



Development of $\text{Ce}^{3+}/\text{Nd}^{3+}$ -engineered TiO_2 Nanoplatforms with Optimized Cytotoxic and Antioxidant Properties Guided by Machine Learning-based Predictive Modeling

Rekha Anantharaman¹, Alagendran Subbarayalu², N. Selvam³, L. R. Sujithra^{4*}, R. Subbulakshmi⁵ and S. Ragamayi⁶

¹Department of Obstetrics and Gynecology, Saveetha Medical College and Hospital, Chennai, TN, India

²Department of Research, Saveetha College of Nursing, Chennai, TN, India

³Department of Electrical and Electronics Engineering, M. Kumarasamy College of Engineering, Karur, TN, India

⁴Department of Artificial Intelligence and Data Science, Sri Eshwar College of Engineering, Coimbatore, TN, India

⁵Department of Computer Science and Engineering, Karpagam Institute of Technology, Coimbatore, TN, India

⁶Department of Engineering Mathematics, Koneru Lakshmaiah Education Foundation, Guntur, AP, India

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*Irsujithra9@gmail.com



ABSTRACT

Lanthanide-engineered TiO_2 nanostructures offer a promising strategy for tuning biological activity through controlled modification of their physicochemical properties. In this work, Ce^{3+} -doped, Nd^{3+} -doped, and $\text{Ce}^{3+}/\text{Nd}^{3+}$ co-doped TiO_2 nanoparticles were synthesized and evaluated to investigate the influence of dual-lanthanide incorporation on cytotoxic and antioxidant performance. The results demonstrated that $\text{Ce}^{3+}/\text{Nd}^{3+}$ co-doping effectively modulated the biological response of TiO_2 by reducing cytotoxicity while enhancing antioxidant activity compared with pristine TiO_2 . Antioxidant assays revealed improved radical scavenging efficiency against DPPH, ABTS, and H_2O_2 radicals following lanthanide incorporation. To further establish structure–activity relationships, machine learning models were developed to predict cytotoxic behavior using physicochemical and experimental parameters. Among the evaluated models, Gradient Boosting achieved the highest predictive accuracy ($R^2 = 0.8728$, RMSE = 11.436), outperforming the other algorithms considered in this study. Feature importance analysis identified nanoparticle concentration as the dominant factor governing cytotoxic response, while structural and surface properties provided secondary contributions. Overall, the findings demonstrate that $\text{Ce}^{3+}/\text{Nd}^{3+}$ co-doping is an effective approach for tailoring the biological performance of TiO_2 nanoparticles, while machine learning-assisted analysis provides valuable insights for the rational optimization of lanthanide-modified nanomaterials for biomedical applications.

Keywords: $\text{Ce}^{3+}/\text{Nd}^{3+}$ -doped TiO_2 ; Lanthanide nanoparticles; Cytotoxicity; Antioxidant activity; Gradient boosting; Machine learning.

1. INTRODUCTION

Recent advancements in nanostructured materials have significantly expanded their applicability across biomedical, environmental, and catalytic domains, particularly through the integration of metal and metal oxide nanocomposites with enhanced multifunctionality. Green-synthesized $\text{Ag}/\text{TiO}_2/\text{graphite}$ nanocatalysts have demonstrated high catalytic efficiency in the synthesis of pyrazolopyrimidine derivatives, coupled with notable antioxidant and anticancer activities, where molecular docking further validated strong bio-interactions, highlighting their sustainable biomedical potential (Alhar *et al.* 2026). Similarly, Cu-grafted TiO_2 nanoparticles exhibit superior cytotoxic, antioxidant, anti-inflammatory, and photocatalytic properties compared to pristine TiO_2 , primarily driven by enhanced

hydroxyl radical generation and dye degradation efficiency (Chhabria *et al.* 2025). Hybrid systems such as CuO/TiO_2 incorporated into AN-co-St grafted sodium alginate matrices have further improved structural stability and bioactivity, enabling promising anticancer and antioxidant performance (Nemr *et al.* 2024). In drug delivery, Ag– TiO_2 /PLA nanohybrids have enabled pH-responsive co-delivery of norfloxacin and tenoxicam, achieving controlled release, enhanced antibacterial efficacy, and reduced side effects (Salahuddin *et al.* 2021).

Plant-mediated synthesis routes have also gained prominence due to their eco-friendly nature and enhanced biological compatibility. Titanium nanoparticles derived from *Ziziphora clinopodioides* extract exhibit strong antioxidant, antibacterial, and

antifungal activities with non-cytotoxic behavior, while in vivo studies confirm improved wound healing and reduced inflammation (Seydi *et al.* 2019). In parallel, CeO₂-based nanomaterials have emerged as versatile platforms for biomedical applications. Bacterial cellulose-reinforced CeO₂ composites exhibit excellent biocompatibility and protective biological performance, reducing oxidative stress without cytotoxic or genotoxic effects (Butulija *et al.* 2024). Moreover, green-synthesized CeO₂ nanorods and nanoparticles using plant extracts such as *Dalbergia sissoo* and *Alternanthera sessilis* exhibit multifunctional properties, including antioxidant, anticancer, anti-inflammatory, and photocatalytic dye degradation, with optimization studies confirming high efficiency (Alam *et al.* 2022; Rajkumar *et al.* 2026).

Advanced nanocarrier systems have further improved targeted therapeutic performance. Alginate-coated ceria nanoparticles enable immune evasion and enhanced anticancer efficacy when loaded with chemotherapeutic agents, providing a promising platform for personalized drug delivery (Pramanik *et al.* 2022). Rare-earth-doped CeO₂–SiO₂ ternary systems and lanthanide-based nanostructures have introduced new dimensions in biomedical functionality, offering enhanced thermal stability, optoelectronic behavior, and superior anticancer activity (Vargas-Muñiz *et al.* 2025). Nd³⁺-sensitized upconversion nanoparticles and co-doped lanthanide nanocrystals further enable efficient photon conversion, tunable emission, and improved photodynamic and photothermal therapy through enhanced reactive oxygen species generation, thereby advancing applications in bioimaging and cancer treatment (Zhang *et al.* 2021; Jiang *et al.* 2023). Additionally, lanthanide–organic hybrid composites and advanced spectroscopic–computational approaches have facilitated deeper insights into structural, luminescent, and biochemical interactions, supporting their roles in sensing and therapeutic systems (Matsia *et al.* 2025), (Nielsen *et al.* 2025).

Multifunctional nanocomposites based on TiO₂ and CeO₂ continue to exhibit significant promise in biomedical engineering. CaF₂-based Ce/Gd/Nd-doped nanoparticles demonstrate strong NIR-II emission, excellent biocompatibility, and multimodal imaging capabilities, including fluorescence, MRI, and photoacoustic imaging (Yu *et al.* 2022). Furthermore, TiO₂-based nanostructures with tunable bandgaps and morphology offer tailored optoelectronic properties (Paul *et al.* 2025), while TiO₂/SiO₂-reinforced PEEK nanocomposites enhance antibacterial performance, thermal stability, and cell viability for implant applications (Thanigachalam and Muthusamy, 2022). Triphasic TiO₂/WO₃/CeO₂ nanocomposites demonstrate improved visible-light absorption and photocatalytic efficiency alongside antibacterial activity, reinforcing their dual environmental and biomedical relevance

(Subramanian *et al.* 2025). In addition, functionalized nanocellulose hybrids and nanofluid systems incorporating metal oxide nanoparticles have shown improved thermal conductivity and optimized rheological behavior, supporting applications in heat transfer, hyperthermia, and drug delivery (Manimaran *et al.* 2025), (Zhang *et al.* 2024). Complementary systems such as hydroxyapatite–TiO₂ nanocomposites further enhance thermal performance and biomedical compatibility, with machine learning models enabling accurate prediction of system behavior (Shahgholi *et al.* 2022). Finally, hydrothermally synthesized TiO₂ nanoparticles exhibit strong antibacterial activity while maintaining lymphocyte viability, confirming their safety and effectiveness for biomedical use (Mahalakshmi and Vijaya, 2021).

Although TiO₂ nanoparticles have been extensively investigated for biomedical applications, existing studies have primarily focused on pristine TiO₂ or single-lanthanide doping systems, with limited attention given to the synergistic effects of Ce³⁺/Nd³⁺ dual doping on both cytotoxic and antioxidant performance. Furthermore, the relationship between physicochemical characteristics and biological response remains inadequately understood, and machine learning-assisted prediction of cytotoxic behavior in lanthanide-modified TiO₂ systems is rarely reported. To address these gaps, the present study explores the simultaneous incorporation of Ce³⁺ and Nd³⁺ into the TiO₂ lattice to tailor its structural, optical, and biological properties. The novelty of this work lies in the integration of dual-lanthanide engineering with machine learning-based predictive modeling to establish structure–activity relationships, identify the dominant factors governing cytotoxic response, and provide a data-driven framework for the rational design and optimization of multifunctional TiO₂ nanomaterials for potential biomedical applications.

2. MATERIALS AND METHODOLOGY

2.1 Synthesis of Nanoparticles

Pure and Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles were synthesized by a solution–polymerization method. Initially, 0.2 g of polyvinyl alcohol (PVA) was dissolved in 100 mL of deionized water under continuous stirring at 80 °C until a clear homogeneous solution was obtained. Subsequently, the required stoichiometric quantities of Ti(NO₃)₄, Ce(NO₃)₃·5H₂O, and Nd(NO₃)₃·5H₂O were gradually added under constant stirring to ensure uniform distribution of the precursor species. The resulting solution was maintained at 80 °C until solvent evaporation produced a viscous precursor gel, which was subsequently dried at 200 °C for 3 h and calcined at 450 °C to obtain the final nanoparticle powders. The prepared samples were designated as T (pure TiO₂), TC (10 at% Ce³⁺-doped TiO₂), TCN (5 at%

Ce³⁺ and 5 at% Nd³⁺ co-doped TiO₂), and TN (10 at% Nd³⁺-doped TiO₂), based on their dopant composition.

2.2 Characterization of the Nanomaterials

The structural characteristics of the synthesized Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles were investigated using X-ray diffraction (XRD) with Cu K α radiation ($\lambda = 1.5406 \text{ \AA}$), recorded over a 2θ range of 20° – 70° with a step size of 0.01° . Surface morphology was examined using field-emission scanning electron microscopy (FESEM, Gemini, ZEISS, Germany). The elemental composition was analyzed by energy-dispersive X-ray spectroscopy (EDS) attached to the FESEM system, while crystallinity was further evaluated through selected area electron diffraction (SAED). Specific surface area and pore characteristics were determined using the Brunauer–Emmett–Teller (BET) method with a BelJapan MiniSorp II surface area analyzer (MicrotracBEL Corp., Japan). Optical properties were examined using a Cary 5000 UV–Vis–NIR spectrophotometer (Agilent Technologies, USA) equipped with a polytetrafluoroethylene integrating sphere. Surface chemical states and elemental oxidation states were investigated using high-resolution X-ray photoelectron spectroscopy (HR-XPS) employing a monochromatic Al K α X-ray source (1486.6 eV), operated at a pass energy of 15 eV. The spectra were calibrated using the C 1s peak at 284.8 eV and deconvoluted using AAnalyzer® software with appropriate background correction.

2.3 Analysis of Biological Activities

2.3.1 Cytotoxic Activity

The cytotoxic activity of pure and Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay against RAW264.7, HEPG-2, U87, and CACO-2 cell lines. The cells were maintained in Dulbecco's Eagle Medium F-12 supplemented with 10% fetal bovine serum under controlled conditions (37°C , 5% CO₂, humidified environment). Approximately 1.5×10^4 cells were seeded per well in 96-well plates and allowed to stabilize, after which the culture medium was refreshed and the nanoparticle samples were introduced at concentrations of 10–250 $\mu\text{g/mL}$. Following a 24 h exposure period, 25 μL of MTT reagent was added, leading to the formation of insoluble formazan products that were subsequently dissolved using dimethyl sulfoxide, and optical density was recorded at 490 nm; all measurements were conducted in triplicate to ensure reproducibility.

2.3.2 Antioxidant Activity

Antioxidant performance of T, TC, TCN, and TN, representing pure and Cerium (Ce³⁺)/Neodymium (Nd³⁺) incorporated Titanium oxide (TiO₂) nanoparticles, was evaluated through ABTS, H₂O₂ and DPPH radical

scavenging. In the DPPH test, 4 mg of DPPH were dissolved in 100 mL of ethanol and kept under dark stirring for 1 h, after which 200 μL of solution was combined with 20 μL of nanoparticle suspensions at 10–250 $\mu\text{g/mL}$, and absorbance was measured at 517 nm by Shimadzu UV-2600i Plus. For the ABTS method, 18.5 mg ABTS were dissolved in 50 mL of deionized water and reacted with 175.1 mg K₂S₂O₈ for 1 h under dark conditions, followed by mixing 200 μL of the solution with 20 μL of nanoparticle samples, and the absorbance was recorded at 734 nm after 6 min of incubation. In H₂O₂ evaluation, 70 μL of 40 mmol L^{−1} H₂O₂ were blended with 100 μL of nanoparticle dispersions at varying concentrations, incubated for 30 min in the absence of light and analyzed at 230 nm by the same instrument. Ascorbic acid was employed as the reference standard in antioxidant evaluations to validate radical scavenging efficiency.

2.4 Statistical Analysis

Statistical analyses were performed using Minitab Statistical Software. Data are presented as mean $\pm$ standard deviation of three independent experiments. Statistical significance was evaluated using one-way analysis of variance (ANOVA) followed by Tukey's HSD post-hoc test, with $p < 0.05$ considered statistically significant. The obtained results for Cerium (Ce³⁺) and Neodymium (Nd³⁺) modified Titanium oxide (TiO₂) nanoparticles were statistically evaluated using analysis of variance (ANOVA), followed by Tukey HSD post-hoc comparison at a 95% confidence level. The level of statistical relevance was indicated using asterisk notation based on probability values.

2.5 ML Modeling

Machine learning was employed to capture the complex nonlinear relationships between nanoparticle physicochemical properties and cytotoxic response. Gradient Boosting and Random Forest were selected due to their strong predictive capability, robustness against overfitting, and effectiveness in handling heterogeneous materials datasets. In addition, Random Forest enables reliable feature importance analysis, while Gradient Boosting improves prediction accuracy through ensemble learning, making both models suitable for biological response prediction in nanomaterial systems. The dataset was compiled from the experimentally obtained cytotoxicity results and corresponding physicochemical characteristics of the synthesized nanoparticles. Prior to model development, the dataset was randomly divided into training (70%) and testing (30%) subsets. All machine learning models were implemented using Python and the Scikit-learn library. Model performance was evaluated using MAE, RMSE, and R² metrics on the testing dataset. A fixed random state was used during data splitting to ensure reproducibility of the results. A machine learning-based

predictive framework was developed to estimate the cytotoxic behavior of TiO₂-based nanoparticles using their physicochemical properties and experimental conditions. The dataset comprised input parameters including nanoparticle concentration, material type (T, TC, TCN, TN), cell line type (RAW264.7, HEPG-2, U87 and CACO-2), and relevant material descriptors such as bandgap energy, crystallite size, elemental composition (Ti and O atomic percentages), surface area, pore diameter, and zeta potential. The target response variable was cell viability (%).

Initially, categorical variables such as material type and cell line were transformed into numerical format using one-hot encoding to enable their integration into machine learning models. All numerical features were subsequently normalized using Min–Max scaling to ensure uniform contribution of each parameter during model training. The processed dataset was then divided into training and testing subsets in a 70:30 ratio to evaluate model generalization performance.

Multiple regression models, including Decision Tree (DT), Random Forest (RF), Gradient Boosting (GB), Support Vector Regression (SVR), and K-Nearest Neighbors (KNN), were implemented to capture both linear and nonlinear relationships within the dataset. These models were selected due to their proven capability in handling complex interactions in materials science and biological response prediction.

Model performance was evaluated using statistical error metrics such as Mean Absolute Error (MAE), Root Mean Square Error (RMSE), and the coefficient of determination (R²). Among the evaluated models, the Gradient Boosting algorithm demonstrated the highest predictive accuracy, achieving the lowest prediction error and highest coefficient of determination. Therefore, Gradient Boosting was selected as the primary optimized model for cytotoxicity prediction. Random Forest was additionally employed for feature importance analysis owing to its robustness and interpretability.

To enhance model interpretability, permutation-based feature importance analysis was performed using the Random Forest model, which provides a robust framework for evaluating the relative influence of input variables on cytotoxic response. This method evaluates the influence of each input variable by measuring the increase in prediction error when the feature values are randomly shuffled. This approach enabled the identification of key factors governing cytotoxic response.

3. RESULTS AND DISCUSSION

3.1 Material Characterization

The influence of Ce³⁺ and Nd³⁺ incorporation on the crystal framework of TiO₂ nanoparticles was examined using X-ray diffraction analysis (Fig. 1a, b). The diffraction peaks of all samples were indexed to the characteristic crystal structure of TiO₂, consistent with the corresponding reference diffraction pattern. No secondary phases associated with Ce- or Nd-containing oxides were detected, indicating successful incorporation of the dopant ions into the TiO₂ lattice. The introduction of Ce³⁺ and Nd³⁺ ions resulted in a reduction in crystallinity without generating additional impurity phases, along with minor shifts in peak positions and a decrease in crystallite dimensions. Structural parameters, including lattice constants, crystallite size, and unit cell volume, were derived and are summarized in Table 1. The substitution of Ti sites with larger ionic radius dopants (Nd³⁺: 0.86 Å, Ce³⁺: 0.89 Å) compared to Ti⁴⁺ (0.74 Å) induced lattice distortion, defect generation such as oxygen vacancies, and internal strain, which collectively broadened and reduced the intensity of diffraction peaks. These structural modifications influenced grain boundary characteristics and inhibited crystal growth, particularly along the (002) orientation, as shown in Fig. 1c. Furthermore, TiO₂ exhibits polarity due to alternating Ti and O arrangements along the c-axis, where lattice a and c were associated with (101) and (002) planes. The dominance of polar facets such as (001) and (002), in contrast to non-polar (100) and (101) planes, plays a significant role in enhancing reactive oxygen species formation. Such structural modifications may influence the physicochemical behavior of the nanoparticles and have been reported to affect their functional properties, including charge separation efficiency, surface reactivity, and defect-mediated processes in doped TiO₂ systems.

Table 1. Geometric comparison of doped and undoped TiO₂ nanoparticles

Material	Lattice Parameter (Å)		D(nm) ± 5%	V _{cell} (Å)
	a	c		
T	3.782	9.502	117.6	30
TC	3.768	9.528	118.2	34
TCN	3.755	9.546	118.8	31
TN	3.762	9.515	117.9	32

Fig. 1d presents the proposed energy level interactions associated with Ce³⁺ and Nd³⁺ incorporation in the TiO₂ lattice. The introduction of lanthanide ions can modify the electronic structure and optical response

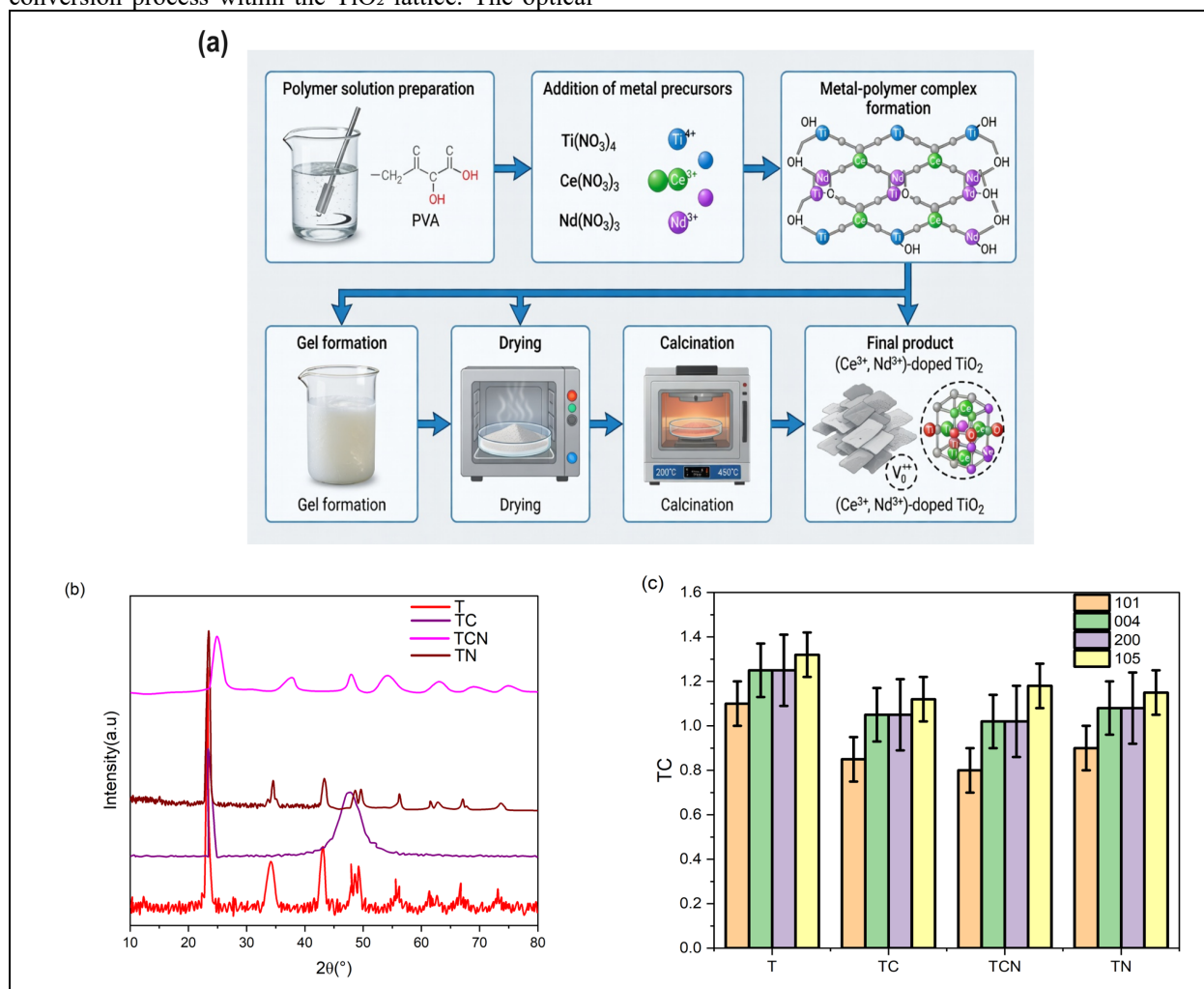
of TiO₂ through the creation of additional energy states within the band structure. These modifications are consistent with the observed changes in the optical absorption characteristics and bandgap values of the synthesized nanoparticles.

Fig. 1e presents the UV–Vis absorption profiles of pure and Ce³⁺/ Nd³⁺ modified TiO₂ nanoparticles over the wavelength range 300–1000 nm, where samples display a characteristic absorption onset at 380 nm associated with the intrinsic bandgap of TiO₂. A detailed view in Fig. 1f (400–1600 nm) highlights multiple absorption features attributed to electronic transitions of Ce³⁺ and Nd³⁺ ions. In Ce³⁺-containing samples, distinct peaks correspond to transitions from the ground state to higher energy levels, including near-infrared (~978 nm and ~780 nm), visible (~656 nm), and green region (~543 nm and ~521 nm), along with a near-UV feature around 381 nm. These transitions confirm the role of Ce³⁺ and Nd³⁺ ions in facilitating photon absorption and the energy conversion process within the TiO₂ lattice. The optical

bandgap values were further estimated from the absorption data using the Kubelka–Munk approach, indicating that lanthanide incorporation modifies the electronic structure and optical response of the nanoparticles:

$$F(R_{\infty}) = \frac{(1-R_{\infty})^2}{2R_{\infty}} \quad \dots (1)$$

Here, R_{∞} represents the absolute reflectance determined from the ratio of reflected intensity of the sample to that of a Spectralon standard ($R_{\text{sample}}/R_{\text{Spectralon}}$). Furthermore, positions of valence and conduction bands for pure and Ce³⁺/ Nd³⁺ doped TiO₂ nanoparticles were estimated as illustrated at Fig. 1g. The evaluated optical bandgap energies for T, TC, TCN, and TN samples were found to be 3.2, 3.20, 2.95, and 2.2 eV, respectively, indicating slight modifications in the electronic structure due to Ce³⁺ and Nd³⁺ incorporation.



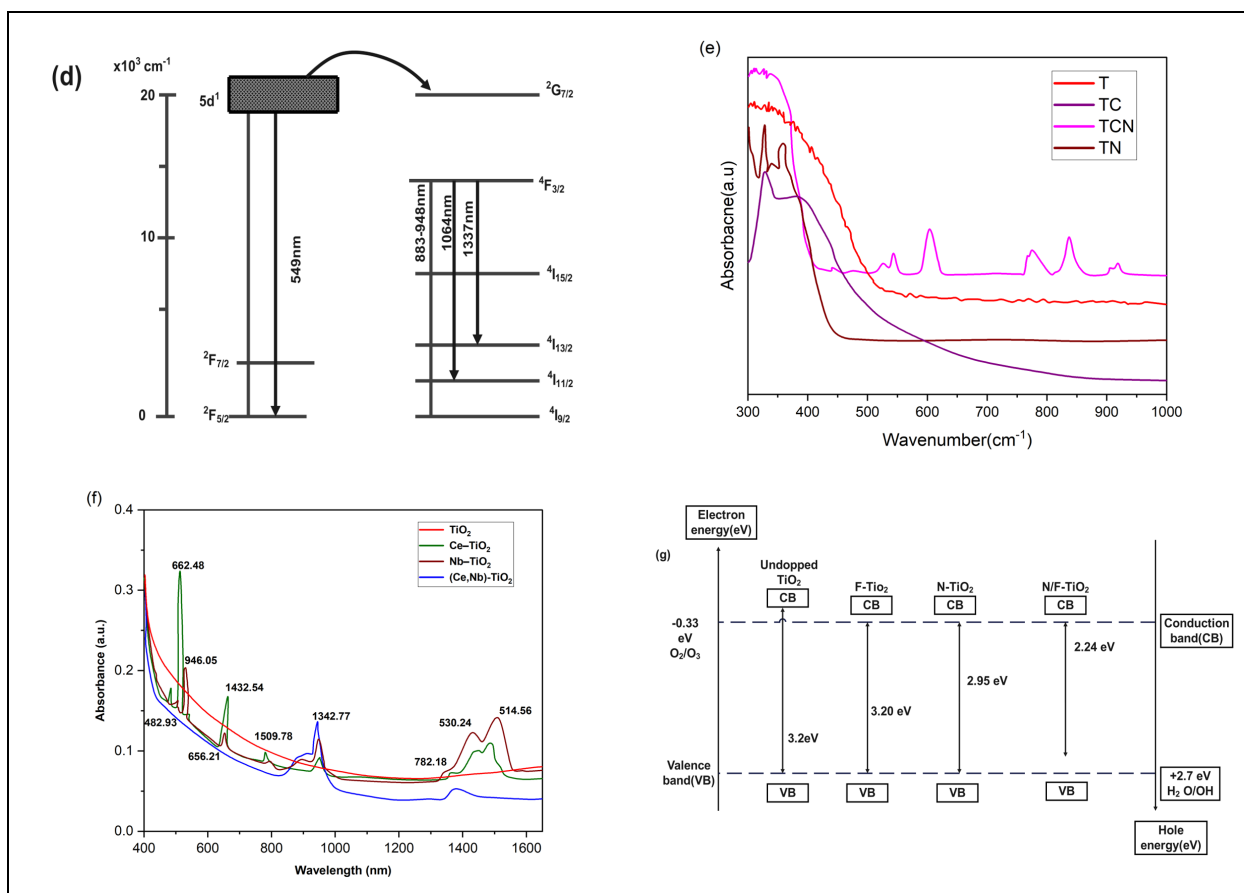


Fig. 1: (a) Synthesis, (b) XRD, (c) texture coefficient, (d) energy levels, (e) absorbance spectra and (f) band structure of the (Ce, Nd)-doped TiO₂ NPs

Fig. 2 presents representative scanning electron microscopy (SEM) images of Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles, where polyvinyl alcohol (PVA) was employed as a capping and stabilizing agent to regulate particle morphology and prevent agglomeration during synthesis.

SEM observations (Fig. 2a) revealed that all samples exhibited well-defined nanoscale sheet-like morphologies with porous surface features. The incorporation of Ce³⁺ and Nd³⁺ influenced the microstructural characteristics of TiO₂ by modifying grain growth behavior and promoting structural heterogeneity. The observed porous architecture and layered morphology are expected to contribute to the enhanced surface area and surface reactivity of the doped samples, which may subsequently influence their optical and biological performance (Fig. 2b). These findings indicate that lanthanide incorporation alters the microstructure of TiO₂ without significantly changing the overall morphology of the nanoparticles.

Fig. 2c presents pore characteristics and specific surface area of T, TC, TCN, and TN samples of pure and Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles determined via the BET method, where SBET was 15.82, 42.65, 58.74, and

55.38 m²/g, and corresponding pore sizes were 24.36, 36.82, 41.27, and 38.94 Å, respectively. The BET results demonstrate an increase in specific surface area and pore size following lanthanide incorporation, indicating modifications in the microstructural characteristics of the synthesized nanoparticles. The observed trend suggests that dopant incorporation influences pore development during synthesis, contributing to the enhanced surface characteristics of the doped samples. All samples exhibited mesoporous behavior with type IV nitrogen adsorption-desorption isotherms and H3 hysteresis loops. Figure 2d shows hydrodynamic diameters of 680, 1700, 1100, and 900 nm for TC, T, TN, and TCN, which are larger than crystallite sizes from XRD/SEM, indicating particle aggregation in liquid media. Zeta potential measurements (Fig. 2e) revealed values of -34.7, -10.4, -8.6, and -16.1 mV, respectively, suggesting that Ce³⁺ and Nd³⁺ incorporation modifies surface charge distribution and electrostatic interactions by altering lattice composition and ion adsorption behavior. The zeta potential results indicate that Ce³⁺ and Nd³⁺ incorporation modifies the surface charge characteristics of TiO₂ nanoparticles. Variations in zeta potential suggest changes in surface chemistry and electrostatic interactions following dopant incorporation. However, conclusions regarding colloidal stability and

aggregation behavior should be interpreted cautiously, as statistical analysis and repeated measurements are required for definitive assessment. Nevertheless, the observed trends indicate that lanthanide doping influences the surface properties and dispersion behavior

of the nanoparticles. Earlier studies have shown that Ce^{3+} doping increased the surface area and mesoporosity (type IV isotherm with H3 hysteresis) due to enhanced pore formation during synthesis (Narayanan *et al.* 2024).

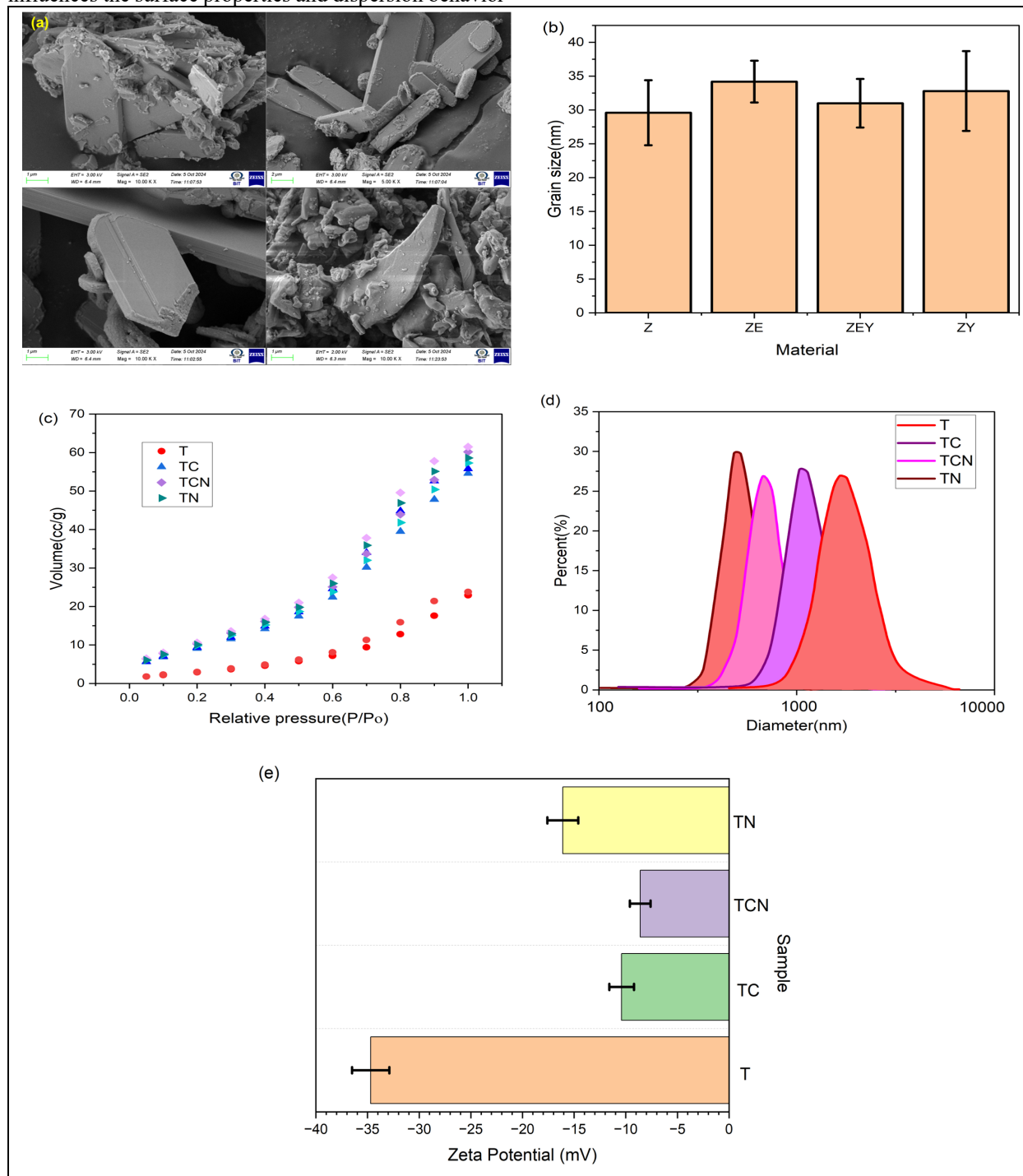


Fig. 2: (a) Low and high SEM morphologies, (b) grain size distribution and (c) N_2 adsorption-desorption isotherms (d) DLS size analysis and (e) zeta potential comparison

The chemical states and surface composition of pure and $\text{Ce}^{3+}/\text{Nd}^{3+}$ -doped TiO_2 nanoparticles were examined by X-ray photoelectron spectroscopy (XPS) as

illustrated in Fig. 3, with spectra fitted simultaneously to ensure accurate interpretation. The $\text{Ti}2p$ spectrum (Fig. 3a) displayed a characteristic spin-orbit splitting of 464.3

eV, where the primary doublet peak with associated satellite features corresponded to Ti species within the TiO₂ lattice, and additional peaks in the higher binding energy range were attributed to plasmon-related contributions. The O 1s region (Fig. 3b) was resolved into two components associated with lattice oxygen and oxygen vacancy defects, indicating structural imperfections induced by dopant incorporation. The Ce_{3d} and Nd_{3d} spectra (Fig. 3c, d) were analyzed over a broad binding energy range using appropriate background correction and peak fitting, confirming the presence of Ce³⁺ and Nd³⁺ oxidation states through characteristic multiplet splitting features arising from partially filled 4f orbitals. The relative elemental composition summarized in Table 2, revealed that the Ti/O ratio was close to stoichiometric in pure TiO₂ but decreased upon Ce³⁺ and Nd³⁺ incorporation, indicating the generation of lattice distortions and oxygen vacancies, which significantly influence the surface chemistry and functional properties of the nanoparticles. Previous studies suggest that X-ray photoelectron spectroscopy confirmed the successful incorporation of Ni²⁺ ions into the TiO₂ lattice without forming secondary phases. The spectra revealed

characteristic Ti, O, and Ni binding states, indicating strong interaction and stable chemical composition of the doped nanoparticles (Vindhya *et al.* 2025).

Table 2 presents the elemental composition of Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles, determined by high-resolution X-ray photoelectron spectroscopy, providing atomic percentages of Ti, O, Ce, and Nd present on the nanoparticle surface.

Table 2. Composition of modified titanium oxide nanoparticles

Sample	Ti(at%)	O(at%)	Ti / O	Ce(at%)	Nd(at%)
T	31.2	68.8	0.45	-	-
TC	29.2	66.8	0.44	3.7	-
TCN	28.2	64.9	0.43	2.1	4.8
TN	27.9	63.4	0.44	-	8.6

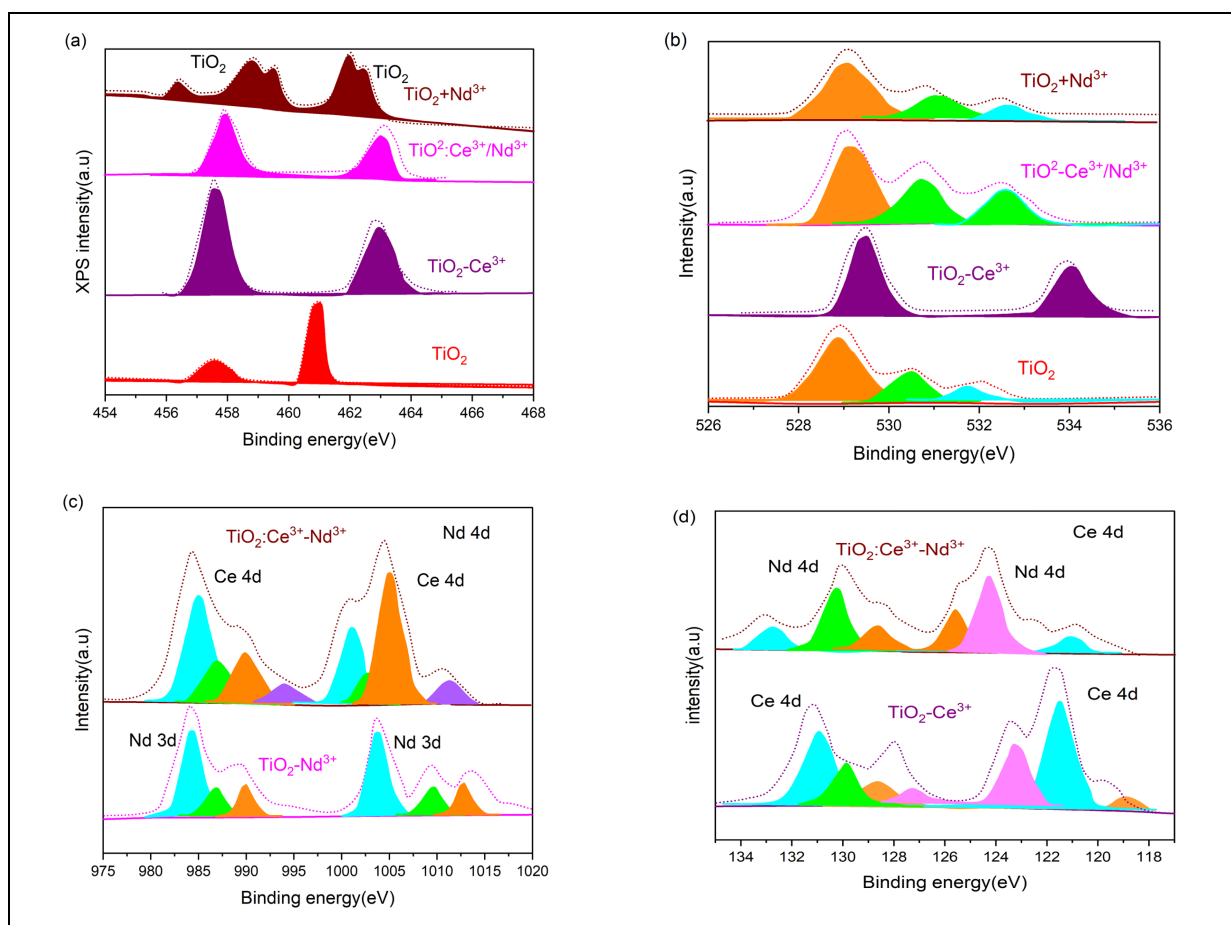
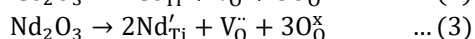
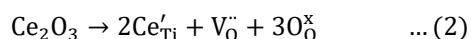


Fig. 3: HR-XPS core-level spectra of (a) Ti 2p, (b) O 1s, (c) Nd 4d and (d) Ce 4d in Ce/Nd-doped TiO₂ nanoparticles

The valence states of dopant ions within the Titanium oxide (TiO₂) lattice play a crucial role in governing their electronic, optical, and structural behavior. Incorporation of Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles, typically existing in a +3-oxidation state, introduces new electronic interactions that alter the band structure and enhance n-type conductivity of TiO₂. Nd³⁺ functions as an isovalent substituent, influencing electronic transitions and defect interactions within the lattice, while facilitating energy transfer processes between Ce³⁺ ions. These modifications support applications in optoelectronic devices, sensing systems, and energy conversion technologies. The inclusion of Ce³⁺ and Nd³⁺ also induces lattice distortion, leading to structural imperfections such as oxygen and titanium vacancies, as confirmed by XRD analysis. To maintain charge balance due to the introduction of higher valence ions, the TiO₂ matrix compensates through the formation of oxygen vacancies, which play a significant role in tuning electrical and optical properties. The absence of secondary phases indicates successful substitution of Ti sites by Ce³⁺ and Nd³⁺ ions, further contributing to defect generation and modified lattice characteristics:



Defect formation induced by Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles significantly influences its optoelectronic and structural behavior by modifying electronic band structure and generating localized energy states that facilitate diverse electronic transitions. Such defect-engineered metal oxide systems are highly advantageous due to their broad functional applications. Antibacterial performance of TiO₂ under dark conditions was primarily governed by defect states rather than bandgap energy (Govindasamy *et al.* 2024). Additionally, the integration of Ce³⁺ and Nd³⁺ within TiO₂ has been extensively associated with improved performance in photovoltaic and energy-related applications.

3.2 Cytotoxic Activity

The cytotoxic behavior of Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles was evaluated using cell models representing major cancer types, including colorectal adenocarcinoma, glioma, and hepatocellular carcinoma, along with a macrophage-origin cell line for comparative analysis of biological response. The experimental assessment was carried out using RAW 264.7, HEPG-2, U87 cells, and CACO-2 lines to determine the variation in cytotoxic effects of the synthesized nanomaterials.

RAW264.7, a murine macrophage cell line, was employed to evaluate the cytotoxic response of the synthesized nanoparticles and to assess their interaction with immune-related cells, as shown in Fig. 4b. As shown in Fig. 4a, exposure to pure TiO₂ nanoparticles at 10, 25,

and 50 µg/mL as 2.5%, 5.8%, and 12.4% cell death, which further increased to 18.6% and 28.9% at 100 and 250 µg/mL. For Cerium (Ce³⁺) modified TiO₂, treatments at 25, 50, and 100 µg/mL yielded 7.6%, 15.8%, and 24.3% cytotoxicity, while 250 µg/mL produced 35.7% cell death. The co-doped Ce³⁺/Nd³⁺ system exhibited 20.6% cell mortality at 50 µg/mL, increasing to 30.5% and 42.8% at 100 and 250 µg/mL, respectively. Likewise, Nd³⁺ doped TiO₂ showed 18.2% and 28.1% cell death at 50 and 100 µg/mL, reaching 40.12% at 250 µg/mL, indicating a strong concentration-dependent cytotoxic effect across all modified TiO₂ systems.

HEPG-2 serves as a standard *in vitro* model to evaluate the therapeutic response of nanomaterials in hepatocellular carcinoma. As shown in Fig. 4b, all samples exhibited a concentration-dependent cytotoxic response across the investigated cell lines. Cell viability decreased progressively with increasing nanoparticle concentration, indicating enhanced biological activity at higher dosages. Among the investigated compositions, dopant incorporation significantly influenced the cytotoxic behavior, with distinct responses observed between the undoped, single-doped, and co-doped TiO₂ systems. The differences in cellular response can be attributed to dopant-induced modifications in the physicochemical properties of the nanoparticles, which affect their interaction with biological systems. In comparison, Ce³⁺ modified TiO₂ exhibited minimal effects at 25 and 50 µg/mL (15.62% and 32.18%), but significantly increased cell death to 55.73% and 75.41 % at 100 and 250 µg/mL. The co-doped Ce³⁺/Nd³⁺ TiO₂ system showed lower cytotoxicity at 10, 25, and 50 µg/mL (2.31%, 10.45%, and 26.52%), followed by a sharp rise to 68.22% and 78.64% at higher concentrations. Similarly, Nd³⁺ doped TiO₂ demonstrated 13.87%, 30.64%, and 52.16% cell death at 25, 50, and 100 µg/mL, with a maximum of 72.64% observed at 250 µg/mL, indicating concentration-dependent biological activity influenced by dopant incorporation.

The cytotoxic response of pure and Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles was further evaluated using the U87 glioma cell model, as illustrated in Fig. 4c. Exposure to undoped TiO₂ at 10, 25, and 50 µg/mL as 10.2%, 30.4%, and 55.8% cell death, increasing to 70.6% and 85.3% at 100 and 250 µg/mL. In comparison, Ce³⁺ modified TiO₂ showed lower toxicity at 10 and 20 µg/mL (12.5% and 35.6%), while higher concentrations of 50, 100, and 250 µg/mL produced 60.7%, 75.4%, and 88.6% cell death. The co-doped Ce³⁺/Nd³⁺ system exhibited 15.3%, 40.8%, and 65.2% cytotoxicity at 10, 25, and 50 µg/mL, rising to 80.6 % and 90.2% at higher doses. Similarly, Nd³⁺ doped TiO₂ induced 13.6%, 38.5%, and 62.4% cell death at 10, 25, and 50 µg/mL, and 78.2% and 89.5% at 100 and 250 µg/mL.

The CACO-2 representing colorectal adenocarcinoma with enterocyte-like characteristics, was

used to evaluate the cytotoxic response of pure and $\text{Ce}^{3+}/\text{Nd}^{3+}$ -doped TiO_2 nanoparticles, as shown in Fig. 4d. Exposure to undoped TiO_2 at 10, 25, and 50 $\mu\text{g/mL}$ as 2.6%, 8.4%, and 25.7% cell death, which increased to 43.5% and 68.5% at 100 and 250 $\mu\text{g/mL}$. In contrast, Ce^{3+} modified TiO_2 exhibited lower cytotoxicity at 10, 25, and 50 $\mu\text{g/mL}$ (3.1%, 10.2%, and 28.6%), with moderate increases to 50.4% and 72.1% at higher concentrations. The co-doped $\text{Ce}^{3+}/\text{Nd}^{3+}$ system showed 12.5%, 32.6%, and 55.6% cell death at 25, 50, and 100 $\mu\text{g/mL}$, reaching 75.3 at 250 $\mu\text{g/mL}$. Among all samples, Nd^{3+} doped TiO_2 demonstrated the lowest cytotoxic activity with values of

3.5%, 11.3%, and 30.14% at 10, 25, and 50 $\mu\text{g/mL}$, and 52.2% and 73.6% at 100 and 250 $\mu\text{g/mL}$, indicating reduced biological impact compared to other compositions. In previous investigations reported the biofunctionalized TiO_2 and Ag- TiO_2 nanoparticles synthesized using *Aegle marmelos* seed extract showed enhanced anticancer, antioxidant, and anti-inflammatory activities. Ag doping significantly improved cytotoxicity and biological performance, indicating strong potential for biomedical and therapeutic applications (Tabassum *et al.* 2025).

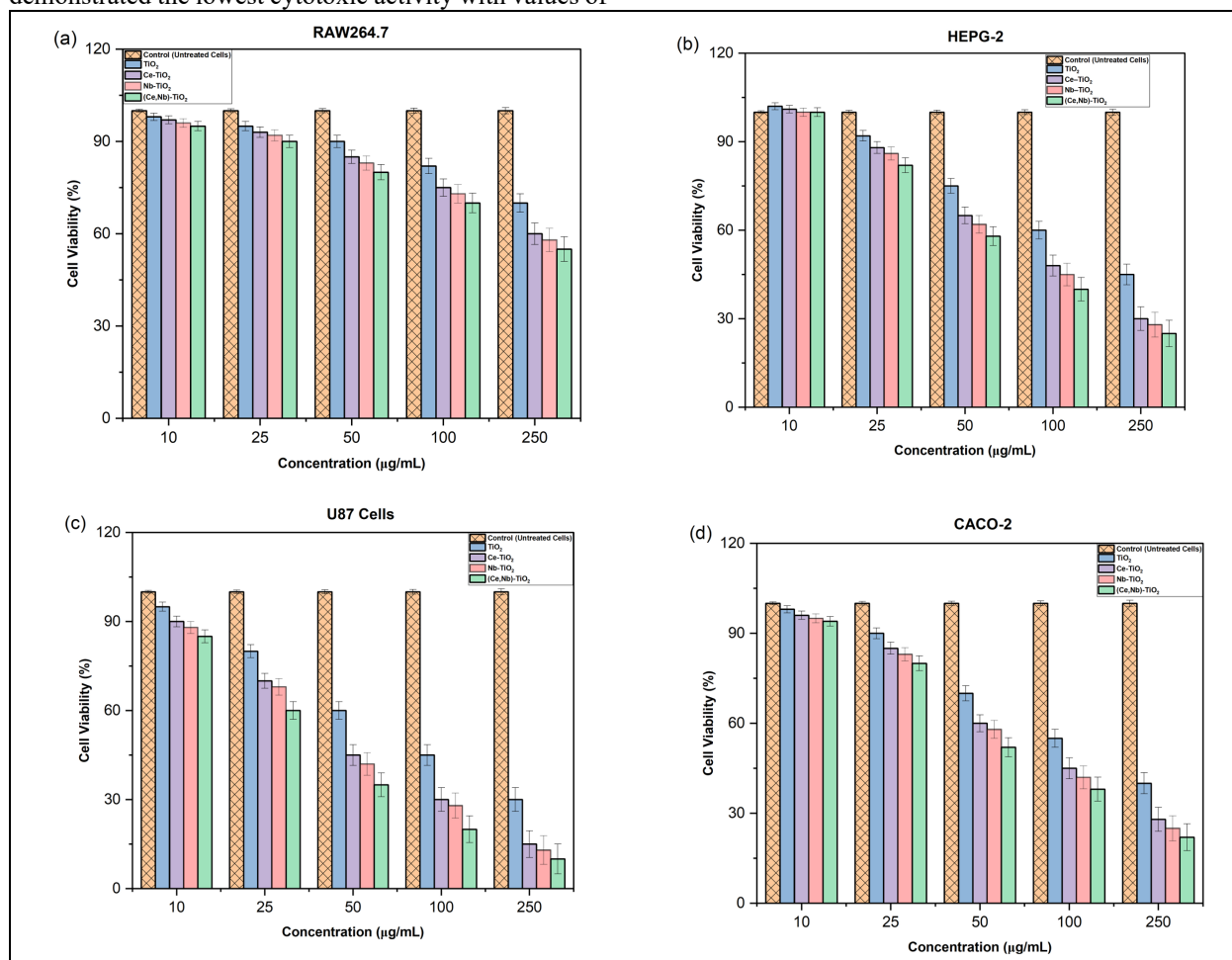


Fig. 4: Cytotoxicity of (Ce,Nd)-doped TiO_2 NPs on (a) RAW264.7 (b) HEPG-2, (c) U87 cells and (d) CACO-2

The IC_{50} values for all samples were determined by correlating concentration with cell viability (Table 3), indicating moderate cytotoxic behavior against CACO-2, U87, and HEPG-2 cell lines, while for RAW 264.7 cells, $\text{Ce}^{3+}/\text{Nd}^{3+}$ modified samples showed moderate activity

and undoped TiO_2 exhibited comparatively higher toxicity. The underlying mechanism of reduced cell viability induced by these nanoparticles is schematically represented in Fig. 5.

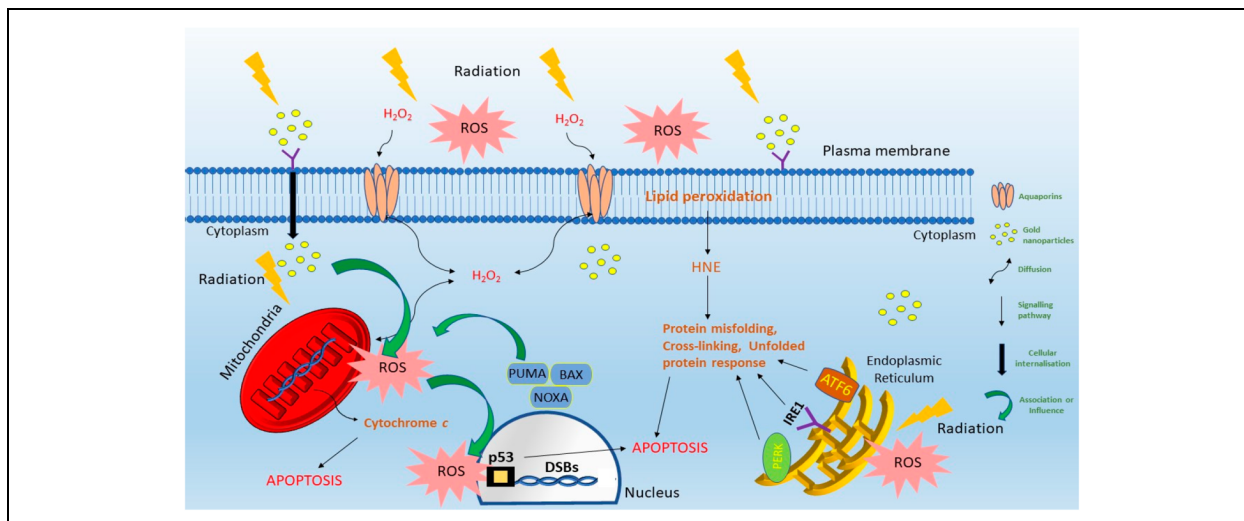


Fig. 5: Anticancer mechanisms of Ce/Nd- TiO₂ NPs

Table 3. IC₅₀ values across tested cell lines

Material	RAW 264.7	HEPG-2	U87	CACO-2
T	>250 μg/mL	86.22	52.11	101.11
TC	>250 μg/mL	112.11	81.11	191.11
TCN	>250 μg/mL	115.22	72.11	161.11
TN	>250 μg/mL	132.22	42.11	261.11

Recent investigations indicate TiO₂ nanoparticles can trigger cell death in cancer models through multiple pathways, and this behavior is influenced by Ce³⁺ and Nd³⁺ incorporation (Priyanka *et al.* 2022). For example, TiO₂ nanoparticles synthesized using plant-derived extracts have showed concentration-dependent reduction at HEPG-2 cell viability (20–100 μg/mL) by enhancing reactive oxygen and nitrogen species generation. Likewise, TiO₂ nanoparticles produced via combustion-based synthesis methods have shown the ability to reduce the viability of human glioma cells within 3.12–200 μg/mL, where the observed biological response is partly attributed to reduced particle size and morphological characteristics of the nanostructures.

In contrast, lanthanide-modified systems such as Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles have been shown to influence cancer cell viability through mechanisms including cell cycle arrest, activation of apoptotic pathways, DNA disruption, and enhanced intracellular reactive oxygen species generation. Ce³⁺/Nd³⁺ doped TiO₂ nanostructures have also demonstrated the ability to induce chromatin condensation and fragmentation in

colon cancer cells, indicating apoptosis-driven cytotoxicity. However, such effects may vary depending on the target cell type, as some normal cell models exhibit limited morphological or genetic alterations despite reduced viability after prolonged exposure. These differences in biological response are primarily associated with variations in synthesis methods, particle morphology, size distribution, crystal structure, and dopant concentration within the TiO₂ nanomaterials.

3.3 Antioxidant Activity

The antioxidant activity of the synthesized nanoparticles was evaluated using DPPH, ABTS, and H₂O₂ scavenging assays. These methods were employed to assess the free-radical scavenging capability of the samples, with ascorbic acid used as the reference standard. The obtained results provide insight into the influence of Ce³⁺ and Nd³⁺ incorporation on the antioxidant behavior of TiO₂ nanoparticles. According to prior studies demonstrated that, the green-synthesized Ce³⁺ using *Origanum majorana* extract exhibited spherical morphology with strong antioxidant and selective cytotoxic activity against cancer cells. Enhanced expression of CAT and SOD genes indicates their potential role in redox regulation and anticancer therapy (Aseyd *et al.* 2020).

3.4 DPPH Assay

The DPPH assay based on a stable violet radical with strong hydrogen-accepting ability is commonly applied to assess antioxidant efficiency due to its sensitivity and simple procedure. As illustrated in Fig. 6a, pure TiO₂ nanoparticles exhibited radical scavenging efficiencies of 50.8%, 54.6%, and 58.3% at 10, 25, and 50 μg/mL, increasing to 60.2% at 100 μg/mL. In comparison, Ce³⁺ doped TiO₂ showed 49.2% and 52.7% inhibition at 10 and 20 μg/mL, while 50 and 100 μg/mL

as 56.4% and 58.6% scavenging. The co-doped $\text{Ce}^{3+}/\text{Nd}^{3+}$ TiO_2 system demonstrated improved activity with 54.1%, 58.6%, and 64.7% inhibition at 10, 25, and 50 $\mu\text{g/mL}$, maintaining 70.5% at 100 $\mu\text{g/mL}$. Similarly, Neodymium (Nd^{3+}) doped TiO_2 achieved 55.3 % and 59.8% scavenging at lower concentrations, which increased to 69.2% and 72.4% at 50 and 100 $\mu\text{g/mL}$, indicating concentration-dependent antioxidant performance influenced by dopant incorporation.

The results confirm that TiO_2 nanoparticles modified with Ce^{3+} and Nd^{3+} effectively neutralize DPPH radicals over a range of concentrations. Comparable studies on lanthanide-based oxides have reported moderate radical scavenging efficiencies across varying dosage ranges, indicating the influence of synthesis route and material characteristics.

3.5 ABTS Analysis

The ABTS method, a colorimetric approach based on the reduction of ABTS radical from deep blue-green to a lighter shade in the presence of antioxidants, was employed to evaluate the radical scavenging efficiency of pure and $\text{Ce}^{3+}/\text{Nd}^{3+}$ -doped TiO_2 nanoparticles due to its sensitivity and reliability. As shown in Fig. 6b, undoped TiO_2 exhibited inhibition efficiencies of 45.8%, 51.4%, and 56.7% at 5, 10, and 50 $\mu\text{g/mL}$, increasing slightly to 62.5% and 69.3% at 100 and 250 $\mu\text{g/mL}$. In comparison, Ce^{3+} modified TiO_2 showed 51.4% and 56.7% scavenging at lower concentrations, rising to 56.7%, 62.5%, and 69.3% at higher dosages. The co-doped $\text{Ce}^{3+}/\text{Nd}^{3+}$ system demonstrated 48.6%, 54.2%, and 60.8% inhibition at 10, 25, and 50 $\mu\text{g/mL}$, with 66.9% and 73.6% at elevated concentrations. Similarly, Nd^{3+} doped TiO_2 achieved 50.2% and 56.3% inhibition at 10 and 25 $\mu\text{g/mL}$, increasing to 62.4%, 69.8%, and 77.2% at 50, 100, and 250 $\mu\text{g/mL}$, indicating consistent antioxidant activity influenced by dopant incorporation.

Studies on the ABTS radical scavenging behavior of $\text{Ce}^{3+}/\text{Nd}^{3+}$ -doped TiO_2 nanoparticles remain limited; however, their antioxidant performance can be attributed to the intrinsic characteristics of lanthanide-based systems, including shielded 4f electrons, dopant concentration, and modified lattice configuration. The observed ability of $\text{Ce}^{3+}/\text{Nd}^{3+}$ modified TiO_2 to neutralize ABTS radicals is primarily associated with enhanced electron or hydrogen donation capacity, which facilitates effective reduction of radical species and improves overall antioxidant efficiency.

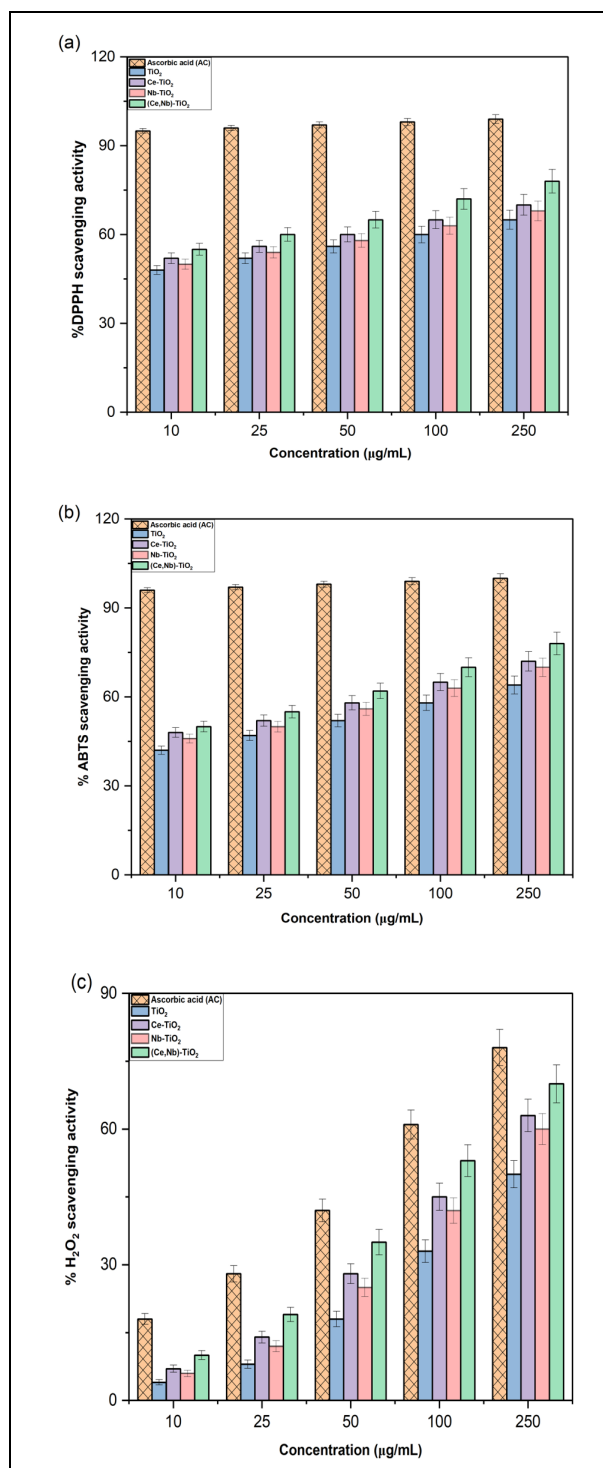


Fig. 6: (a) DPPH radical scavenging activity, (b) ABTS radical scavenging activity and (c) Hydrogen peroxide scavenging activity

3.6 H₂O₂ Assay

In contrast to DPPH and ABTS, H₂O₂ is a strong oxidizing species that can be quantified using spectrophotometric, fluorometric, or electrochemical methods and plays a dual role in cellular regulation and oxidative stress. As shown in Fig. 6c, pure TiO₂ nanoparticles exhibited low scavenging at 10 and 25 µg/mL (5.2% and 12.6%), increasing to 28.4%, 38.7%, and 50.3% at 50, 100, and 250 µg/mL. Ce³⁺-doped TiO₂ showed 6.8%, 14.9%, and 30.6% inhibition at 10, 25, and 50 µg/mL, rising to 44.2% and 63.5% at higher concentrations. The co-doped Ce³⁺/Nd³⁺ system demonstrated 10.4%, 18.7%, and 35.2% scavenging at lower doses, followed by 52.8% and 70.6% at 100 and 250 µg/mL. Nd³⁺-doped TiO₂ exhibited the highest activity, achieving 9.1%, 16.8%, and 33.7% at 10, 25, and 50 µg/mL, and 50.6% and 72.8% at elevated concentrations. The enhanced antioxidant behavior is attributed to increased reactive sites and surface area that facilitate interaction with H₂O₂, while lanthanide incorporation may also promote enzymatic-like pathways aiding decomposition into oxygen and water, reducing oxidative stress.

3.7 Machine Learning Modeling

The predictive performance of developed machine learning models was systematically evaluated by MAE, RMSE, and R² metrics. Among the models, Gradient Boosting (GB) demonstrated superior performance with the lowest error values (MAE = 8.5598, RMSE = 11.436) and highest coefficient of determination (R² = 0.8728), indicating its strong capability at capturing the nonlinear relationships among nanoparticle properties and cytotoxic response. In contrast, K-Nearest Neighbors (KNN) exhibited the lowest predictive accuracy (MAE = 27.2886, RMSE = 30.9444, R² = 0.0688), reflecting its inability to generalize effectively for the given dataset. The Decision Tree (DT) and Random Forest (RF) models showed moderate predictive capability with comparable RMSE values of 17.9003 and 18.2689, respectively, and R² values around 0.67–0.69, suggesting acceptable but less optimal performance compared to GB. Meanwhile, Support Vector Regression (SVR) resulted in relatively high prediction error (RMSE = 26.9433, R² = 0.2941), indicating limited suitability for modeling the complex behavior of the system. Recent studies have demonstrated the growing potential of machine learning techniques in nanotoxicology for predicting nanoparticle-induced biological responses and improving nanosafety assessment. Machine learning models have been shown to effectively establish relationships between physicochemical descriptors and biological outcomes, enabling reliable toxicity prediction and risk evaluation (Khokhlov *et al.* 2024). Furthermore, artificial intelligence-assisted approaches have been reported to enhance the interpretation of complex in vitro

nanotoxicology datasets and support the development of predictive frameworks for nanomaterial safety assessment (Campagnolo *et al.* 2024). The findings of the present study further support the applicability of machine learning-assisted approaches for predicting the cytotoxic behavior of Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles.

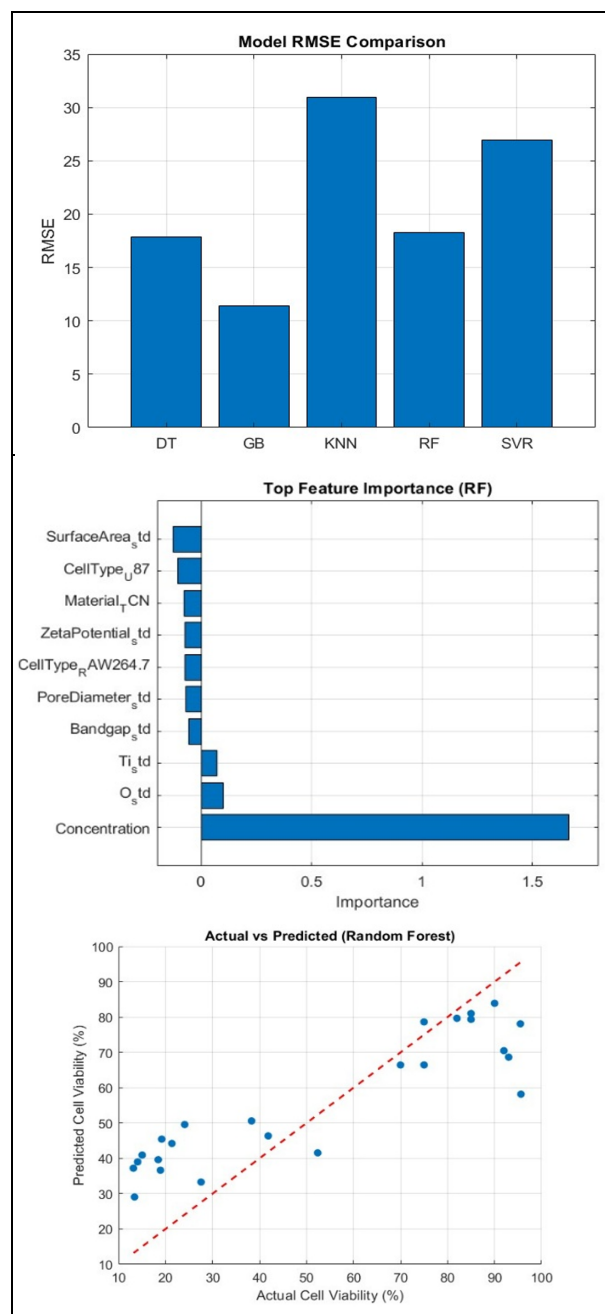


Fig 7: RMSE-based comparison of machine learning models for cytotoxicity prediction

Although Gradient Boosting achieved the highest predictive accuracy, Random Forest was additionally utilized for feature importance analysis because of its inherent capability to provide reliable and interpretable estimates of variable importance. The permutation-based feature importance plot reveals that

nanoparticle concentration is the most influential parameter, exhibiting a significantly higher importance score than all other features, thereby confirming its dominant role in governing cytotoxic behavior. Secondary contributions were observed from oxygen content, titanium content, bandgap energy, and structural parameters such as pore diameter and zeta potential, while variables such as surface area and certain categorical features showed minimal influence, indicating their relatively lower contribution to the predictive model. Machine learning-assisted analysis integrated with molecular dynamics and free energy calculations enabled accurate prediction of ligand–receptor binding behavior in FA-functionalized TiO₂ nanodevices as reported in previous studies (Donadoni *et al.* 2023).

The actual versus predicted analysis using the Random Forest model demonstrates a reasonable agreement between experimental and predicted values with most data points distributed around the 45° reference line, particularly within the moderate cell viability range (30–70%). However, deviations are observed at higher viability levels (>80%), where the model tends to underpredict, suggesting the presence of complex nonlinear interactions and possible limitations in high-value data representation. Overall, the outcome shows that ensemble-based models, particularly Gradient Boosting and Random Forest, are more effective in capturing the intricate relationship between physicochemical properties and biological response, while also confirming that concentration is the primary governing factor influencing cytotoxicity, with material properties acting as secondary modifiers.

4. CONCLUSION

Ce³⁺/Nd³⁺-doped TiO₂ nanoparticles were successfully synthesized and comprehensively characterized using advanced spectroscopic and microscopic techniques. Structural analysis revealed that rare-earth incorporation reduced crystallinity, modified lattice structure, and slightly tuned the optical bandgap (2.2–3.2 eV), thereby influencing the biological response. The cytotoxic response was strongly dependent on both nanoparticle composition and cell type. Variations in cytotoxic activity were observed among the undoped, single-doped, and co-doped TiO₂ nanoparticles, indicating that Ce³⁺ and Nd³⁺ incorporation significantly influenced the biological behavior of the materials. Additionally, Ce³⁺/Nd³⁺ incorporation enhanced antioxidant activity against DPPH, ABTS, and H₂O₂ radicals, demonstrating potential for oxidative stress-related biomedical applications.

Machine learning analysis supported the experimental findings by identifying Gradient Boosting as the most reliable predictive model ($R^2 = 0.8728$), while also confirming that nanoparticle concentration is the

primary factor governing cytotoxic behavior, with other physicochemical properties contributing as secondary modifiers. Ensemble-based approaches, particularly Gradient Boosting and Random Forest, demonstrated reliable predictive performance, with Gradient Boosting providing the highest prediction accuracy and Random Forest offering complementary interpretability through feature importance analysis.

Overall, this study establishes that controlled bandgap tuning and concentration optimization are key parameters in modulating the cytotoxic and antioxidant performance of doped TiO₂ nanomaterials. The integration of experimental investigation with data-driven modeling provides a reliable pathway for designing advanced, tunable nanomaterials for targeted nanobiotechnological and biomedical applications.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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