups were responsible for the reduction of these NPs. It also showed a good in vitro cytotoxicity effect towards human periodontal fibroblasts cells. Agarose is a natural matrix and has been used as a stabilizing and capping agent for CeO₂ NPs. NPs obtained have spherical morphologies with a diameter of 10.5 nm. NPs were characterized using various methods, including UV, FESEM, FT-IR, TGA/DTA, PXRD, and TGA/DTA techniques. As revealed by FT-IR analysis, it was found that the hydroxyl, ether, phenol, and amide groups were involved in biosynthesis.⁴⁵ Starch has also been exploited as a novel source for the synthesis of nano-ceria, with the results revealing spherical shape NPs with a diameter of 6 nm.¹²

Spherical shaped CeO₂ NPs, with a size of 5–10 nm, were synthesized from dextran. The resultant NPs exhibited strong anti-cancer potential.⁴⁶ Gum tragacanth reported by Darroudi et al⁴⁹ was used in the biosynthesis of CeO₂ NPs. These NPs were mono-dispersed shape with an average size range from 20–40 nm. The CeO₂-NPs exhibited very low cytotoxic effects on Neuro2A cell lines, making them suitable candidates for various biomedical and pharmacological applications.⁴⁹ Some other biological products which have been used for synthesis of CeO₂ NPs are listed in Table 3. Despite their biological applications these biogenic NPs could be used as a promising candidate in diseases treatment, drug delivery, and packing food. Some other products have also been explored for the synthesis of CeO₂ NPs which are shown in Table 3.

Biological Activity of Green-Mediated Cerium Oxide Nanoparticles

Antimicrobial Activity of Green-Mediated Cerium Oxide Nanoparticles

In the last few years, nanotechnology-based therapies have been exploited in disease diagnostics, treatment, and

Table 3 Bio-Mediated CeO₂ Nanoparticles from Different Sources of Biological Products

S. NO	Name	Characterization	Shape	Size nm	FT-IR Group	Ref
1.	Egg protein	UV-Vis, FESEM, FT-IR, TGA/DTA & PXRD	Spherical	8–17	-OH, Ce-O, Ce-O-Ce, C-H & N=O	[48]
2.	Honey	UV-Vis, FESEM, FT-IR, TGA/DTA, EDS & PXRD	Spherical	23	O-H, Ce-O, Ce-O-Ce, Ce-O-C & N=O	[67]
3.	Agarose	UV-Vis, FESEM, FT-IR, TGA/DTA & PXRD	Spherical	10.5	O-H, Ce-O, Ce-O-Ce & N=O	[45]
4.	Starch	UV-Vis, PXRD & TEM	Spherical	6	–	[12]
5.	Dextran	TEM, DLS, XPS & UV-Vis	Spherical	5–10	–	[46]
6.	Polyethylene glycol	HRTEM, TEM, UV-Vis & SLS-DLS	Spherical	~2	–	[68]
7.	Chitosan	XRD, HRTEM, FT-IR, TGA/DTA & UV-Vis	Spherical	~ 4	–	[69]
8.	Pectin	DLS, FESEM, EDSS, XRD, FT-IR, NMR, PL, FESEM, EDSS & UV-Vis	Spherical	≤ 40	-OH, C-H, C=O, -O-CH ₃ , C-O-C, N=O & Ce-O	[47]
9.	Tannic acid	FT-IR, XPS, XRD, HRTEM & UV-visible	Polycrystalline	~ 10	–	[15]

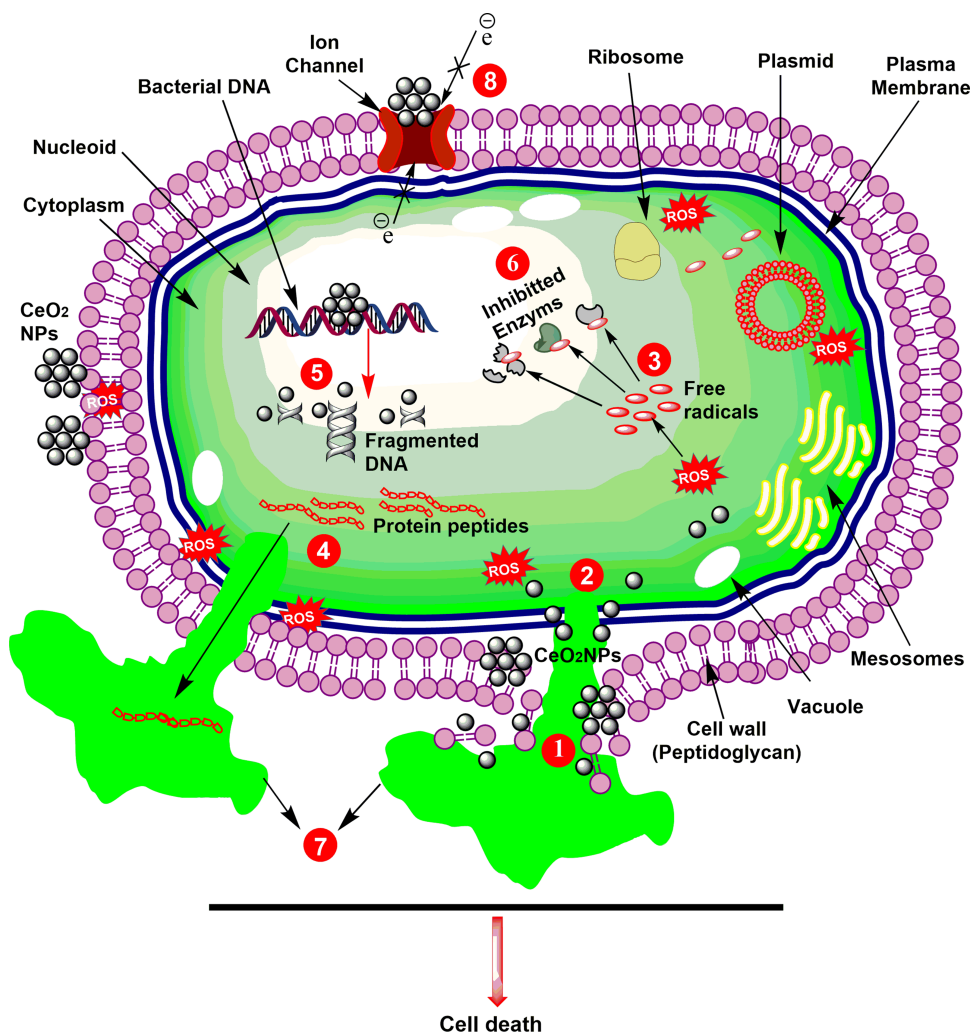


Figure 3 Schematic representation of antibacterial activity of CeO₂ nanoparticles. (1) Cell wall disruption; (2) Cell membrane disintegration; (3) Free radicals productions; (4) Loss of protein peptides; (5) DNA fragmentation; (6) Vital enzymes inhibition; (7) Loss of cellular fluids; and (8) Disruption in electron transport.

formulations of novel drugs.¹ For instance, the antimicrobial potential of NPs has been mostly exploited; and has showed substantial outcomes.^{23,24} Presently, CeO₂ NPs have attracted great interest as an antimicrobial agent, in particular against bacterial pathogens.^{15,16,50} The exact mechanism of killing microbes is yet not clearly elucidated. However, it is proposed that CeO₂ NPs mostly kill microbes via a massive production of reactive oxygen species (ROS) in cells, as shown in Figure 3.^{15,51} The bactericidal potential of CeO₂ NPs is attributed to strong electrostatic properties, distinctive morphologies, small size, and low band energy.^{16,52} Due to strong electrostatic potential CeO₂ NPs interact with membrane proteins thiols groups, which results in protein denaturation, membrane impermeability eventually leads to microbial death^{42,53} (Figure 3). Exposure to CeO₂ NPs kills microbes via membrane collapse by attachment with mesosomes,

malfunctioning of cellular compartments, and bio organic molecules, which ultimately lead to abnormal metabolism and physiology.^{16,42} Similarly, green mediated NPs kill-pathogens in a similar fashion and various biological species have been exploited and tested against a wide variety of microbes^{13,16} (Table 4). However, biogenic CeO₂ NPs unique morphologies, small size and bio-compatible nature were found to be more efficient and have the potential to treat a wide range of pathogenic bacterial species.^{11,13,15,16,42} Moreover, it also has the potential to kill both gram-positive and gram-negative bacteria, but due to structural complexity of gram-negative bacteria's membranes, it is more sensitive against gram-positive species.^{13,21,37,47,54} The difference in antimicrobial activity is due to differences in electrostatics between NPs and the bacterial wall, plant species, and wall composition.

Table 4 Various Microbes Tested Against Biogenic CeO₂ Nanoparticles

S. NO	Source	Microbes Tested	Ref
1.	<i>Olea europaea</i>	Fungus (<i>Aspergillus flavus</i> , <i>Fusarium solani</i> , and <i>Aspergillus niger</i>) Bacterial sps (<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> and <i>Klebsiella pneumoniae</i>)	[26]
2.	<i>Moringa oleifera</i>	<i>S. aureus</i> and <i>E. coli</i>	[36]
3.	<i>Curvularia lunata</i>	<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> and <i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i> , <i>Proteus vulgaris</i> and <i>Klebsiella pneumoniae</i>	[54]
4.	<i>Leucas aspera</i>	<i>Klebsiella aerogenes</i> , <i>Escherichia coli</i> , <i>Pseudomonas desmolyticum</i> and <i>Staphylococcus aureus</i>	[63]
5.	<i>Acalypha indica</i>	<i>Escherichia coli</i> and <i>Staphylococcus aureus</i>	[13]
6.	<i>Annona muricata</i>	<i>Enterococcus faecalis</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i>	[50]
7.	<i>Gloriosa Superba</i>	<i>Staphylococcus aureus</i> and <i>Streptococcus pneumoniae</i> , <i>E.coli</i> , <i>Proteus vulgaris</i> , <i>Klebsiella pneumoniae</i> , <i>Shigella dysenteriae</i> and <i>Pseudomonas aeruginosa</i>	[37]
8.	<i>Aspergillus niger</i>	<i>Streptococcus pneumoniae</i> , <i>Bacillus subtilis</i> , <i>Proteus vulgaris</i> and <i>Escherichia coli</i>	[21]
9.	<i>Fusarium solani</i>	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i>	[42]
10.	<i>Justicia adhatoda</i>	<i>Staphylococcus aureus</i> and <i>Escherichia coli</i>	[17]
11	<i>Euphorbia amygdaloides</i>	<i>P. acidilactici</i>	[31]
12	<i>Pectin</i>	<i>E. coli</i> and <i>B. subtilis</i>	[47]

Due to rapid evolution of the bacterial genome, bacteria have evolved to confer resistance to antimicrobial agents.^{55,56} Thus, in quest of a new treatment, biogenic CeO₂ NPs has shown promising results in treating multi-drug resistance bacteria and could be a promising candidate against such refractory pathogenesis.²⁶ CeO₂ NPs along other conjugates have been amalgamated with various organic and inorganic hybrids to enhance the antimicrobial response.^{17,46} Similarly, bio-mediated CeO₂ NPs kills fungi by producing a mass number of free radicals and ROS which causes distorted structure and physiology and leads to fungus death.¹⁶ However, a few studies have only been conducted on fungi. Despite the increasing knowledge on the antimicrobial activity of CeO₂ NPs much remains unknown about their exact mechanism of encountering bacteria, toxicity, in vivo studies, and environmental concerns, which needs to be addressed. Moreover, the low band energy potential of CeO₂ NPs could be used in fabricating sterile surfaces at hospital or lab settings and will diminish nosocomial and other acquired infections.

Other Potential Biomedical Applications

Beside anti-microbial therapies CeO₂ NPs have also been used in management of other ailments.^{35,57} For instance,

biogenic CeO₂ NPs have been mostly used in treatment of various cancers, such as osteosarcoma, colon, cervical, and breast cancers.^{18,20,27,46,52} Results indicated that these NPs exhibited strong anticancer potential and could be used as a chemotherapeutic agent thanks to their minimal toxicity, capacity to induce apoptosis, and/or necrosis in cancer cells.⁴⁶ CeO₂ NPs synthesized from *Origanum majorana* and *Ceratonia siliqua* showed high antioxidant activity.^{18,31,57} Results showed higher expression of antioxidant enzymes which in turn eradicated free radicals and improved cellular functions.³¹ Furthermore, antioxidant potential was higher when compared to commercial synthetic antioxidants.¹⁸ CeO₂ NPs synthesized from fruit extract of *Morus nigra* exhibited excellent anti-diabetic activity on L6 cell lines. The treatment was dosage dependent and NPs with lesser size resulted in higher uptake of glucose in vitro.³⁵ Though biogenic CeO₂ NPs have shown excellent pharmacological potential, however, the mechanism of action, minimum inhibitory concentration, and best possible delivery system should need to be determined. Moreover, cytotoxicity and genotoxicity should be tested in vivo models to evaluate the compatibility in both in vivo and in vitro models.

Conclusions and Future Prospects

In this paper we have reviewed the recent trends and understandings of biogenic CeO₂ NPs and their pharmaceutical applications. Various sources such as plants, microbes, and other biological products have been discussed with the mechanism of synthesis and their biomedical applications. Due to their unique surface morphologies, crystal small nature, and biocompatible nature biogenic CeO₂ NPs have got phenomenal interest in biomedical and other fields. For instance, it has been used in treating various cancers, antimicrobial, and antioxidant therapies. In particular, the green synthesized nanoparticles have shown significant antimicrobial potential against a wide range of bacterial species. The mechanism of combating such pathogens have also been elucidated and supposed to be due to the mass production of reactive oxygen species and deactivation of scavenging enzymes. The ROS impedes the membranes, disrupts the cellular compartments, and disintegrates the bio organic molecules and hampers the associated functions and ultimately causes death. It has also shown promising results against multi-drug bacteria, and could be a potential antimicrobial agent in future against such refractory pathogens. However, further studies should conduct in vivo models, to reveal the full mechanism alongside any side-effects. Moreover, it has also shown excellent anticancer and antioxidant potential in vitro setups, but their toxicity and dosage are yet unknown, which needs to be addressed. Despite their role in various therapies their mechanism of synthesis needs to be optimized, whereas in vivo evaluation as well as toxicity should be further screened.

Abbreviations

CeO₂ NPs, cerium oxide nanoparticles; DGA, differential thermal analysis; DSL, dynamic light scattering; EDS, energy-dispersive X-ray spectroscopy; FESEM, field emission scanning electron microscopy; FT-IR, Fourier transform infrared spectroscopy; HRTEM, high-resolution transmission electron microscopy; PL, photoluminescence; PXRD, powder X-ray diffraction; ROS, reactive oxygen species; SLS, static light scattering; TEM, transmission electron microscopy; TGA, thermal gravimetric analysis; UV-Vis, UV-visible spectroscopy; XPS X-ray, photoelectron spectrometry; XRD, X-ray diffraction.

Disclosure

The authors report no conflicts of interest for this work.

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