



Reconciling the Green Route for Amalgamation of Cerium Oxide Nanoparticles using *Syzygium Cumini* and Identifying their Potential Biomedical Application

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ABSTRACT:

Introduction: Nanotechnology has gained a lot of attention in biomedical and environmental applications due to its potential to enhance antimicrobial and antioxidative properties. Cerium Oxide nanoparticles have emerged as a promising candidate for their redox and ROS scavenging properties. The green synthesis of nanoparticles using plant extracts is an environmentally friendly and sustainable approach that reduces the use of toxic chemicals. *Syzygium cumini*, commonly known as Jamun, is rich in bioactive compounds with potent antioxidative and antimicrobial properties. Our study focuses on the synthesis of composite of *Syzygium cumini* seed extract and Cerium oxide nanoparticles (SC-CNP) and evaluates their properties.

Objectives: The primary objective is to synthesize and characterize the SC-CNP conjugate and then evaluate the free radical scavenging activity of the synthesized SC-CNP conjugate through SOD and H₂O₂ Scavenging assays and then assess the antimicrobial properties.

Methods: The SC-CNP conjugate synthesized by Soxhlet extraction of *S. cumini* seed extract conjugate with cerium oxide nanoparticles through continuous stirring. The physicochemical characterization of synthesized nanomaterial was done by UV-spectroscopy and Diffraction Light Scattering (DLS). The antioxidant activity was determined by Superoxide Dismutase (SOD) and Hydrogen Peroxide (H₂O₂) scavenging assays. The antimicrobial efficacy of SC-CNP conjugates was evaluated using the broth dilution method against *Escherichia coli* (E. coli), with optical density (OD) measurements recorded at 600 nm.

Results. UV-VIS spectroscopy revealed the effective synthesis of SC-CNP conjugates, with an absorbance peak at 320 nm, suggesting the presence of Ce⁴⁺. The DLS research demonstrated an increase in hydrodynamic radius from 110 nm to 165 nm, indicating surface conjugation. SC-CNP conjugates outperformed bare CNPs (34.2%) and crude extract (16.57%) in terms of ROS scavenging activity, achieving 51.4% H₂O₂ degradation. Similarly, SC-CNP conjugates exhibited the greatest SOD mimetic activity (38.88%) when compared to bare CNPs (22.22%) and pure extract (7.4%). The antimicrobial assay showed that SC-CNP conjugates have higher antibacterial activity.

Conclusions: Through this study, we were successfully synthesized SC-CNP conjugates by using an eco-friendly green synthesis approach the synergistic enhancement of antimicrobial and antioxidative properties ensure the potential application of conjugates in biomedical and antimicrobial properties.



1. Introduction

Reactive oxygen species, often referred to as ROS, are produced as by-products of regular oxygen metabolism and are significant players in inflammatory responses. This ROS damages cell membranes, proteins, and DNA, which disrupts normal cellular function and contributes to pathological processes by increasing cell death. A modest quantity of ROS can promote vascularization and aid in protecting wounds against microbial infections by triggering many cellular signaling pathways. However, oxidative stress and inflammation are caused by excessive ROS production, which hinders effective wound healing. If there is delayed or inadequate ROS detoxification, the wound often becomes chronic and non-healing, which poses significant treatment issues. Therefore, it is required to develop innovative therapeutics agents with strong antibacterial, anti-inflammatory, and ROS detoxifying capabilities [1]. Nano-technological research gained enormous attention from researchers and became one of the most studied scientific fields. Nanoparticle-based studies were found useful due to their vast applications in different types of fields, such as biomedicine, drug delivery, diagnostics, optics, and electronics [2]. Nanoparticles have an extremely large specific surface area (area per unit volume), so the interaction of electron activity with external influences is important [3]. Cerium oxide nanoparticles (CNP) have received a lot of interest owing to their remarkable catalytic and multi-enzyme-mimetic properties [4]. Due to their electric configuration, the electric structure of cerium atoms is very adaptable, allowing them to easily conform to their surroundings. The simple and dynamic redox cycling on the surface of Ce^{3+} and Ce^{4+} oxidation states on the nanoparticle's surface allows for a quick and suitable response to the surrounding stimulus. Hence Cerium oxide nanoparticles (CNPs) have a unique capability for oxygen species release and absorption. Due to these features, CNPs are endowed with essential capabilities, which leads to their use as antibacterial, antifungal, anti-inflammatory, anticancer and antioxidative agents [5]. The chemical conventionally employed in cerium oxide nanoparticle synthesis as stabilizing agents often present significant drawbacks leading to toxicity during the preparation process and creation of highly acidic or basic reaction environments. To address these limitations and synthesize biocompatible CNPs, a green synthesis route

utilizing *S. cumini* as a stabilizing agent is proposed, leveraging its inherent therapeutic properties to manage diabetic stress.

S. cumini seeds boast a rich history in traditional medicine and are renowned for their diverse pharmacological benefits. The bioactive constituents of *S. cumini* seeds comprise a diverse array of phytochemicals, including anthocyanins, triterpenoids, oleic acid, essential oils, saponins, and glycosides, with various other flavonoids. Consequently, these plant seeds are emerging as a significant source of compounds with demonstrated antimicrobial, anti-inflammatory, anti-fungal, and anti-diabetic activities [6]. Notably, the pronounced anti-diabetic effects of the seed extract of *S. cumini* may be attributed to the presence of individual or synergistic combinations of these bioactive components, potentially exerting direct or indirect influence on β -cell activity and insulin resistance [7].

The Proportion of combining CNPs and *Syzygium cumini* seeds, hereafter referred to as SC-CNP, unveils an opportunity to investigate potential synergistic interactions between these two components. Therefore, a series of assays will be conducted to elucidate the mechanisms underlying this amalgamation, which could potentially result in our expectation that combining the robust antioxidative properties of CNPs with the established medicinal benefits of *S. cumini* seeds in managing diabetes may lead to enhanced reactive oxygen species(ROS) scavenging, diminished oxidative stress, and augmented regenerative processes.

2. Objectives

The primary objective of this research is to create and analyze *Syzygium cumini* seed extract-conjugated cerium oxide nanoparticles (SC-CNPs) via a green production method. Characterization of SC-CNP conjugate confirmed through UV-VIS absorption spectra for absorption peak and Diffraction Scattering Light(DLS) analysis for Hydrodynamic radius. The study evaluates the free radical scavenging or antioxidative activity of the produced SC-CNP conjugates using Superoxide Dismutase (SOD) and Hydrogen Peroxide (H_2O_2) scavenging tests. Furthermore, the antibacterial activity of SC-CNPs against *Escherichia coli* (*E. coli*) is determined using the broth dilution technique. By analyzing the physicochemical properties and biological activity of SC-CNPs, this research seeks to determine



their potential applications in biomedical and pharmaceutical fields.

3. Material and Methods:

3.1 Material:

Cerium Nitrate Hexahydrate (Hi-Media Catalogue No. – GRM1441), *Syzygium cumini* seed extract powder from SA herbal bioactives LLP (Bixa botanical approved by FDA), Ammonium solution 30% (Catalogue No. L376452107), Hydrogen peroxide (Cat. No. – PCT1511), Ascorbic acid (Cat. No. – 01550, by Loba Chemie), Methionine (Cat. No. PCT0315 by Hi-Media), LB Broth (Cat. No. L24060, Make-Hi-Media), α -amylase (Cat. No. GRM638, Make-Hi-Media), Starch (Cat. No. GRM425, Make-Hi-Media),

3.2 Synthesis of extract of *S. cumini* seed powder and Cerium Oxide Nanoparticle conjugate (SC-CNP)

S. cumini seed powder will be utilized for the conjugation of interfused CNP nanomaterial. Initially, a crude extract was obtained through Soxhlet extraction in which we used methanol as the solvent. Subsequently, a 0.1 M solution of Cerium Nitrate Hexahydrate was prepared in distilled water with continuous stirring for 60 min at 550 rpm. Following this, 40 ml of aqueous plant extract was added, followed by 120 minutes of stirring. The resulting homogenous mixture was then evaporated at approximately 80°C and calcinated at 400°C for 40 minutes using a muffle furnace. In a separate procedure, bare CNPs were synthesized by adding 2.5 gm of Cerium Nitrate Hexahydrate to 100 ml of Milli-Q water in a beaker and stirring for 30 minutes at High temperature. Then, 10 ml of 1N NH_4OH (30%) is added and stirred for 4 hours (prepared by adding 6.881 ml of 30% NH_4OH to 100 ml of Milli-Q water). Following this, centrifugation was performed at 8000 RPM for 10 minutes, and the solvent was removed after. The resulting pellet was resuspended in 250 μl of fresh Milli-Q water. This washing process was repeated twice, and the final volume was adjusted up to 50 ml through the addition of Milli-Q water. The pH was then adjusted to 3 (acidic), and the solution was stored in a dark place, free from contamination, for 48 hours (Figure 1).



Fig 1. This image depicts the raw material and synthesized Conjugate (a) commercially available Jamun (*Syzygium cumini*) seed powder (Bixa Botanical). (b) Finely powdered Jamun seed powder with a distinctive brown color and powdery texture. (c) Finely white, crystalline bare CNPs powder (d) A granular form of *Syzygium cumini* and Cerium Oxide Nanoparticles (SC-CNP) Conjugate to enhance medication delivery or stability

3.3 Physicochemical characterization (UV-VIS Spectroscopy and DLS)

The synthesized materials were comprehensively characterized via a suite of analytical techniques, including dynamic light scattering (DLS) and UV-visible (UV-VIS) spectroscopy. Novostrix Nanodrop UV-Vis spectrophotometer was used for UV-VIS spectra. Analysis of these spectra confirmed the presence of the Ce^{4+} surface oxidation state, as the confirmatory peak lies between the 220-720 nm range. Nanoparticle size analysis was conducted by using a Zetasizer Nano ZS instrument. Hydrodynamics radius analysis, derived from DLS measurements, indicated a particle size distribution ranging from 50-250 nm. Then, these samples were ultrasonicated for 15 minutes prior to DLS analysis to ensure uniformity in nanoparticle dispersion within the solvent, minimize aggregation, and enhance the accuracy of size measurements. The crystalline nature of the synthesized nanomaterial was rigorously investigated using X-ray diffraction (XRD) analysis. This technique provided information regarding the atomic arrangement within the material, and the crystal lattice structure was determined through the



identification and interpretation of crystallographic planes observed in the XRD patterns. SEM can be employed in future to investigate the morphology of the sample's surface by providing detailed information regarding nanoparticle texture, shape, and arrangement, thereby validating the structure and integrity of the nanomaterial.

3.4. Free radical scavenging activity of SC-CNP conjugate:

To evaluate the catalytic behavior, the Superoxide Dismutase (SOD) assay was performed. For each test tube, the following reagents were added sequentially: 1700 μL of Tris-HCl buffer, 300 μL of EDTA, 400 μL of methionine, and 250 μL of NBT solution. Subsequently, 200 μL of bare CNP, seed powder extract of *S. cumini*, and SC-CNP conjugate were added to three test tubes, marked as samples A, B, and C, respectively. The fourth test tube served as a control. Finally, 200 μL of Riboflavin was added to all test tubes, including the control, and the tubes were exposed to white light. Absorbance was measured at 560 nm using a spectrophotometer, with PBS as the blank. Similarly, for the H_2O_2 Scavenging activity, 4 ml of cold PBS solution was added to each of the four test tubes. Then, 200 μL of SAMPLE A, B, and C were added to three designated test tubes, respectively. Ascorbic acid (200 μL) and cold H_2O_2 solution (100 μL) were added simultaneously to the control test tube. Finally, 600 μL of cold H_2O_2 sol. was introduced to each of the four test tubes. The tubes were incubated at room temperature for 15 minutes, and absorbance was measured at 230 nm by using a cold PBS solution as the blank.

3.5 Antimicrobial activity of SC-CNP conjugate:

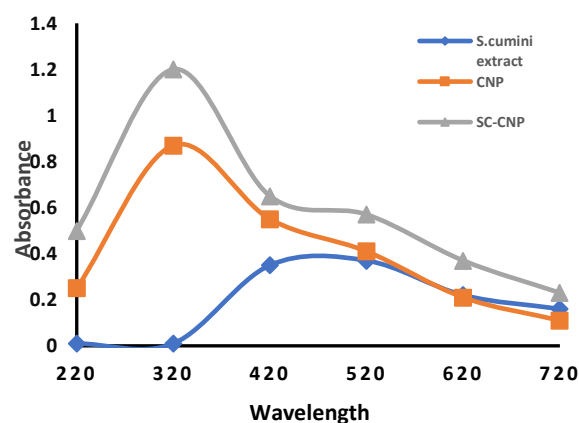
The Broth Dilution method, a fundamental technique for assessing the antimicrobial properties of compounds, was employed for initial screening to evaluate the antimicrobial properties of the conjugate. All glassware and media (LB Broth) were sterilized via autoclaving. Five individual test tubes were prepared, each containing 5 ml of LB Broth. Subsequently, 200 μL of bare CNP, seed powder extract of *S. cumini*, and SC-CNP conjugate (designated as SAMPLE A, B, and C, respectively) were added to separate tubes. Each test tube was then inoculated with microorganisms (a fresh culture of *E. coli* formulated to a defined density of cells) using a sterile loop. A fourth test tube, containing only LB broth

and microorganisms devoid of nanoparticles, served as a positive control. A final test tube containing LB broth alone served as a negative control. All tubes were incubated at 37 $^\circ\text{C}$ for 24 h. After incubation, the Optical Density (OD) at 600 nm was recorded for each tube

4. Results

4.1 Synthesis and Characterization of SC-CNP Conjugate

Conjugates of *Syzygium cumini* and Cerium oxide nanoparticles (SC-CNP) were successfully synthesized by using a green synthesis approach. This method harnessed the properties of plant-derived phytoconstituents, which were obtained through Soxhlet extraction and served a dual purpose as an oxidizing agent as well as a stabilizing agent course of synthesization of conjugate material. Following the calcination process, the resulting SC-CNP conjugate underwent thorough characterization to ascertain its physicochemical properties and confirm the successful conjugation of the plant extract with the nanoparticles. Primary confirmation of the conjugation was achieved through UV-Vis spectroscopy. The absorbance peak of Ce^{4+} was obtained at 320 nm (as depicted in Figure 2a). Furthermore, Dynamic Light Scattering (DLS) measurements were conducted to assess the size distribution and hydrodynamic radius of both the bare Cerium oxide nanoparticles (CNPs) and the SC-CNP conjugate. The hydrodynamic radius increased from approximately 110 nm for the bare CNPs to 165 nm after conjugation. This confirmed the successful surface conjugation of *Syzygium cumini* extract onto the CNPs (Figure 2b).



(a)

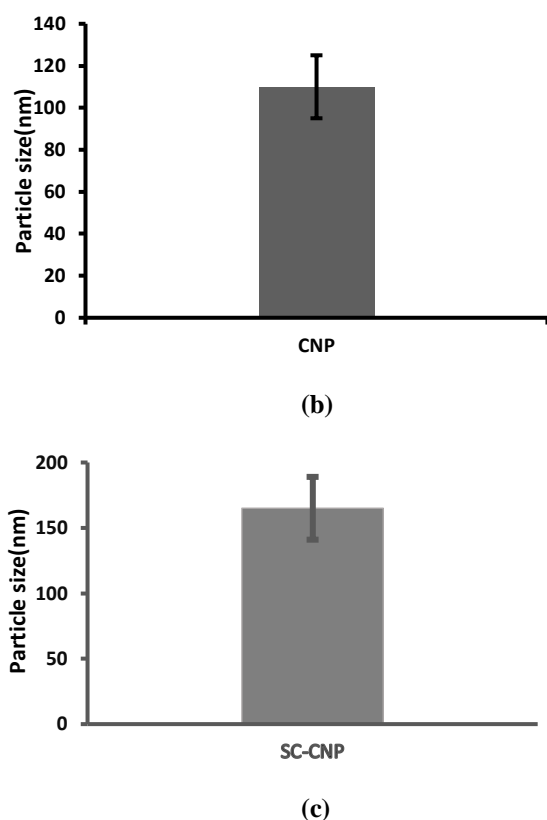


Fig. 2. a) Represents the UV-visible characterization of *S.cumini* seed Extract, bare CNP and SC-CNP Conjugate nanomaterial. b) and c) the Dynamic Light Scattering characterization for the size

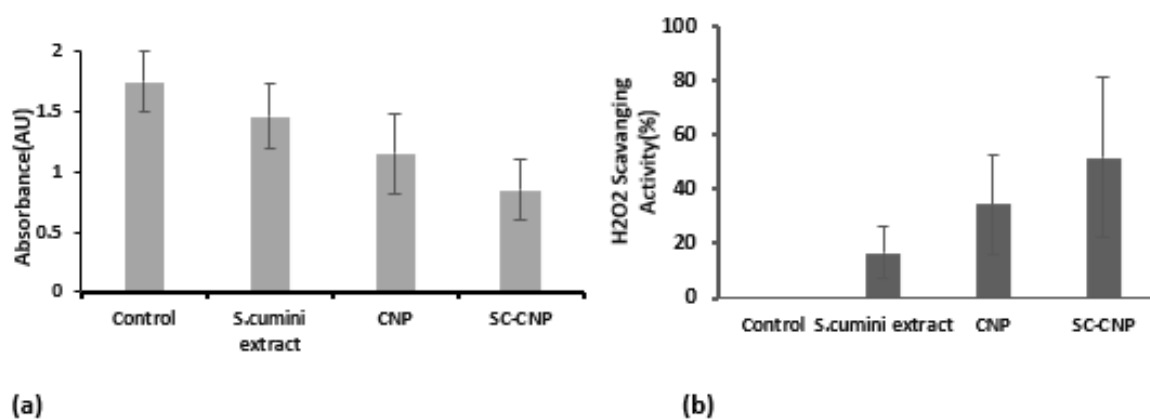


Fig. 3. The catalase mimetic activity of synthesized SC-CNP nanomaterials. Catalase mimetic assay demonstrated the H₂O₂ scavenging activity of all samples at different concentrations. (a) The absorption of the Samples-S. cumini extract, bare CNP and SC-CNP in comparison of H₂O₂ (control), b) The percentage scavenging activity of samples in comparison to the control.

analysis of synthesized cerium oxide nanoparticles conjugate in comparison of bare CNP.

4.2 Reactive Oxygen Species (ROS) scavenging Antioxidant assay

Biochemical assays assessed the antioxidative efficacy of the SC-CNP conjugate, evaluating its catalytic activity as a catalase and superoxide dismutase (SOD) mimetic. The biochemical analysis for catalase mimetic activity assessed H₂O₂ degradation parameters and found that the crude extract of the seed of *Syzygium cumini*, bare CNPs, and SC-CNP conjugate had varied levels of scavenging activity (Fig. 3). Crude *Syzygium cumini* extract exhibits the lowest H₂O₂ scavenging activity (16.57%), followed by bare CNP (34.2%), with the SC-CNP conjugate demonstrating the highest activity of catalase mimetic activity, which is 51.4%. indicating a synergistic effect. Superoxide dismutase (SOD) mimetic activity of the SC-CNP conjugate was evaluated via Nitroblue Tetrazolium (NBT) reduction assay which was conducted utilizing riboflavin-methionine-mediated superoxide radical production. Plant seed extract, unconjugated CNP, and SC-CNP conjugate were analyzed. The plant seed extract exhibited reduced activity (7.4%) compared to both unconjugated CNP (22.22%) and SC-CNP conjugate 38.88% (Figure. 4). A direct correlation between SC-CNP conjugate concentration and SOD mimetic activity was observed.

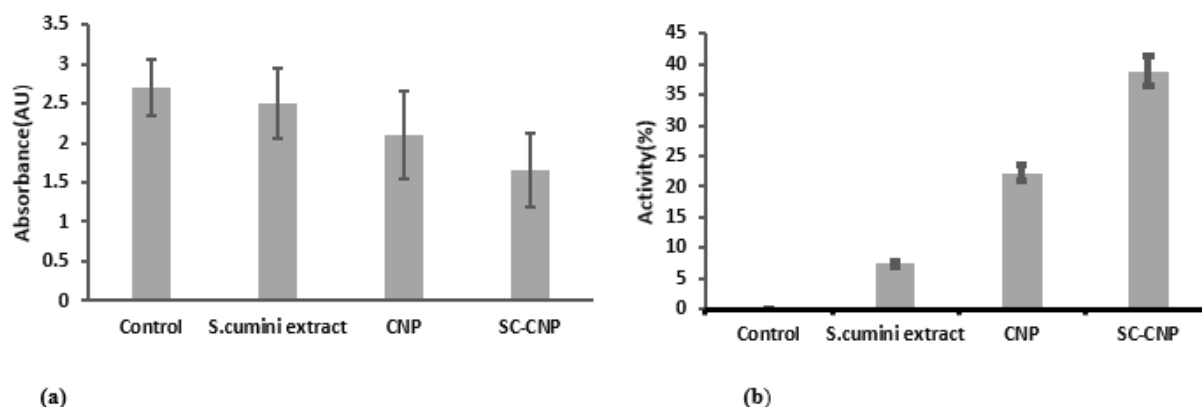


Fig.4. The superoxide dismutase mimetic activity of *S.cumini* extract, Bare CNP, and SC-CNP nanomaterials. Superoxide Dismutase mimetic assay demonstrated the superoxide ions scavenging activity of all samples. a) Absorption of all samples- *S. Cumini* extract, Bare CNP, and SC-CNP conjugate in comparison with control. b) The percentage inhibition of all samples in comparison to the control

4.1 Anti-microbial analysis of SC-CNP conjugate

The anti-microbial effectiveness of SC-CNP conjugate against *E. coli* was evaluated by utilizing a Minimum Inhibitory Concentration assay at 10^6 fold concentration. It was observed that the Conjugation resulted in a synergistic enhancement of anti-microbial activity as the crude *Syzygium cumini* extract exhibited approximately 16.2% activity, unconjugated CNPs demonstrated 32.43% activity, while the SC-CNP conjugate displayed 51.35% activity (Figure 5). The antimicrobial efficacy of the SC-CNP conjugate was directly related to its concentration of nanoparticles.

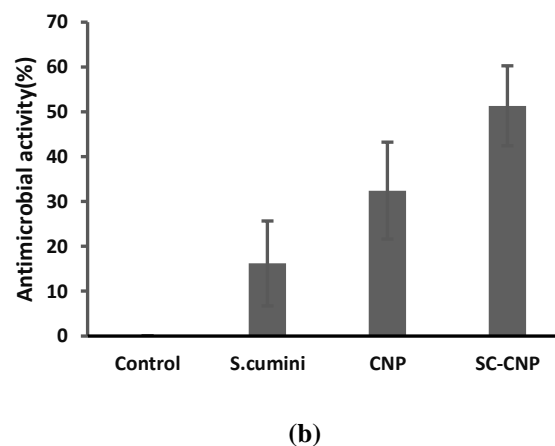
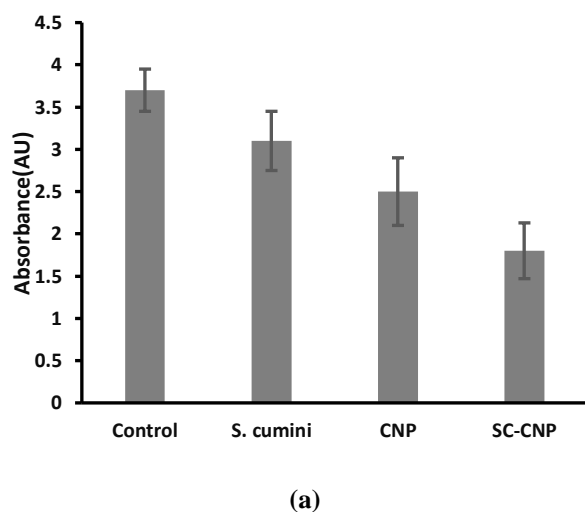


Fig. 5. The antimicrobial efficiency of different samples against 10^6 folds of *E. coli*. The absorption of the different Samples-*S. cumini* extract, bare CNP, and SC-CNP in comparison to the control treatment. b) The percentage inhibition of the different samples in comparison to the control treatment

5 Discussion

In the last decades, nanotechnology has been emphasized its area widely in almost every sector. One of the most significant reaches of nanotechnology is its application in the biomedical sector, owing to its unique physical and chemical characteristics. Nanoparticles range from 1-100 nm, making them liable for various applications [8]. They can be in the form of nanotubes, nanowires, or



nanoparticles, in which synthesis and characterization play a crucial part. Given that the morphology of nanomaterials significantly influences their properties, a comprehensive investigation into the morphological characteristics of nanomaterials and their consequential impact on optical, electrical, magnetic, electronic, and thermal properties is essential [9]. There are many methods for the synthesis of nanoparticles, making them compatible with various applications. However, in the biomedical area, some issues need to be addressed, like toxicity, biodegradability, and biocompatibility. Nanoparticles have a high surface/volume ratio, which enhances their reactivity, mobility, dissolving characteristics, and mechanical strength. Nanoparticles are manufactured using a variety of methods and occur naturally in terrestrial habitats such as soil, water, volcanic emissions, and mineral deposits. A wide range of sectors, including food and beverage, agriculture, and pharmaceuticals, are taking use of nanoparticles. The incorporation of nanoparticles into biocompatible materials for the creation of hybridized scaffolds is gaining worldwide interest [10]. One of the best materials for biomedical purposes is Cerium oxide nanoparticles, which can be synthesized using diverse methods; however, employing green chemistry principles presents a simplified and environmentally conscious alternative. The conjugation of crude *Syzygium cumini* with cerium oxide nanoparticles (CNPs) has demonstrated beneficial synergistic effects, particularly in the bioactivity of the SC-CNP conjugate. Conjugation was confirmed using various physicochemical characterization techniques, with initial confirmation obtained via UV-visible spectroscopy (Fig. 2a). As illustrated, prominent peaks observed at 320 nm indicate the substantial presence of the Ce⁴⁺ oxidation state. Prior research suggests that an elevated Ce⁴⁺/Ce³⁺ oxidation state exhibits significantly enhanced catalase mimetic activity in comparison to superoxide dismutase(SOD) mimetic activity [11]. The Dynamic Light Scattering (DLS) approach verified the hydrodynamic radius of the conjugated nanomaterial(165nm) and bare CNP(110nm), and the radius parameters were determined by earlier findings [12]. The change in radius observed between the bare CNPs and SC-CNP conjugate suggests successful conjugation of materials. Specifically, the radius of the CNPs increased from 110nm to 165nm upon

conjugation, with this size range consistent with nanoscale dimensions (Fig. 1b), and it can also be escalated with the addition of the crude extract of *Syzygium cumini*. The crystalline structure of the synthesized conjugate nanomaterial was assessed by comparison with previously published data [13]. It has been shown that the SC-CNP conjugate has significantly enhanced catalase mimetic activity, demonstrating a performance up to two-fold greater than that of bare CNP (fig 4). The graph clearly shows that the conjugated nanomaterial SC-CNP had 51.4% catalase mimetic activity, bare CNP had 34.2%, and plant extract had 16.57%. This notable increase in activity proposed that the conjugation of CNP with crude plant seed extracts introduces bioactive components that substantially augment its redox capabilities. This enhanced property holds considerable promise for various applications [14,15]. Whereas Superoxide Dismutase(SOD) mimetic activity moderately increases. It has been shown in the graph that plant extract has 7.4%, CNP has 22.2% and SC-CNP conjugate has 38.8% SOD mimetic activity in comparison to the control, which can also be further optimized for enhancement (Fig 5) [16]. The biological properties of SC-CNP were also enhanced in several ways. Fig. 6 illustrates the 1.5-fold increase in antibacterial activity. Plant extract had an antibacterial activity of 16.2%, bare CNP had 32.43%, and SC-CNP conjugated nanomaterial was found at 51.35%. CeO₂ NP's remarkable electrostatic characteristics, distinctive morphologies, tiny particle size, and low band gap energy are all factors in their bactericidal effectiveness [17]. CeO₂ NP's powerful electrostatic potential makes it easier for them to bind with the thiol groups of membrane proteins, which denatures the proteins and compromises the integrity of the membrane, ultimately killing the microorganism [18]. Flavonoids, Terpenoids, and phenols found in *Syzygium cumini* have bioactive qualities [19]. The biological effectiveness of these two powerful chemical entities' combined impacts may be increased by their conjugation. This initial demonstration of positive synergism serves as a framework for our research to improve possibilities of enhancing the potential of conjugated nanomaterial SC-CNP as a next-generation therapeutic agent. Given the novelty of this conjugation, researchers may explore the therapeutic applications of *Syzygium cumini* and cerium oxide nanoparticles (SC-CNP), using the improved



characteristics and biological effectiveness achieved through their conjugation for a variety of therapeutic applications. The promising results of this study offer a solid basis for future mechanistic investigations focused on identifying the unique and signature phytochemicals from *Syzygium cumini* and elucidating their synergistic role.

5. Conclusion

Through this study, we reported for the first time a sustainable and environmentally friendly method for the fabrication of Cerium oxide nanomaterial from *Syzygium cumini* plant extract. This innovative approach utilizes the crude extract of *Syzygium cumini*, providing a green alternative to conventional synthesis methods. By incorporating these plant extracts, we succeeded in enhancing the redox potential of cerium oxide nanoparticles. These materials, synthesized via this method, exhibit notable antioxidative activity, demonstrated by their efficient reactive oxygen species scavenging capabilities. Our data supports their potential efficacy as antimicrobial agents. Furthermore, the synthesized SC-CNP conjugates exhibit unexpected beneficial properties, indicating a potential role in diabetes management. We believe that these findings will significantly contribute to future pharmaceutical research. The insights derived from this research might help guide drug development strategies, especially for a range of biological uses, and this research will facilitate the development of novel therapeutics with improved efficacy and reduced adverse effects, ultimately benefiting patients and advancing the field of biomedicine. The sustainable and biocompatible nature of the synthesis method further enhances the attractiveness of these nanomaterials for future therapeutic interventions.

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