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Plant-mediated green synthesis of cerium oxide nanoparticles: A critical perspective of some unclear issues

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ABSTRACT

Nanotechnology is undoubtedly our century's leading scientific and technological breakthrough since it encounters applications in several fields. In parallel, modern societies are facing drawbacks related to environmental concerns. For this reason, several areas are attempting to make the production process eco-friendly. In this direction, the first work using plant extracts to obtain cerium oxide nanoparticles (CNPs) was published in 2011. After more than 10 years, many advances were achieved regarding this green synthesis (GS) route, using a variety of plant types. However, some critical issues remain unclear or with less experimental evidence, such as the role of plant extracts during the synthesis (reducing, oxidizing, chelating, stabilizers, or capping agents) and difficulties in obtaining CNPs with shapes different from spherical ones. Considering the broad possible applications of these nanoparticles in many fields and the importance of their properties, this review aims to critically discuss some uncovered/unsolved issues related to the role of phytocompounds during the CNPs green synthesis and the shape of the produced nanoparticles. Environmental and scale-up aspects are also briefly discussed. The main limitations found are the lack of agreement about the mechanisms of formation of CNPs by plant-mediated green synthesis and the difficulty in obtaining morphologies like nanocubes, nanotubes, and nanowires. Despite the challenges, the various suggestions and insights presented may help overcome these limitations and expand the potential of CNPs.

1. Introduction

Cerium oxide nanoparticles (CNPs), or nanoceria, are nanomaterials with exceptional surface chemistry, stability, and biocompatibility [1–3]. These features enable promising applications in medicine [4–6], agriculture [7–9], catalysis [10–12], energy [1], electronics [13], etc. The synthesis of CNPs is conventionally performed by methods that are not eco-friendly, such as hydrothermal, chemical precipitation, and sol-gel [14,15]. Recently, many attempts have been made to make CNP's conventional synthesis eco-friendly and more sustainable using natural sources to reduce hazardous chemicals and severe synthesis conditions. Among these sources, plant extracts are commonly used for synthesizing nanoparticles (NPs) due to their rich content in secondary metabolites, which play a crucial role in plant-mediated green synthesis [16]. They offer a viable alternative for economically, simply, safely, and efficiently producing NPs through green synthesis. This is because plants are renewable, available, and diverse in species [17–19]. These advantages of using plant extracts are reflected in the many papers published on the green synthesis of CNPs mediated by plants, with more than 90 species already used (Table S1, Supplementary Material), strengthening the effort dedicated to this issue.

Despite the many articles and reviews published, most of the reviews

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have explored the application of CNPs [2,4,5,13–15,20–31] rather than aspects related to green synthesis. Still, recent works present a section of proposed reaction mechanisms for the plant-mediated synthesis of CNPs. However, the routes do not converge to a single explanation, showing different reactions without presenting a critical analysis [22]. This scenario illustrates that the formation mechanism of CNPs has no consensus among researchers. This is crucial because there are contradictory reports: biocompounds as reducing [7,32–35] or oxidizing [[36–39]] agents when dealing with the same cerium precursor. The investigation of these aspects is an opportunity to address gaps in the literature. As a result, the CNPs plant-mediated green synthesis process variables can be more effectively controlled, producing nanoparticles with well-defined properties. This enhances the suitability of the synthesized material for advanced applications.

In addition, valorizing the final or possible commercial application of nanoparticles - which is essential since materials development aims to apply nanomaterials to generate new technologies or solve old problems [41,42] - appears to mobilize more efforts than the synthesis process in experimental articles. Focusing on the application without an in-depth analysis of the synthesis aspects is a paramount gap because adequate use of NPs depends on a well-controlled synthesis, especially concerning using natural sources and biomedical applications widely researched for CNPs.

Microorganisms [43,44] are also used in green synthesis but require special treatment for culture and purification. Additionally, animal-derived products such as honey [45] or egg white [46] were used, whereby the green synthesis is mainly mediated by carbohydrate sugars or essential amino acids, respectively. This differs from plant-mediated synthesis, in which primarily secondary metabolites are associated with the synthesis process.

Further, the CNPs obtained via GS are usually spherical, but there is no consideration of it as a limitation to be overcome. This aspect is relevant because the application of NPs is directly influenced by their physicochemical properties, including morphology, which comprises shape and size. Also, the advanced applications of CNPs, which include sensors, pharmaceuticals, energy, and catalysis, demand products with strict properties, such as narrow-range specifications for purity and crystallinity. The physicochemical properties, in the meantime, are markedly affected by the synthesis route, as will be discussed throughout this review, and previous articles agree that more studies on green synthesis are needed [37].

Additionally, the market report produced by Mordor Intelligence, Cerium oxide nanoparticles market—growth, trends, COVID-19 impact, and forecasts (2023–2028), expected a market growth at a Compound Annual Growth Rate (CAGR) higher than 15% globally in the mentioned period. Increasing demand from the semiconductor industry, polishing agents, and biomedical applications will drive market growth in the following years. This market trend supports the paramount importance of cerium oxide nanoparticles and needs an in-depth study of green synthesis.

Considering gaps and opportunities, the present work intends to bring light to unsolved issues about the plant-mediated green synthesis of CNPs, emphasizing the importance of in-depth knowledge about this process without letting the spotlight of the “green aspect” hide the chemical details involved.

Herein, this review aims to provide a critical perspective on the plant-mediated green synthesis of CNPs, particularly emphasizing the unclear role of phytocompounds and the challenges of obtaining non-spherical shapes by green synthesis. Issues considered open questions are presented throughout the synthesis process in Fig. 1.

For this review, the search methodology considers the worldwide scientific production on the subject. The CNPs are presented to bring out the physicochemical properties of the compound, as well as to elucidate fields of application. The influences of the synthesis on material utilization are also pointed out. Further, we discuss green synthesis and some unclear issues, such as obtaining CNPs with different shapes from spherical shapes and possible mechanisms involved in crystal growth. The role of biocompounds is under discussion. Finally, suggestions are presented for overcoming the limitations and environmental issues in the green synthesis process, including scaling up and generating waste.

2. Search methodology

A bibliometric analysis was performed in Scopus on November 1st, 2023, to understand the critical points. The investigation used the following delineation: TITLE-ABS-KEY ("cerium oxide” AND “nanoparticles” AND “green synthesis” OR “biosynthesis”) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”) AND (LIMIT-TO (LANGUAGE, “English")). The result returned 211 papers, including research articles and reviews. Despite the filter applied, the documents were analyzed to remove those inconsistent with the present work. The selection was made by reading the abstract of all the documents found, and, in case any doubts remained, additional information was searched throughout the full text. The criteria for the selection were the use of green synthesis to obtain CNPs or the discussion about it. Papers that used other synthesis routes (*e.g.*, conventional synthesis) and those that purchased CNPs and investigated the application of this material were discarded. In addition, reviews that did not evaluate the green synthesis of CNPs were also disregarded. According to these criteria, 168 papers were selected. The number of published documents per year is presented

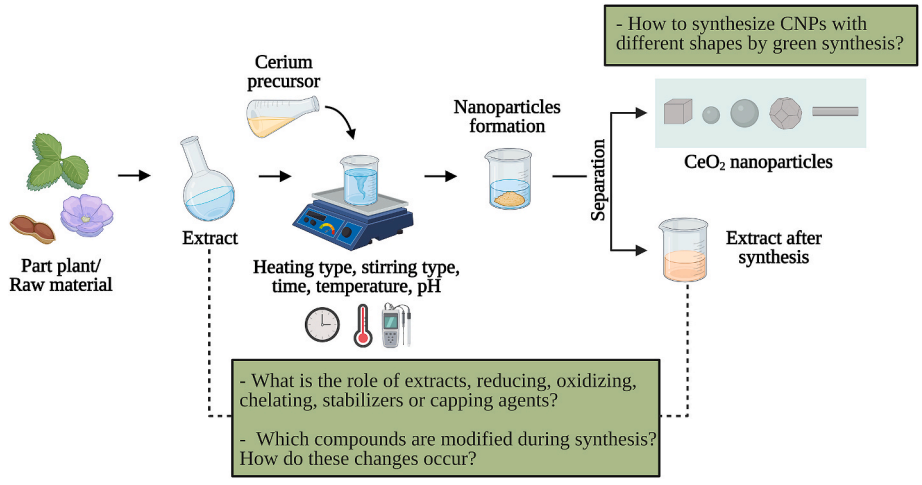

Fig. 1. Open questions about the green synthesis of CNPs. Created with BioRender.com. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

in Fig. 2, and the countries associated with the authors of these scientific publications are in Fig. 3.

Most studies were developed in Asia, mainly from India, Iran, Pakistan, Brunei Darussalam, and China. Among the possible explanations for the concentration of studies on the subject in this region, it can be mentioned that (i) China and India have extensive scientific production in various knowledge and research domains; (ii) the countries present great plant biodiversity; (iii) the need for sustainable solutions for technological development [47]; and (iv) many biomedical CNPs synthesis studies employ plants traditionally used as medicinal products. However, we emphasize that these are hypotheses to explain these issues. Also, there has been an increasing number of reviews and articles in the last few years, strengthening the growing interest in this field.

3. Cerium oxide nanoparticles

Cerium (atomic number 58) is the most abundant rare earth metal. It belongs to the lanthanide series and presents two oxidation states, +3 and +4. Cerium is the first element of the periodic table to show a ground state electron in a 4f orbital (Xe $4f^1 5d^1 6s^2$). This electron is directly associated with its redox potential, allowing it to cycle between two ionic states: the ceric ion, Ce^{4+} (Xe ground state), and the cerous ion, Ce^{3+} (Xe $4f^1$) [48].

Cerium oxide (CeO_2) is a lanthanide metal oxide used as a polishing agent, catalyst, sensor [13], ultraviolet (UV) absorber [49,50], etc. Structurally, CeO_2 has each atom bonded to eight oxygen atoms (eightfold coordinated), while each oxygen atom is four-fold coordinated (Ce_4O_8) [48]. In the bulk state, cerium oxide can be CeO_2 or Ce_2O_3. However, on the nanoscale, a mixture of Ce^{3+} and Ce^{4+} is on the material's surface [14]. Based on the redox-cycling states, CNPs are regenerative antioxidants due to their surface's self-regeneration, making them a promising material for biomedical applications [20,51].

Due to its unusual redox behavior, CeO_2 can form oxygen vacancies by releasing oxygen from the cubic fluorite structure and reducing two ceric ions ($Ce^{4+} + 1e^- \rightleftharpoons Ce^{3+}$). This phenomenon occurs mainly at the surface and is influenced by the microenvironment. The characteristic of the store/release oxygen is called oxygen storage capacity. It is crucial to its catalytic reactivity because solid ceria particles can provide or remove oxygen reversibly to/from the surroundings by responding to a lack or excess of oxygen in that environment [48]. The increase in oxygen storage capacity is associated with the decreasing particle size once this parameter represents the exchange of oxygen at the surface [52].

To ceria's unique properties are added the possibilities of nanotechnology. This provides many opportunities to solve real-world problems, from health to food, energy, and electronic components. This is due to fine-tuning physical, chemical, and biological properties at the molecular and atomic levels. The properties of NPs are enhanced when compared to the same materials on a bulk scale. The greater surface area available for carrying out reactions is one of the explanations for the more significant activity [53].

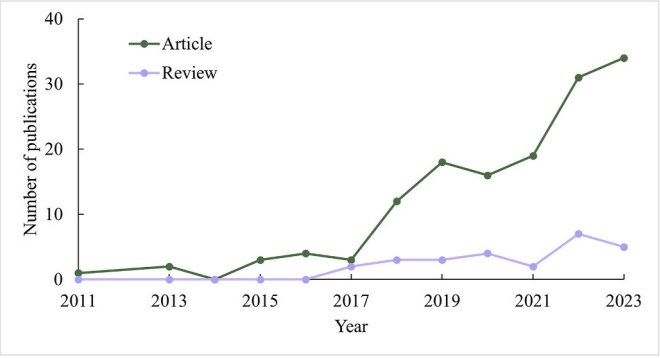

Fig. 2. Bibliometric analysis: number of publications per year.

Because of the mentioned CNPs properties and the potential applications, there are also several studies on the correlation between the properties and their application. The size, charge, surface properties, solubility, morphology/shape, and Ce^{3+}/Ce^{4+} ratio affect the interaction with biological systems. The toxicity to microalgae (*Pseudokirchneriella subcapitata*) occurred mainly due to Ce^{3+} on the surface [54]. The surface Ce^{3+} fraction also impacts their enzyme mimetic activities, such as pro-oxidation or antioxidants [55,56]. Regarding photocatalytic properties, the degradation rate of Rhodamine B dye increased with the decreasing particle size, which increased the band gap energy [12]. In the catalytic ozonation of *p*-nitrophenol, the difference in the catalytic activity of ceria shapes was related to the differences in the abundance of basic surface sites, defects densities/oxygen vacancies, and coordination number of surface atoms [57]. For sensor applications, the electrochemical behavior of CNPs depends on their morphologies. The switch between oxidation states of Ce^{3+} and Ce^{4+} enhances electrochemical properties, and using NPs increases the surface area and the electron transfer rate [13].

Comparing CNPs from conventional and green synthesis routes is important due to significant impacts on physical, chemical, and biological properties. This way, green synthesized cerium oxide nanoparticles (GS-CNPs) were obtained with an aqueous extract of *Polygonum bistorta* root, and conventional CNPs were produced via a facile precipitation approach using NH_4OH. The chemical-synthesized CNPs showed higher yield and specific capacitance than GS-CNPs. However, the GS-CNPs were biologically more active, with better antioxidant and bactericidal properties and superior leishmanicidal activities, against *Leishmania tropica* [58]. The performance of GS-CNPs using sweet basil was also compared with those synthesized conventionally with NaOH and aqueous chemical surfactant. Both NPs were agglomerated, with the GS-NPs having a smaller particle size. The chemical-synthesized CNPs were more lethal to the pathogens studied [59]. Similarly, using *Jatropha curcas* extract, CNPs were approximately four times smaller than those synthesized by the chemical route using NH_3 and NaOH. The CNPs showed 99.6%, 100%, and 93.2% photocatalytic activity of acetaldehyde degradation into CO_2 using GS, NH_3, and NaOH, respectively [60].

In this context, it was possible to observe the variability properties of CNPs and their influence in some applications. Thus, understanding the synthesis process in depth is essential to matching the suitable properties of each application.

4. Green synthesis of CNPs

Despite the broad potential of nanotechnology, conventional synthesis of NPs uses heavy chemical reagents and environmentally unfavorable synthesis conditions (*e.g.*, high temperatures, pressure, long reaction times). In addition, CNPs produced by conventional methods tend to be toxic and unstable, leading to reduced efficiency. Consequently, there has been a notable paradigm shift towards green synthesis methods [23]. These changes align with the global need to decrease the environmental impact of industrial processes and the Sustainable Development Goals (SDG) (SDG 12 - Responsible consumption and production, SDG 13 - Climate action, SDG 15 - Life on land) [42].

Green nanotechnology applies green chemistry concepts such as reducing or eliminating the use or generation of hazardous substances in designing, manufacturing, and applying chemical products to produce nanomaterials. Plants and microorganisms can mediate the green synthesis of CNPs [14] instead of the synthetic chemical compounds used in larger quantities in conventional synthesis. Special attention will be given to synthesis procedures that use plants to obtain CNPs.

In this regard, extracts from plants are advantageous because they can perform functions usually performed by two or more different chemicals (*e.g.*, particle synthesis agent, capping/stabilizing agent). Stabilizers can be interesting in improving biocompatibility for therapeutic purposes. Still, as an advantage of the green method, green extracts can increase the yield of NPs produced [20], and the waste

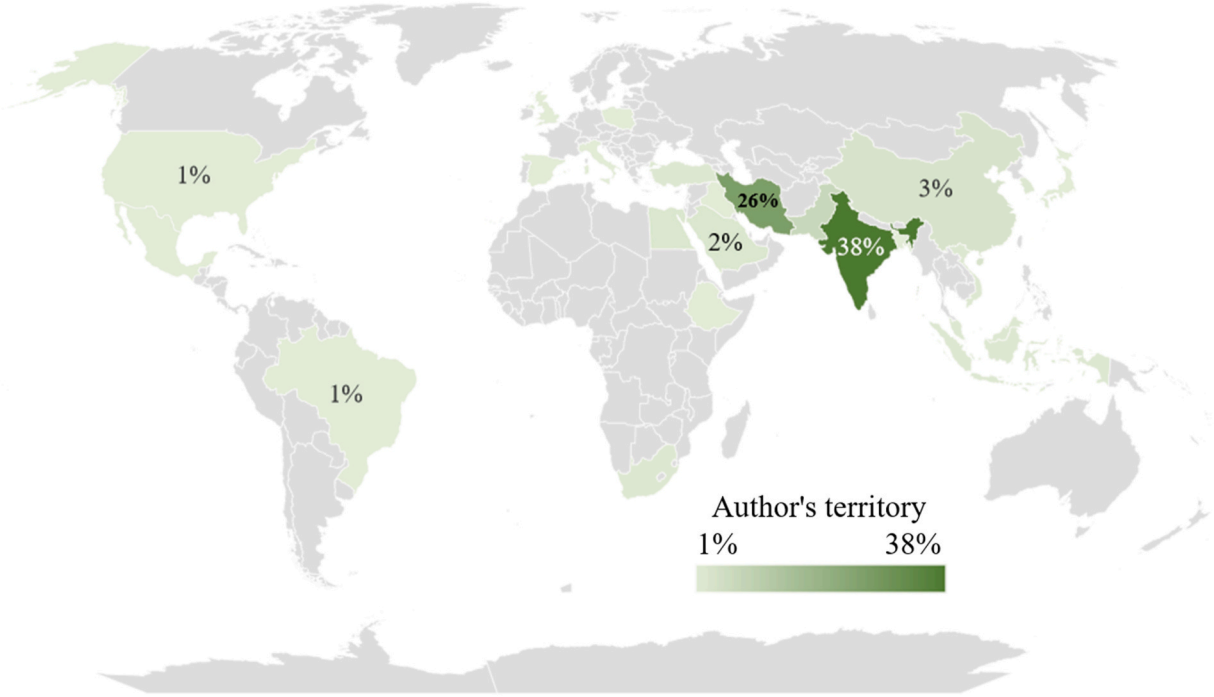

Fig. 3. The territory of authors of the papers found in the bibliometric analysis.

generated can be more easily handled. In addition, the reactions can be conducted under ambient temperature and pressure conditions and without hazardous chemicals [36,61].

Over the last decade, advances have been achieved regarding synthesizing CNPs mediated by plant extracts, including using different extracts and synthesis conditions. Generally, the green synthesis is carried out through the following steps: i) obtaining the extract of the plant under study is performed by infusing or boiling parts of the plant in a chosen solvent, usually water; ii) the extract obtained is mixed with a solution containing the cerium precursor, such as $Ce(NO_3)_3.6H_2O$ or $CeCl_3$. This solution can previously have its pH adjusted; iii) the reaction between the biocompounds and cerium is conducted with or without stirring and heating; iv) as the reaction occurs, the formation of a precipitate can be observed [7,35,62–65]; vi) after obtaining CNPs, some procedures, such as centrifugation [6,66–68], can be performed to separate the synthesized material; vii) the material is dried and calcined. Alternatively, the synthesized NPs are kept in the original solution for subsequent application or dried. This process is presented in Fig. 4.

Critical parameters for this process are the ratio precursor:extract [11,12,34,69], extract composition [38], type of stirring and heating, temperature, time, pH [34], and calcination temperature [70]. In a different way from the one shown in the scheme above, some procedures do not report the occurrence of a precipitate. The resulting reaction mixture is dried and calcined [71–75].

Table 1 presents reports on using different plants and the characteristics of nanoparticles produced (size and shape). Table S1 (Supplementary Material) continues Table 1, showing the plants used and the products obtained.

Table 1 and Table S1 show that many plants have already been employed for this green synthesis (more than 90 species), which may be attractive for larger-scale production purposes and to adapt to local plant availability. Leaves are used in more than 50% of the reports, but the use of different parts of the same plant is also reported, for example, for *Moringa oleifera* leaf [91,92], peel [66], seed [93], and flower [94].

Despite numerous reports, different extract preparation methods and synthesis conditions make direct comparisons between plant performances based on NP properties difficult, even when the same species are used. Also, the plant's chemical composition can vary considerably depending on season, growth location, and soil conditions [95]. Furthermore, the lack of qualitative and quantitative extract chemical composition data hinders meaningful comparisons and inferences regarding extract performance. These aspects reinforce the limited understanding of biocomposites' primary role in green synthesis.

The most commonly used cerium precursor is $Ce(NO_3)_3.6H_2O$. Similarly, some works also report using $Ce(NO_3)_2.6H_2O$ as cerium precursor [38,63,96–99], which is considered a mistake or typing error because cerium has two oxidation states: +3 and + 4, not +2. Also, the report of $CeSO_4$ [93] as precursors instead of $Ce(SO_4)_2$ or $Ce_2(SO_4)_3$ is

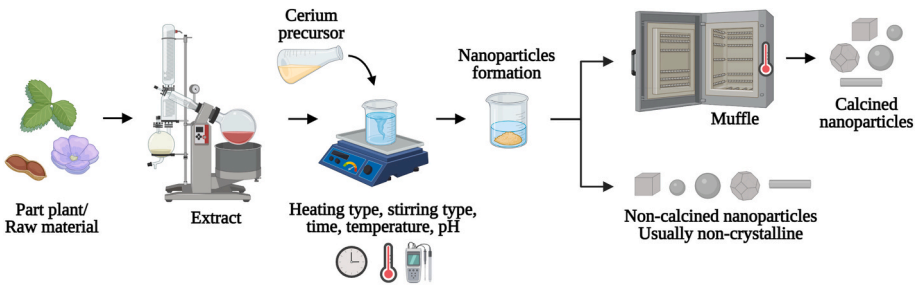

Fig. 4. Schematic representation of the plant-mediated green synthesis of cerium oxide nanoparticles. Created with BioRender.com. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Green synthesis of CeO_2 nanoparticles using different plant parts and their effect on the size and shape of nanoparticles.

Year	Plant	Plant part	Precursor	Shape	Size (nm)	Ref
2011	China rose	Petal	$Ce(NO_3)_3.6H_2O$	Nanosheet	7[a]	[76]
2014	*Acalypha indica*	Leaf	$CeCl_3.7H_2O$	Sheet and spherical-like	25–30[a]	[67]
2014	*Aloe vera*	Leaf	$Ce(NO_3)_3.6H_2O$	Spherical	64[b]	[77]
2015	*Gloriosa superba*	Leaf	$CeCl_3$	Spherical	5[a]	[62]
2015	*Hibiscus sabdariffa*	Flower	$Ce(NO_3)_3.6H_2O$	Spherical	3.9[a]	[78]
2016	*Moringa oleifera*	Peel	$(NH_4)_2.Ce(NO_3)_6$	Spherical	45[a]	[66]
2016	*Olea europaea*	Leaf	$Ce(NO_3)_3.6H_2O$	Spherical	24[a]	[79]
2017	*Azadirachta indica*	Leaf	$Ce(NO_3)_2.6H_2O$	Spherical	10–15[a]	[63]
2017	*Rubia cordifolia*	Leaf	$Ce(NO_3)_3.6H_2O$	Spherical, hexagonal	26[a]	[35]
2018	*Prosopis farcta*	Aerial parts	$Ce(NO_3)_3.6H_2O$	Spherical	30[a]	[80]
2019	*Origanum majorana*	Leaf	$Ce(NO_3)_3.6H_2O$	Spherical	20[a]	[81]
2019	*Salvia macrosiphon*	Seed	$Ce(NO_3)_3.6H_2O$	Spherical	20–47[a]	[12]
2020	*Justicia adhatoda*	Leaf	$CeCl_3.7H_2O$	Spherical	36[c]	[82]
2020	*Salvadora persica*	Bark	$Ce(NO_3)_3.6H_2O$	Spherical	5–6.5[a]	[49]
2021	*Morinda citrifolia*	Fruit	$Ce(NO_3)_3$	Spherical	40–80[a]	[39]
2021	*Musa sapientum* (Banana)	Peel	$Ce(NO_3)_3.6H_2O$	Spherical	4–13[a]	[74]
20222023	*Acacia concinna*	Fruit	$(NH_4)_2.Ce(NO_3)_6$	Porous network-like	22.7[c]	[83–86]
2022	*Olea europaea*	Leaf	$Ce(NO_3)_3.6H_2O$	Nanorod	Diameter: 29–37[a] Length: 250-500	[68]
2022	*Oryza sativa* (black rice)	Seed	$Ce(NO_3)_3.6H_2O$	Nanorod	70[c]	[87]
2023	*Chenopodium quinoa*	Leaf	$CeCl_3$	Spherical	7-10[c]	[88]
2023	Coffe-waste	Seed	$Ce(NO_3)_3.6H_2O$ and $Ti[OCH(CH_3)_2]_4$	Information not found.	20[c]	[89]
2023	*Nyctanthes arbor-tristi*	Leaf	$Ce(NO_3)_3.6H_2O$	Spherical	2-14[c]	[90]

[a] Particle size is determined by electron microscopy, such as Transmission Electron Microscopy (TEM) or Scanning Electron Microscope (SEM); [b]Particle size is determined by particle size analyzer, such as Dynamic Light Scattering (DLS); [c]Crystallite is size determined by X-ray diffraction (XRD) and Scherrer equation.

not considered correct. The cerium precursor is essential because the initial oxidation state of cerium in the reaction medium influences the subsequent synthesis. If it is initially Ce^{3+} and, in the cerium oxide, there is Ce^{4+}, the synthesis process is expected to occur through cerium oxidation. On the other hand, if the cerium precursor starts in the +4 state, the reaction that occurs must maintain this charge (or generate intermediate species) until the CeO_2 has been formed. In $CeCl_3$, $Ce(NO_3)_3$, and $(CH_3CO_2)_3Ce$, the cerium is in the oxidation state +3, while in $Ce(SO_4)_2$ and $(NH_4)_2Ce(NO_3)_6$, the cerium ion is +4. Ce_2O_3 production was also reported [93,100,101].

Furthermore, Table S1 shows particles ranging in size from 2 nm [102] to 900 nm [7], and most synthesized particles are spherical. More than 70% of the articles obtained spherical CNPs, 7% did not describe the shape, and the others had various morphology (porous, irregular, cubic, elliptical, hexagonal, etc.).

4.1. Influence of process parameters

The synthesis conditions, including the reaction time, pH, heating type (microwave, hotplate, etc.), stirring type (ultrasonic, mechanical, etc.), synthesis route, and calcining temperature, influence the nanoparticle shape and size. Despite the current developments discussed, more investigations are needed to determine how these variables influence CNPs' properties. In this sense, some methodologies and results described in the literature are presented herein.

The role of varying the quantity of extract on the resultant nanoparticles was analyzed using *Salvia macrosiphon* seeds. Increasing the amount of extract from 10% to 30% (v/v of the reaction volume) resulted in smaller particles, with an increased band gap energy, due to the ability of the extract to prevent particle aggregation. However, 40% of the extract resulted in larger particles with a reduced band gap energy, which was attributed to the higher viscosity of the reaction medium [12]. Furthermore, by comparing the plant-mediated green synthesis and the conventional synthesis (without plant extract) using *Jatropha curcas* [60] and *Polygonum bistorta* extract [58], smaller particles were obtained by green synthesis.

Some works do not calcine CNPs, as was done using *Aloe vera* leaf extract to obtain 2–3 nm almost spherical CNP with a low crystalline nature [102]. Using *Morinda tinctoria* plant extract, spherical CNPs with cubic phase were obtained, although these NPs were not calcined but only dried at 100 °C [40]. *Cassia angustifolia* leaves' extract mediated the synthesis of nanoceria with a structure like a honeycomb, circular and cubic, with smooth surfaces and sizes ranging from 50 to 100 nm. Despite not being calcined, the synthesized material also presented a cubic phase-centered structure [103].

Linum usitatissimum seeds extract was applied to obtain CNP with spherical morphology. CNPs obtained after calcination at the lowest temperature of 400 °C presented the smallest size [70]. The results corroborate other works that used *Pinus halepensis* pollen extract [104] and *Cucurbita pepo* peel extract [105]. The crystallite size of the synthesized NPs, calculated with the Scherrer equation, at temperatures of 300, 500, and 700 °C, was 4, 19, and 24 nm, respectively [104].

Further, various polymorphs such as spherical, trigonal, tetragonal, and octahedron CNPs are reported using an aqueous extract of *Picrasma quassioides* bark. Interestingly, the shape of the nanostructure has not changed appreciably with an increase in annealing temperature from 200 °C to 600 °C. However, an improvement in the catalytic activity of the nanostructures was observed and related to i) the higher crystallinity of the nanostructures, reducing the crystalline defects and decreasing the residual elements from the leaf extracts, and (ii) a large surface area providing more electrons [106].

Regarding the synthesis influence on the CNPs properties, a green route using *Dillenia indica* aqueous extract shows an increase in crystallite size from 7.0 nm (as prepared) to 26.2 nm with calcination. This increasing crystal size is associated with an interfacial reaction at a higher temperature. A reduction of the aggregations is observed and related to enough energy of the calcination, resulting in the separation of particles from each other [107]. A similar disaggregation with the increasing annealing temperature was shown using an aqueous extract of *Picrasma quassioides* bark [106]. In contrast, the agglomeration increased as the calcination temperature was raised from 500 °C to 700 °C in a process involving NaOH and carbohydrate sugars as a capping agent [108].

The synthesis of doped materials and nanocomposites containing cerium oxide is also described. *Euphorbia tirucalli* plant latex was used in green combustion, a different approach than the one traditionally referred to as green synthesis. The plant is a fuel in the synthesis of CeO_2: Eu^{3+} nanophosphors and obtains a cubic fluorite phase with a flaky structure [109]. *Aloe vera* leaf gel [98], aqueous extract of *Cassia angustifolia* [110], and *Jacaranda mimosifolia* leaf extract [111] are also

used in green synthesis via combustion. In this approach, the extract is mixed with cerium nitrate in a preheated muffle furnace maintained at 400 °C, and the reaction is completed in 4–6 min [110].

Similarly, coffee waste was mixed, ground with cerium nitrate in a mortar, and calcined at 600 °C. TiO_2 modified with CeO_x was synthesized using the sacrificial template technique, allowing for the manipulation of morphology and porosity, ultimately improving catalytic performance [89].

Justicia adhatoda leaves extract and ionic liquid were used to synthesize CeO_2/ZrO_2 core metal oxides. The NPs obtained were an agglomerated nano stick-like structure with 20–45 nm size [112]. [BMIM] PF6 ionic liquid and *Pedalium murex* leaf extract were also reported to mediate the green synthesis of ceramic SrO/CeO_2, obtaining NPs with a nanorod-like structure and crystallite of 5 nm [113]. Regarding the influence of dopant materials, the size of CNPs synthesized with *Stevia rebaudiana* leaf extract was decreased as a function of the increased percentage of Ni doping in the crystal structure [114]. CNPs doped with $MnSO_4$ (II) and synthesized with *Pedalium murex* extract were also smaller than pure CNPs, measuring 12 and 18 nm, respectively [115]. Using dopant materials also enabled different shapes to be obtained than those spherical usually found [109,112,113,116,117].

Only a few studies have reported the plant-mediated green synthesis of CNPs nanorods without adding dopants [68,87]. *Oryza sativa* extract was used in a microwave-assisted process. The mixture of cerium precursor and the extract was magnetically stirred for 1 h and, in the sequence, was irradiated for 20 min in a microwave oven at 2.45 GHz and 800 W. Afterward, the solution with a brown precipitate was centrifugated, washed with ethanol and acetone and, finally, annealed at 500 °C during 1 h [87]. Another approach based on the microwave-assisted hydrothermal method also obtained nanorods of CeO_2 using *Olea europaea* leaf plant extract. In this case, NaOH was first used to precipitate $Ce(OH)_4$. The precipitate was separated, mixed with the extract, put under continuous stirring and sonication for 30 min to form a homogeneous suspension, and then transferred to Teflon vessels at 200 °C for 30 min. Compared to the use of traditional hydrothermal methods without plant extract, the traditional one produced homogeneous nanoparticles with spherical morphology and an average size of 3–6 nm, while the microwave-assisted green synthesis produced a rod-like shape morphology with an average diameter of 29–37 nm and length of 200–500 nm [68]. The nanoparticles obtained in this work can be seen in Fig. 5.

The works that obtain CeO_2 nanorods by plant-mediated green synthesis indicate a possible influence of microwave radiation during crystal growth. However, previous work has obtained spheres using the same radiation [66,118].

4.2. CNPs formation mechanism

The mechanism that governs the formation of CNPs in the presence of plant extracts is not fully clear. Studies report that the phytocompounds in plant extracts act as reductants (mainly) or oxidants. Still, they don't present robust experimental results to show that some compounds suffer oxidation/reduction. Another approach is that the phytocompounds work as capping/stabilizing agents during the reaction [21,103].

In the case of the biocompounds acting as coating and stabilizing agents, carbohydrates, enzymes, vitamins containing hydroxyl, and amine groups in the honey matrix structure are related to an easier complexation of cerium cations (Ce^{3+}) while inhibiting their excessive aggregation or crystal growth [119]. Phytochemicals also have functional groups that generally act as electron donor groups that can coordinate with cerium atoms [12]. A complex formation between cerium and compounds found in the *Camellia sinensis* extract is proposed. The extract has high concentrations of phenolic derivatives, including flavonoids, phenolic acids, and carotenoids [120]. Similarly, using egg white, the electrostatic interaction between Ce^{3+} and oppositely charged proteins is associated with controllable growth and subsequent isotropic formation of small and stable CeO_2 [121]. *Acacia concinna* fruit extract acted as a surfactant, reducing the size and aggregation of the CNPs. These reported properties were associated with saponins in the extract [85]. In another work, the formation of CeO_2 is achieved by adding NaOH, providing slow oxidation because it is a poor oxidizing agent. Then, the plant extract stabilizes the solution [102].

Although a great advantage of green synthesis is the possibility of obtaining a variety of NPs, such as Au [122], Ag [16], Pd [61], Fe_3O_4 [18,123,124], CuO [17], ZnO [68,125] etc., the lack of a forming mechanism of NPs via green synthesis routes is not a problem specific to CNPs. For the green synthesis of Ag NPs, it is also observed that few attempts have been made to investigate the formation mechanism. In addition, complex mixtures found in plant extracts lead to several proposed reactions [16]. In this context, a generalization of mechanisms does not clearly explain the formation and the peculiarities of all nanoparticles. It is necessary to consider the oxidation states of the precursors, the nano products of interest (oxides or metals), and the biomolecules involved. Considering the contradictory reports about biocompounds being bioreductants or bio-oxidants, a more in-depth discussion is presented below.

4.2.1. Plant extracts as bioreductants

Many works in the literature report the biomolecules in plant extract as electron shuttles in metal reduction and as capping agents, controlling the aggregation and crystal growth and acting in surface modification [34]. However, cerium from the salt precursor is most often used in the oxidation state +3 (from $Ce(NO_3)_3.6H_2O$ and $CeCl_3$, for example), and the final product, CeO_2, is mainly in the oxidation state +4 (despite the occurrence of Ce^{3+} by the oxygen vacancies). Additionally, some studies refer to the presence of the intermediates $Ce(OH)_3$ and $Ce(OH)_4$ [33]. Regarding the predominant biocompounds used, phenolics [7,74,78,80,81] and flavonoids [12,81,118,126] are described.

The plant-mediated synthesis using *Pisonia alba* leaf extract presents chemical groups associated with bioreducing activity (hydroxyl, amide,

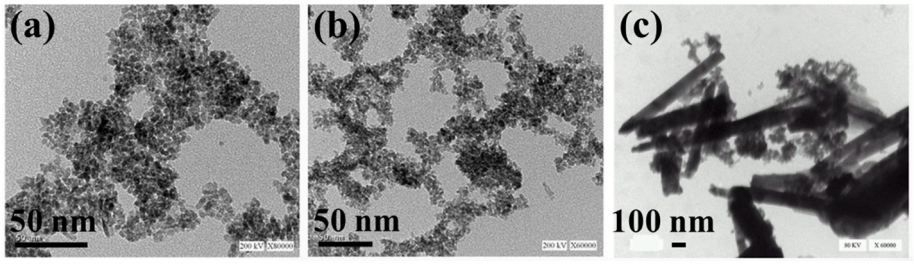

Fig. 5. TEM images of CeO_2 nanoproducts prepared by (a) traditional hydrothermal methods, (b) microwave hydrothermal methods, and (c) microwave hydrothermal adding *Olea europaea* leaf plant extract as a capping agent [68]. This work is licensed under a Creative Commons Attribution 4.0 International license (CC BY 4.0).

amine). These compounds are mentioned as involved in reducing cerium ions to nanoceria [32]. Thus, the formation of CeO_2 in a medium that has electron donor species opens some questions about the possible intermediate steps that are involved and are not yet clearly elucidated. This lack of clear explanation perpetuates the publication of contradictory reports, making it challenging to delineate extract and complex to manipulate CNPs properties.

Previous studies used pectin from *Citrus maxima* peel to synthesize silver, gold, ZnO, CuS, and hydroxyapatite NPs. Pectin acted as an appropriate stabilizing, capping, and reducing agent. The presence of carboxyl groups in pectin is a favorable factor for the synthesis of NPs, but the generalization of the synthesis mechanism of different nanoparticles should be done cautiously. Using pectin, the obtained CNPs showed a polydisperse nature, spherical shape with a cubic fluorite structure, and average particle size smaller than 40 nm. The process occurs initially because the nitrates from $Ce(NO_3)_3$ in the solution are decomposed by heating to NO_2 and oxygen and released from the mixture. With the addition of ammonia to the solution, the hydration of Ce^{3+} ions to $Ce(OH)_3$ precipitates due to its very low solubility constant. The alkaline surplus solution oxidizes $Ce(OH)_3$ to $Ce(OH)_4$, which causes a change in the solution color from colorless to light yellow. The hydroxyl ions play an essential role in the yellow-colored precipitation and the subsequent oxidation of Ce(III) to Ce(IV). Lastly, calcination provides energy for converting $Ce(OH)_4$ into crystallized CeO_2 [33]. However, some works report the preparation of CNPs without calcination/annealing [40,101–103,117,127–129] and do not corroborate the theory that CeO_2 nanoparticles only form after calcination.

The leaf extract of *Flacourtia indica* was also used to synthesize *P–ZrO*$_2$*CeO*$_2$*ZnO* NPs. Although pure cerium oxide was not produced, this work proposed a mechanism to explain the role of biocomposites. It is reported that alkaloids, aldehydes, ketones, carboxylic acid esters, and phenolic compounds like flavonoids are potential reducing and stabilizing agents due to their hydroxyl groups. Due to the free electrons' pairs from the extract, cerium is reduced to Ce^0 through a process in which the first possible reaction is complexation between the phytochemicals and the metal salts; the hydroxyl groups of the phenolic compounds combine with the metal ions to form a transitional complex, transferring e^- to the metal ion to form the zero valent NP ($Ce^{2+} + ROH + 2e^- \rightarrow Ce^0$). Finally, the zero-valent phytochemical stabilized nanoparticles were calcined at 900 °C to form the oxide NPs ($Ce^0 \rightarrow CeO_2$) [34]. A similar mechanism has been proposed for the green synthesis of CuO, in which many phenolic compounds from the *Euphorbia chamaesyce* extract facilitate the formation of zero-valence nano Cu, and the metal has a great tendency to react with oxygen to convert spontaneously to CuO NPs [17].

Using the leaf extract of *Rubia cordifolia*, the active principles present in the plant extract are described as responsible for the rapid reduction of cerium ions to metallic nanocrystals. Also, upon heating, the lone pair of electrons in the oxygen of hexahydrate $Zn(NO_3)_2.6H_2O$ and $Ce(NO_3)_3.6H_2O$ solution might have transferred to the OH of *Rubia cordifolia* leaf extract. Finally, the precipitate was calcined to produce CeO_2 nanoparticles [35].

The synthesis of stable and well-dispersed CeO_2 microparticles using *Petroselinum crispum* and $(NH_4)_2Ce(NO_3)_6$, *i.e.* Ce^{4+}, is also reported. The plant was chosen based on its high content of phenolic metabolites due to the ability of electron donors to join these phenolic compounds. According to the authors, a color change from orange to dull yellow is observed during the reaction due to the conversion of Ce^{4+} to Ce^{3+}, and a white precipitate of $Ce(OH)_3$ is formed. Afterward, Ce^{3+} re-oxidized to CeO_2. $Ce(OH)_3$ can be directly oxidized to CNPs using thermal treatment [7].

Thus, it can be observed that the explanation for the formation of the CNPs mechanism using plant extracts as bioreductants was distinct. However, the presence of OH groups is considered fundamental to this synthesis. Chemical assays to identify the biocompounds are usually presented in the initial extract before the reaction and at the end of the synthesis to verify the formation of CeO_2. Therefore, analyses that evaluate the reaction's course or corroborate with the suggested mechanisms are not presented.

Furthermore, some colorimetric techniques are used to analyze the composition of extracts, which may not be accurate enough to elucidate the mechanism and the main phytocompounds involved. In this regard, better analytical methods for extract characterization are available, such as chromatography (pure and hyphenated, in which chromatography techniques are coupled with spectroscopic methods [130]), spectroscopy (UV–Vis Spectrometry, Mass Spectrometry, Nuclear Magnetic Resonance, Fourier Transform Infrared Spectroscopy), and thermal analysis. This can be helpful for better extract characterization before, during, and after the synthetic process, since extract concentration is one of the variables in the synthesis, phytocompounds identification and quantification are crucial for the scaling-up and standardization process.

4.2.2. Plant extracts as bio-oxidants

In contrast to the previous discussion, some works refer to biocompounds as oxidizing agents [37]. Many times, the same compounds described as reducing agents, like phenols and alkaloids, are now described as oxidizing agents. Thus, some studies that show biocompounds as oxidizing agents are introduced here.

CNPs with a particle size of 5–15 nm and spherical shape were prepared by the precursor cerium nitrate and *Datura metel* leaves extract. Fractionation steps were performed to obtain an extract with a higher concentration of alkaloids and flavonoids. The presence of the C–N group in alkaloids is mentioned as a weak base source, and the flavonoids are referred to as a capping agent. X-ray diffraction (XRD), Transmission Electron Microscopy (TEM), and Fourier transform infrared spectroscopy (FTIR) analysis confirmed the formation of CNPs, but they are not sufficient to elucidate the mechanisms involved [38].

Further, the aqueous leaf extract of *Pometia pinnata* is used to obtain CeO_2 and Zr/Sn-dual doped CeO_2 nanoparticles, using $Ce(NO_3)_3.6H_2O$ as a precursor and the phytochemicals (alkaloids, terpenoids, phenolics, proteins, and sugars) are mentioned as an oxidizing and a capping/stabilizing agent [73]. The aqueous leaf extracts of *Pometia pinnata* are also described in another report as a capping and oxidizing agent that was used to mix and heat with the precursor. A paste containing $Ce(OH)_4$ is obtained, and CeO_2 is formed by calcination. This methodology does not refer to using another compound during the synthesis, presenting itself as a very eco-friendly synthesis [36].

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Morinda citrifolia fruit extracts are a weak base source, oxidizing, and capping agent. Several fractionation processes of the extract were performed (with methanol, n-hexane, ethyl acetate solvent, and chloroform) and by adjusting the pH (with HCl and NaOH) until the final extract was obtained. There is a strong van der Waals interaction between the precursors and the extracts, which is responsible for the oxidation of Ce^{3+} to Ce^{4+}. The presence of alkaloids was found to possess electron pairs on the nitrogen atom, which generate a weak base source of OH^- to hydrolyze Ce^{4+} gradually to $Ce(OH)_4$ due to the equilibrium condition. Also, flavonoids provide electrons to stabilize the formation of $Ce(OH)_4$ gel until the CeO_2 nanoparticles generation. This work also concerns the plant extract as a hydrolyzing agent [39].

Regarding plant extracts as oxidizing agents, despite the statement agreeing with the initial and final NOx of the metal involved if the cerium precursor is Ce^{3+}, most used ($Ce^{3+} \rightleftharpoons Ce^{4+} + 1e^-$), assays comparing the extract before and after the reaction are not presented to verify the reactions that occur.

4.3. Crystal growth mechanism

Nanomaterials have different physicochemical properties than the same compound in bulk scale. The reduction in particle size significantly increases the surface area, and the resulting materials have a greater reactivity because more atoms can react on the surface. Thus, NP

properties depend on shape, size, and surface chemistry. Considering the small number of works reporting on the GS of nanorods/nanowires, the difficulty in producing non-spherical CNPs through green synthesis is evident. For this reason, this topic will explore mechanistic aspects of crystal growth in bottom-up synthesis to address this gap comprehensively.

In the bottom-up synthesis route, the formation of CNPs occurs initially through chemical reactions involving the cerium ions of the precursor, as previously discussed. In parallel with the reaction, nucleation occurs, followed by cluster formation and crystal growth, until a thermodynamically stable NP is obtained. The nucleation begins with a small nucleus in the liquid. It can be homogeneous when the nucleation occurs due to the supersaturation of the medium or heterogeneous when nucleation agents are present [131]. During crystal growth, the nucleated particles agglomerate. These processes are central to controlling the size and shape of interest, as well as for reproducibility. A schematic representation of these events is presented in Fig. 6.

A non-green synthesis method proposes that forming intermediate anisotropic $Ce(OH)_3$ species under basic conditions and converting them into CeO_2 at higher temperatures are critical for shape evolution. For a higher reaction rate, isotropic growth can produce spherical-shaped nanoparticles. CNPs' difficulty growing anisotropically was associated with their isotropic crystal structure. The use of capping agents or templates can help break the symmetry. In that regard, applying a hydrothermal route obtained a morphological phase diagram, producing nanoparticles, nanorods, or nanocubes by varying parameters such as NaOH concentration, reaction time, and temperature [132], demonstrating that the production of several shapes is not a problem for conventional synthesis.

Thus, the difficulty of obtaining shapes other than spherical emphasizes that the shape produced is a limitation to be overcome in green synthesis. Considering the extract as a capping agent and that mostly spherical particles are produced, it highlighted the need to understand the role of bioproducts in the process. The possibility of getting different shapes with a single plant extract by adjusting the process parameters is also an opportunity for improvement for this production route.

5. Suggestions to solve the main gaps and synthesis improvement

Some strategies to overcome the current limitations regarding the gaps presented are suggested. Some of these alternatives are inspired directly by the chemistry of natural products, when, by fractional extraction, the biological activity of each fraction is tested, and the most bioactive is selected and identified. Fig. 7 illustrates an example of the methodology employed.

Similar to the previous process, this methodology can be helpful for nanoparticle green synthesis. By using different forms of extraction (solvent, plant processing, etc.), a suitable route to produce the NPs of interest can be found. For this condition, phytocompounds and the changes they undergo can be identified.

As methodologies can be borrowed from plant characterization, the same can be done from non-green synthesis. Green methods mimic the traditional synthesis but are safer and more eco-friendly [21]. This analogy may help adapt strategies employed in conventional methods to green synthesis settings. In this regard, a strategy was employed to control the size of CNPs using a Ce^{4+} precursor. This approach was chosen because, starting with Ce^{3+}, the compound undergoes harsh oxidation conditions during the formation of CeO_2. In addition, the nucleation and crystal growth steps have been isolated [52].

Another opportunity is to systematically analyze the influence of each process variable (pH, cerium/precursor source, temperature, reaction time, amount of extract and precursors, light conditions, etc.) on the obtained product (size, morphology, surface area, Ce^{3+}/Ce^{4+}, etc.). This can be especially relevant for variables that have proved more difficult to control and may be more critical for a given application.

It is important to emphasize that with non-green methods, it is possible to obtain different morphologies of nanoceria through changes in synthesis parameters such as temperature and pH [132]. Thus, using mild reaction conditions in green synthesis, as reaction temperatures of 50 °C–80 °C [62,77,79,92], can be another cause for obtaining mostly spherical nanoparticles and the symmetry of the crystal structure as mentioned earlier [132].

Separating each reaction step and analyzing the chemical changes between them can also be helpful. Fig. 8 presents some experimental alternatives and assays for this view of the decoupled processes.

The suggestions from Fig. 8 help us understand the mechanism of forming CNPs obtained by green synthesis, identifying the biocompounds of the studied plant and which one is more effective for synthesizing nanoparticles. If the isolated compound is available, the compounds identified as most important for synthesis can be tested separately to compare their effectiveness alone and within the medium extracted from the plant - like in the study of natural products. Also, identifying the functional groups is essential to compare the groups present in the extract before, during, and after the synthesis to verify which were oxidized or reduced, facilitating the understanding of the reaction mechanism and possible intermediate steps present in the reaction. One way to deal with this challenge is by taking samples of the reaction medium and analyzing them as the reaction progresses. However, selecting the appropriate analytical technique to detect changes in the plant's constituents throughout the process is important.

Also, different organic solvents for extract preparation can help build knowledge about GS. However, once liquid waste treatment becomes a problem and is not in harmony with the principles of green chemistry, the larger-scale application of these reagents should be done carefully.

Scaling up and the impact of NPs on the environment are also challenges. Since its production, the adverse effects on the human health of those who handle this material should be engineered to minimize risks. Following the objectives of this review, researchers play an essential role in developing environmentally friendly routes and analyzing the entire life cycle of the products and by-products involved. Using waste for synthesis has advantages, generating smaller amounts of effluent and developing less complex processes [15,133].

Additionally, environmental contamination and the toxicity of CNPs pose a significant concern. Toxicity depends on particle size, chemical species, concentration, etc., for which adequate characterization and

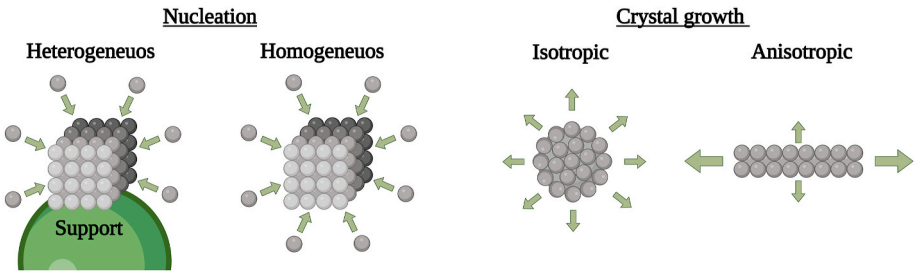

Fig. 6. Schematic representation of the evolution of the nanoparticle shape. Adapted from Harish *et al.* (2022) [131] and created with BioRender.com.

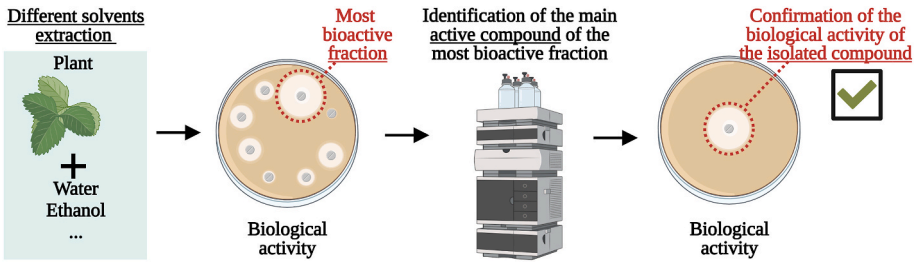

Fig. 7. Example of a methodology for the identification of phytocompounds with biological activity. Created with BioRender.com.

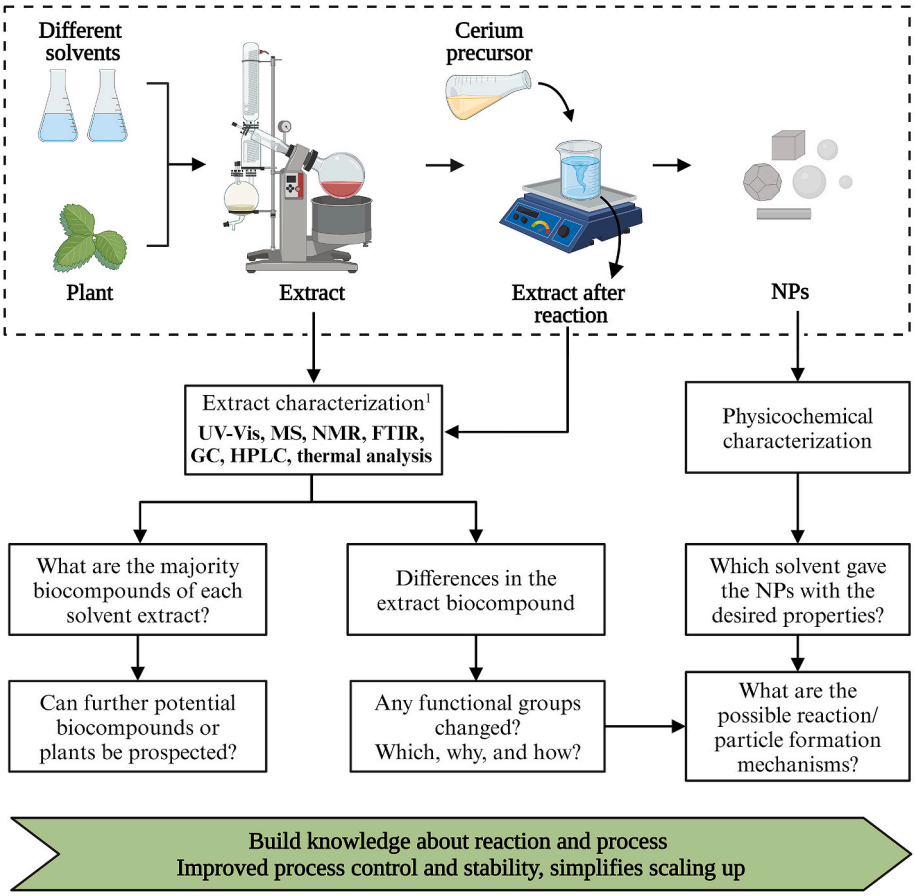

Fig. 8. Experiments that can help in the investigation of reaction mechanisms. [1]Extract characterization by pure or hyphenated techniques: UV–Vis Spectroscopy, MS (Mass Spectrometry), NMR (Nuclear Magnetic Resonance Spectroscopy), FTIR (Fourier Transform Infrared Spectroscopy), GC (Gas Chromatography), HPLC (High-Performance Liquid Chromatography), thermal analysis. Created with BioRender.com.

quantification techniques are not always available in well-established control guidance. Also, the current toxicity of CNPs is contradictory, including conditions under which NPs act as pro- or antioxidants and the influence of environmental factors on nanoparticle behavior, changes in NPs' physicochemical properties under environmental conditions, and tolerable concentration limits in different environments (aquatic, air, and soil ecosystems). These critical points warrant comprehensive attention and should be addressed alongside improvements in CNP synthesis to enhance toxicological and environmental investigations of this promising material [134,135].

Consistent data about the synthesis of CNPs and the properties of the produced materials is also relevant to applying Artificial Intelligence for synthesis and properties optimization. The combination of the solid information from the experimental papers can provide a significant acceleration in identifying optimal combinations of reactants (including biological extracts) and experimental conditions for obtaining nanoparticles with tailored features. This factor can potentially raise the accessibility and operational economy of green synthesis significantly [23].

6. Conclusions and future trends

The present critical review carefully analyzed the plant-mediated green synthesis of cerium oxide nanoparticles. It was observed that only a few studies have focused their efforts on understanding the reaction mechanism and the formation of cerium oxide nanoparticles. However, it is imperative to acknowledge that the progress made in the field of GS methodologies for cerium oxide nanoparticles has had countless broad-reaching effects. They include i) obtaining particles of varied sizes, also comprising very small ones on the order of 3 nm, using a wide range of plants; ii) the use of easy steps/low complex green synthesis routes to obtain CNPs; iii) the development of routes without

hard chemicals; iv) the correlation between particle size and synthesis variables such as calcination temperature, crystallinity, and manufacturing of nanocomposites. Among the plant metabolites that participate in the synthesis, alkaloids, and phenolic compounds are often mentioned.

Despite the progress in the plant-mediated green synthesis of cerium oxide nanoparticles, some aspects remain challenging to the scientific community. Among these challenges is the search for methodologies to answer questions about the role of biocompounds and ways to obtain non-spherical shapes. Integrating the advances with the points highlighted throughout this work is the next step for the safe development of applications with this promising material. The fine control and deep understanding of the synthesis process represent a gain in materials development, especially regarding materials requiring safety-by-design practices, ensuring safe and replicable results.

Realizing the potential of green synthesis to produce CNPs and the points highlighted throughout this review, we present some scope for future works: To perform further studies under different operational conditions (temperature, reaction time, pH) and correlate with physicochemical transformations of the nanoparticles, especially looking to produce various shapes and ratios of Ce^{3+}/Ce^{4+} with the same extract by changing only the synthesis conditions. Design strategies can be proposed using these results to control the synthesized NPs' physicochemical properties. This way, the entire synthesis process can be planned more ecologically, considering the scale-up and process control aspects involved, to facilitate the financial and environmental viability of cerium oxide nanoparticles.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmrt.2024.05.022.

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