



Optimization of Green-synthesized Graphene Quantum Dots using Machine Learning for Neuroprotective Antioxidant Applications

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Received: 17.03.2026 Accepted: 16.04.2026 Published: 30.06.2026

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ABSTRACT

Oxidative stress caused by reactive oxygen species (ROS) plays a major role in neurodegenerative disorders. However, many engineered nanoparticles exhibit unpredictable cytotoxicity, which limits their sustainable biomedical applications. To address this challenge, a novel machine learning-guided nano-Quantitative Structure–Activity Relationship framework (nano-QSAR) was developed to identify low-cytotoxic nanomaterials prior to experimental synthesis, thereby reducing the experimental trials and improving sustainable nanomaterial design. A curated dataset of 443 nanoparticles was analyzed using multiple regression algorithms, where tuned XGBoost showed the best predictive performance ($R^2 = 0.78$, Root Mean Square Error (RMSE) = 6.82, Mean Absolute Error (MAE) = 4.95). Based on these predictions, graphene-based nanomaterials were selected for experimental validation. Subsequently, graphene quantum dots derived from Terminalia arjuna bark (GQD-TA) were synthesized through an eco-friendly hydrothermal method and optimized using central composite design, while ANOVA confirmed the statistical significance of the model ($F = 2.55$, $p = 0.0380$). The optimized nanoparticles exhibited an average hydrodynamic size of ~11 nm and were mainly composed of carbon (67.85 wt%), nitrogen (15.24 wt%), and oxygen (11.03 wt%). Antioxidant evaluation demonstrated concentration-dependent DPPH scavenging activity of 94–95% at ~150 $\mu\text{g/mL}$. Furthermore, MTT assay using SH-SY5Y neuronal cells confirmed high cytocompatibility, maintaining 88.5% cell viability even at 500 $\mu\text{g/mL}$. The developed graphene quantum dots can be utilized in neuroprotective therapies, targeted drug delivery, bioimaging, and neuronal tissue engineering applications. Their high biocompatibility and low cytotoxicity make them promising candidates for sustainable nanomedicine applications.

Keywords: Nanomedicine; XGBoost; Machine learning.

1. INTRODUCTION

Oxidative stress (OS) induced by Reactive Oxygen Species (ROS) is pivotal in health and illness. Water-soluble Graphene quantum dots (GQDs) were synthesized by microwave-assisted green synthesis with *Mangifera indica* leaf extract, producing particles <15 nm confirmed by HR-TEM. The GQDs exhibited bright red fluorescence (Kokulavani *et al.* 2025), excitation-independent emission at 662 nm, and quantum yield of 10.3%, with graphitic (002) plane diffraction at 27.2° and sp^2 crystallinity (JO/IG = 1.12). They showed good biocompatibility, antioxidant activity, and biosensing capability for Ni^{2+} and Fe^{3+} in environmental applications. This research reports first synthesis of GQDs at agricultural waste including Medicago sativa (MS) and groundnut oil cake (GOC) via hydrothermal methods. The monodispersed, hydrophilic GQDs and

ultra-small (~4.17 nm), showed excitation-independent photoluminescence, anti-inflammatory ($\text{IC}_{50} = 20.135 \mu\text{g/mL}$) and antioxidant ($\text{IC}_{50} = 25.51 \mu\text{g/mL}$) activities, notable biocompatibility, highlighting their potential for drug delivery, bioimaging and nanotherapeutics (Godwin *et al.* 2025). Cadmium sulfide quantum dots (CdS QDs) were green-synthesized using cardamom (CdS-Cm QDs) and ginger (CdS-Gi QDs) extracts via a simple one-pot method at room temperature ($25 \pm 2^\circ\text{C}$). The QDs were 2–5 nm in size, amorphous and displayed notable antioxidant, antibacterial and anticancer activities with IC_{50} values comparable to cisplatin in MCF-7 cells (Jarhad *et al.* 2025).

Carbon quantum dots were synthesized from transgenic hairy roots of Centella asiatica carrying At-SS1cDNA as sustainable precursor. The Carbon quantum

dots (CQDs) were 1.07 ± 0.2 nm, spherical, and displayed graphitic crystalline and amorphous regions with surface hydroxyl ($-\text{OH}$), carbonyl ($\text{C}=\text{O}$), carboxyl ($-\text{COOH}$), and amino ($-\text{NH}_2$) groups (Taheri *et al.* 2025). Graphene quantum dots (GQDs) were green-synthesized using *Withania somnifera* leaf extract via an eco-friendly method. The GQDs exhibited antioxidant and antidiabetic activities, with lower IC_{50} values for DPPH, α -glucosidase and α -amylase, compared to leaf extract. These results highlight the potential of *Withania*-derived GQDs as multifunctional nanomaterials for therapeutic applications (Kataria *et al.* 2025). Microwave-assisted green synthesis of GQDs was performed using *Azadirachta indica* (Neem) leaf extract. Characterization confirmed that the synthesized GQDs were stable and photoluminescent and exhibited enhanced antioxidant and antibacterial activities compared with the corresponding leaf extract (Kadyan *et al.* 2025). GQDs were green-synthesized using *Mangifera indica* leaves and comprehensively characterized using standard analytical techniques. The GQDs were spherical and exhibited superior antioxidant and antimicrobial activities compared to the ethanolic leaf extract. They effectively inhibited bacteria (*S. aureus*, *E. coli*, *B. subtilis*, *P. aeruginosa*) and fungi (*A. niger*, *A. flavus*) via reactive oxygen species (ROS)-mediated mechanisms (Kadyan *et al.* 2024). Green-synthesized graphene quantum dots (ssGQDs) were prepared using *Sarcopoterium spinosum* fruit powder extract and characterized. The ssGQDs showed significant electrochemical activity, enabling the detection of dopamine with a detection limit of $0.107 \mu\text{M}$. Additionally, they exhibited antibacterial and antioxidant properties, verified through DPPH and H_2O_2 scavenging assays (Turunc *et al.* 2023). Functionalization with urea (GQDs-U) enhanced singlet oxygen ($^1\text{O}_2$) production, while thiourea-functionalized GQDs (GQDs-TU) acted as $\cdot\text{OH}$ scavengers. GQDs-U showed low cytotoxicity ($<100 \mu\text{g/mL}$) and high photodynamic activity, making them promising agents for photodynamic therapy (Sathishkumar *et al.* 2026).

This study investigated the impact of *Terminalia arjuna* (Arjun) on oxidative stress in the renal system (Haque *et al.* 2025). The research evaluated *Terminalia arjuna* bark powder (TABP) as herbal feed additive at *Labeo rohita* over a 90-day period. Supplementation at 10 g/kg feed enhanced growth performance, nutrient utilization (PER, ANPU, FR, ER), and survival rate, while feed conversion ratio (FCR) decreased (Meena *et al.* 2022). Cadmium sulfide nanoparticles (CdS NPs) were green-synthesized using walnut shell extract and Na_2S and characterized by FTIR, SEM, and XRD. The nanoparticles showed dose-dependent antiproliferative effects against SH-SY5Y neuroblastoma cells, reducing viability up to 40.96% at $100 \mu\text{g/mL}$ and increasing oxidative activity, demonstrating potential for cancer therapy (Yeni *et al.* 2024).

A nanocomposite biopolymer film incorporating *Moringa oleifera* extract and *Terminalia arjuna* cellulose nanofibers has been developed for edible oil packaging, demonstrating notable antioxidant activity and mechanical strength (Rahman *et al.* 2024). Phytochemical investigations indicate that *Terminalia arjuna*, particularly its bark, is rich in phenolic compounds and exhibits antioxidant and anticholinesterase activities (Elwekeel *et al.* 2024). In addition, plant-based extracts containing *Terminalia arjuna* have shown significant antimicrobial and radical scavenging potential against clinically relevant pathogens (Krishnan *et al.* 2026). Furthermore, nanomaterials derived from *Terminalia arjuna*, such as selenium nanoparticles, have demonstrated promising antioxidant, antimicrobial, and cytotoxic properties, highlighting their potential in biomedical applications (Puri *et al.* 2023). However, despite extensive studies on green-synthesized quantum dots, there is a lack of integrated approaches that combine sustainable biomass precursors, systematic toxicity prediction, and data-driven optimization strategies for developing biocompatible nanomaterials, particularly for neuronal applications. Most existing studies rely on trial-and-error synthesis and limited toxicity evaluation, which restricts the scalability, reproducibility, and targeted biomedical applicability of such nanomaterials.

The present work establishes a predictive, machine learning-guided nano-QSAR framework integrated with central composite design for the rational development of green-synthesized graphene quantum dots derived from *Terminalia arjuna* bark. Unlike conventional green nanomaterial studies that rely predominantly on empirical optimization, this study utilizes a curated 443-nanoparticle cytotoxicity dataset to computationally screen and prioritize low-toxicity candidates prior to synthesis. The implementation of tuned XGBoost modeling for cytotoxicity prediction, followed by statistically optimized hydrothermal fabrication and neuronal cytocompatibility validation in SH-SY5Y cells, represents a data-driven strategy that minimizes experimental trial-and-error. This integrative computational-statistical-biological approach advances sustainable nanomaterial design and provides a reproducible framework for developing neurocompatible antioxidant nanomaterials for biomedical applications.

2. MATERIALS AND METHODOLOGY

The nano-QSAR screening approach was utilized to predict the viability of mammalian cells exposed to various nanoparticles using data collected from relevant literature sources (Sifonte *et al.* 2021; Qi *et al.* 2021). Fig. 1 presents schematic representation of nano-QSAR-informed computational and experimental methodology utilized in this investigation. Graphene-based nanoparticles were chosen for further examination

based on screening outcomes from biocompatibility and nano-QSAR assessments.

The synthesis of graphene quantum dots was optimized through a central composite design within the response surface methodology (RSM) framework to systematically optimize the critical reaction parameters. A synthesized nanoparticles was initially characterized by optical absorption via UV-vis spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), X-ray

Diffraction (XRD), and Scanning Electron Microscopy with Energy Dispersive X-ray Spectroscopy (SEM-EDS) to assess their chemical, morphological and structural attributes. Cytocompatibility and antioxidant capacity of produced Graphene Quantum Dots nanoparticles derived from *Terminalia arjuna* bark powder (TA) was assessed by MTT cell viability assay and the DPPH radical scavenging assay, on human neuroblastoma SH-SY5Y cell.

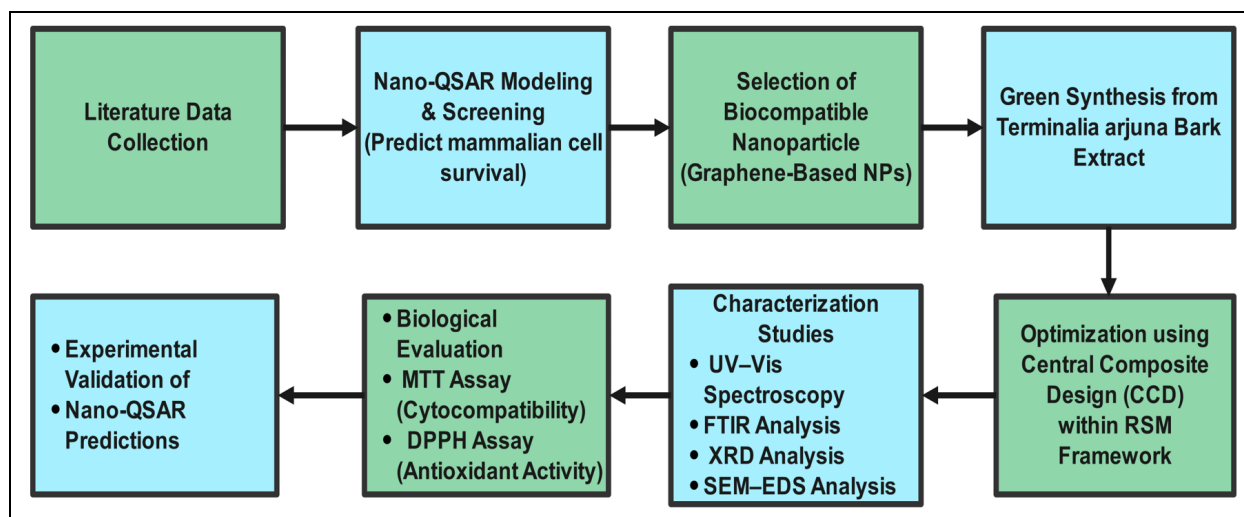


Fig. 1: Nano-QSAR-guided workflow for green g-C₃N₄ optimization and cytotoxicity evaluation

2.1 Materials

DPPH, MTT, and Dulbecco's phosphate-buffered saline were obtained from Bangalore. *Terminalia arjuna* powder was procured local market in Coimbatore, Tamil Nadu, India. Urea, L-ascorbic acid, and DMSO were procured from Matrics Enterprises, Nagercoil, Tamil Nadu, India. Dulbecco's modified eagle medium (DMEM), fetal bovine serum (FBS), SH-SY5Y cells and antibiotics, were sourced from HiMedia and National Centre for Cell Science (NCCS), India.

Nano-QSAR at silico screening were utilized to forecast viability of mammalian cells in response to nanoparticles. Nano-QSAR, an extension of traditional QSAR, links shape, size, charge, surface chemistry and surface area, with biological responses to find nanoparticles with minimum cytotoxicity through methodical model development (Cao *et al.* 2020).

2.2 Optimization Using Machine learning

2.2.1 Compilation and Standardization of Experimental Data

The curated dataset comprising 443nps were compiled and the physicochemical characteristics and mammalian cell viability of 24 hours or less was documented [supplementary file]. Extracted features encompassed size, shape, composition, charge,

hydrophobicity, surface modification, and aggregation; non-mammalian models and exposures exceeding 24 hours were removed, succeeded by data harmonization.

2.2.2 Data Standardization

To maintain cell viability, modeling consistency results from several assays was standardized. Categorical descriptors were transformed into numerical codes to facilitate quantitative analysis using machine learning. The shape of the nanoparticle was classified as follows: star, spherical, hexagonal, polyhedral, or others. Surface charge were categorized as positive, negative, neutral/negative, neutral, slightly negative, or others. Hydrophobicity were categorized as hydrophilic, moderately hydrophilic, and others. Aggregation propensity and cell lines were correspondingly numerically encoded to enhance predictive modeling. To improve model interpretability and predictive efficiency, feature selection was performed prior to model development. Initially, correlation analysis was conducted to identify redundant or highly collinear descriptors. Features with minimal variance or weak correlation with the target variable (cell viability) were excluded. Additionally, feature importance ranking using tree-based models (Random Forest/XGBoost) was employed to identify the most influential descriptors. Based on these criteria, key features such as particle size, surface charge, composition, and surface modification

were retained, as they demonstrated significant contributions toward model performance and biological relevance.

2.2.3 Handling Missing Data

Records with absent values were removed by statistical filtering to maintain data quality and reliability. The completed dataset consisted of 367 entries with nine variables, serving as the foundation for nano-QSAR modeling to identify critical nanoparticle characteristics providing mammalian cell viability. The removal of records with missing values was performed to ensure data integrity and avoid the introduction of noise from imputation methods, particularly given the heterogeneous nature of nanomaterial datasets. Although this approach may introduce a potential reduction in dataset size, the remaining dataset retained sufficient diversity and representation of nanoparticle characteristics. Furthermore, the removal process was carefully evaluated to ensure that no systematic bias toward specific nanoparticle classes or properties was introduced.

2.2.4 ML Algorithms and Model Development

Before modeling, dataset was partitioned into training and testing sets (80:20) with Scikit-learn in Python (v3.11.13). Gradient boosting, extreme gradient boosting, support vector regression, and random forest were implemented (Rajakannu *et al.* 2025). Hyperparameters were refined using GridSearchCV, and performance was evaluated by R^2 , RMSE, and Pearson correlation. The optimal model facilitated the selection of a low-cytotoxic nanoparticle for experimental synthesis from *Terminalia arjuna* with process optimization conducted by the central composite design. In addition to the 80:20 train-test split, a 5-fold cross-validation strategy was implemented on the training dataset to ensure robustness and generalizability of the models. The dataset was divided into five subsets, where each subset was used once as validation while the remaining served as training data. The average performance across folds was used to minimize overfitting and ensure model stability. The optimized XGBoost hyperparameters obtained through GridSearchCV were: $n_estimators = 300$, $learning_rate = 0.05$, $max_depth = 6$, $subsample = 0.8$, and $colsample_bytree = 0.8$. These parameters were selected based on optimal performance in cross-validation.

2.2.5 Empirical Verification of Predictive Models

To assess model performance, predicted nanomaterial were produced and experimentally tested. The findings obtained were compared with the projected values to evaluate model correctness and ascertain the dependability of the nano-QSAR-based predictions (Yuan *et al.* 2023).

2.3 Experimental Design

This investigation identified precursor quantities, duration (h) and reaction temperature ($^{\circ}\text{C}$) as independent variables affecting nanoparticle yield. Statistical analysis was conducted using JMP Pro 18.0.2, and experiments were structured according to the central composite design technique.

$$N = 2k(k - 1) + C_0 \quad \dots (1)$$

In this context, k signifies the quantity of independent variables, while C_0 indicates number of center points. Subsequent to selection of the experimental design, a second-order polynomial model was built to ascertain regression coefficients and forecast response behavior (Park *et al.* 2025):

$$Y = \beta_0 + \sum \beta_i X_i + \sum \beta_{ii} X_i^2 + \sum \beta_{ij} X_i X_j \dots (2)$$

In this context, X_i signifies independent variables (TA, urea, time, temperature); β_0 represents the intercept; β_i , β_{ii} , and β_{ij} imply linear, quadratic, and interaction effects, respectively. The statistical analysis assessed the model's appropriateness and significance.

The evaluation of model performance was conducted by ANOVA, with significance established at $p < 0.05$. The prediction strength and adequacy were further assessed by lack-of-fit testing, coefficient of determination (R^2), root mean square error (RMSE) and adjusted R^2 .

2.4 Green Synthesis of Graphene Quantum Dots Nanoparticles from the Extraction *Terminalia Arjuna* of Bioactive Compounds from Bark

Graphene quantum dots were synthesized by *Terminalia arjuna* (*T. arjuna*) bark fiber as a natural carbon precursor through a green hydrothermal method. Fresh bark fibers were first washed thoroughly with distilled water, dried, and ground into fine powder. About 2 g of the powdered bark was dispersed in 50 mL of DI water and sonicated for 30 minutes to obtain homogeneous suspension (Khichar *et al.* 2025). The mixture was then transferred into Teflon-lined autoclave and subjected to hydrothermal treatment at 170°C .

During the hydrothermal process, carbon-rich bio-compounds in the bark underwent thermal decomposition and carbonization, forming nanoscale graphene domains. The resulting dark brown solution containing GQDs were cooled and centrifuged at 10,000 rpm for 15 minutes to eliminate large carbon particles. The supernatant was further filtered by $0.22\ \mu\text{m}$ membrane to maintain clear GQD solution. Finally, the solution was dialyzed against deionized water for 24 hours to remove residual salts and small molecular impurities. The purified solution was oven-dried and

lyophilized for 1 day to produce dry GQD powder. The percentage yield of GQDs was determined by utilizing a conventional gravimetric formula (Kadyan *et al.* 2024)

$$\frac{\text{Yield of graphene quantum dot nanoparticles (g)}}{\text{Total precursor mass (g)}} \times 100 \dots (3)$$

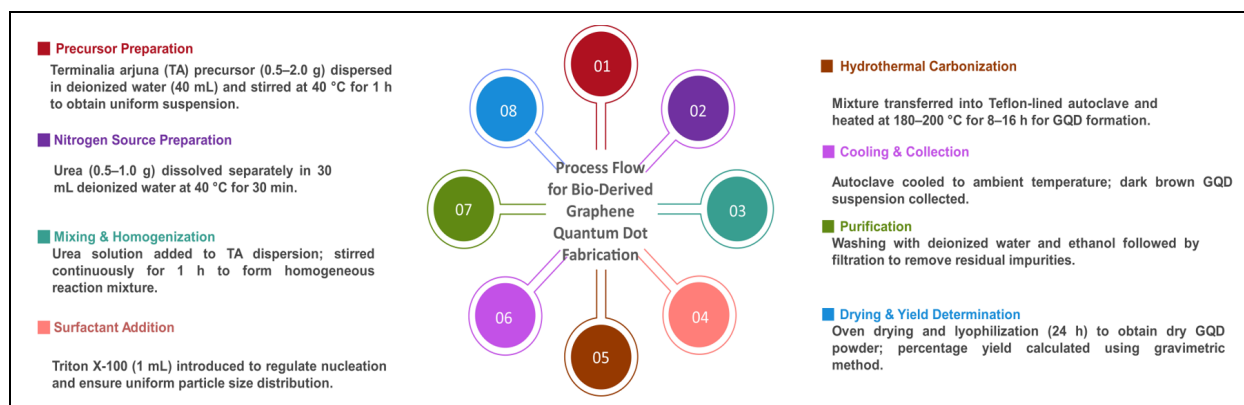


Fig. 2: Process flow for the fabrication of bio-derived graphene quantum dot fabrication

2.5 Characterization

The produced Graphene Quantum Dots from Terminalia arjuna (GQD-TA) was first evaluated for optical absorption properties by UV–Visible spectroscopy (Shimadzu UV-1900i) across a wavelength of 200–800 nm (Mohamed *et al.* 2024).

A thorough physicochemical evaluation of the produced Graphene Quantum Dots from Terminalia arjuna (GQD-TA) was conducted utilizing several analytical techniques. The surface charge and particle size distribution was assessed using by zeta potential dynamic light scattering analysis (Brookhaven ZetaPALS) following a 1:4 dilution of the sample in deionized water (Abdelmonem *et al.* 2024). The elemental composition and surface morphology was analyzed by SEM-EDS (Zeiss Gemini). Functional group analysis was performed using FTIR spectroscopy (Bruker Alpha, Germany) in the range of 4000–400 cm^{−1} with a DLATGS detector. The crystalline structure was assessed using X-ray diffraction (Rigaku SmartLab), with samples cast on glass slides and air-dried analysis (Nalci *et al.* 2020). The antioxidant ability of GQD-TA was evaluated by utilizing the DPPH radical scavenging test (Mamatha *et al.* 2024).

2.6 Evaluation of Antioxidant Capacity via DPPH Assay

A freshly made 0.2% DPPH at 80% methanol were distributed into microcentrifuge tubes, and GQD-TA samples were formulated. An equal volume of 200 µL of nanoparticle suspension were mixed by 200 µL of DPPH solution, resulting a total reaction volume of 400 µL. This mixture was incubated for 25 minutes at ambient temperature in the absence of light to avert the photodegradation. Suitable blanks were preserved for backdrop correction. L-ascorbic acid functioned as

reference standard, whilst 80% methanol was utilized as reagent blank, and DPPH alone served as the control. Absorbance was measured at 522 nm with microplate reader, and percentage radical scavenging activity was calculated by standard equation (4) (Xie *et al.* 2025).

$$\%RSA = [(A_{\text{control}} - A_{\text{sample}}) / A_{\text{control}}] \times 100 \dots (4)$$

Where, A means the control which denotes absorbance of control (DPPH solution devoid of sample), whereas A sample refers to absorbance of GQD-TA sample. This assay quantifies antioxidant capacity by measuring nanoparticles to neutralize DPPH free radicals. To enhance the assessment of cytocompatibility, neuronal SH-SY5Y cells were cultivated for the subsequent in vitro cytotoxicity evaluation of GQD-TA.

2.7 Neuronal Cell Culture

The SH-SY5Y human neuroblastoma cell line is widely utilized as an in vitro neuronal model in neuroscience, neurotoxicity, and neuroprotection studies because of its responsiveness to oxidative and morphological changes. This work aimed to investigate the nanomaterials with antioxidant and neurotherapeutic capabilities, utilizing SH-SY5Y cells as biologically pertinent platform for cytocompatibility evaluation. The cells were grown in Dulbecco's Modified Eagle Medium (DMEM) enriched with 10% fetal bovine serum and 1% antibiotic-antimycotic solution in a humidified environment with 5% CO₂ and 18–20% O₂ at 37 °C. The Luna automatic cell counter determined the cell density to be 5.22 × 10⁶ cells/mL. Subsequently, 100 µL of cell suspension were inoculated into each well of 96-well plate and cultured for 71–95 hours until about 80% confluence was attained, after which the cells underwent the MTT experiment.

2.8 MTT Assay for Cytotoxicity Evaluation in Neuronal Cells

The in vitro cytocompatibility of GQD-TA was evaluated using the colorimetric MTT test. When the confluence reached roughly 80%, the culture media was meticulously aspirated, and 50 μ L of MTT solution were introduced to all well. Plates were protected from light and incubated at 37 °C for 30 minutes to facilitate the development of insoluble formazan crystals (Fathima *et al.* 2025). After incubation, MTT solution were discarded, and 100 μ L dimethyl sulfoxide were provided to solubilize crystals. The complete dissolution was achieved with moderate agitation and periodic pipetting. Absorbance were measured at 522 nm with, percentage of cell viability and microplate spectrophotometer were determined by standard formula.

$$\text{Cell Viability (\%)} = \frac{\text{Mean Absorbance of treated cells}}{\text{Mean absorbance of Untreated cells}} \times 100 \quad (5)$$

Results were presented as percentage IC₅₀ values and cell viability (the concentration necessary to diminish cell viability by 50%). An increased IC₅₀ signifies less cytotoxicity, suggesting that cells preserve metabolic activity at larger doses of the test substance, thereby showing enhanced biocompatibility and cellular tolerance.

3. RESULTS AND DISCUSSION

3.1 Data Acquisition and Organization

A 443 nanoparticles and nanocomposites were compiled from peer-reviewed research that reported cytotoxicity at cell viability experiments (S File 1). Data were extracted from experiments performed on various mammalian cell lines and categorized into 14 variables, encompassing nanoparticle identity, size (diameter), molecular weight, zeta potential, morphology, hydrophobicity/hydrophilicity, surface charge, aggregation behavior, concentration, temperature, exposure duration, cell type and percentage cell viability. This integrated dataset allowed for systematic assessment of cytotoxic reactions across various experimental circumstances and permitted identification of correlations among nanoparticle physicochemical characteristics and biological results. Thereafter, the data was standardized by numerical encoding and employed for predictive modeling based on machine learning (Supplementary File 2).

3.2 Validation of Cytotoxicity Prediction Using XGBoost

The comparative performance analysis presented in Table 1 demonstrates that the tuned XGBoost regression model achieved strong predictive capability for nanoparticle cytotoxicity estimation. The

model yielded a COD ($R^2 = 0.78$), indicating that approximately 78% of the variability in mammalian cell viability is effectively explained by the selected descriptors. Furthermore, the relatively low RMSE (6.82) and MAE (4.95) values confirm reduced prediction error and improved generalization performance on unseen data. The close agreement among experimental and predicted values highlights robustness of optimized hyperparameter configuration. Overall, these metrics validate the suitability of the tuned XGBoost model as a reliable machine learning framework for nano-QSAR-based cytotoxicity prediction and subsequent data-driven nanoparticle selection. The optimized XGBoost model achieved high external validation accuracy (85%) and balanced accuracy (83%), showing superior predictive capability compared with several existing literature models. The model also improved reliability through FAIR data curation, applicability domain analysis, and web-based virtual screening support (Varsou *et al.* 2026).

Table 1. Comparative performance metrics of ML models

Model	R ²	RMSE	MAE
Tuned XGBoost	0.78	6.82	4.95

Fig. 3 shows the tuned XGBoost model's actual vs. predicted scatter distribution. Most points cluster around the ideal 1:1 agreement line, indicating that the model captures the overall response trend reasonably well. A moderate spread around this line reflects residual prediction errors, with slight under/over-prediction observed at a few extreme response regions. A small number of outliers indicate sample-specific deviations, likely due to unmodelled variability or noise in the descriptors. Overall, the plot suggests acceptable generalization performance and supports using the trained model for subsequent interpretation such as feature-importance analysis. The close agreement between training and predicted values, along with low RMSE and MAE, suggests that the model avoids overfitting while maintaining good generalization. Additionally, the absence of extreme deviation in the scatter plot confirms that the model is neither underfitted nor overfitted.

Figure 4 presents the XGBoost feature-importance ranking, showing how strongly each input variable contributes to the prediction. Precursor type has the highest influence on the model output, followed by pH, indicating that reaction chemistry and medium conditions primarily govern the response. In contrast, reaction time and temperature exhibit comparatively lower contributions, suggesting secondary effects within the studied range. Overall, the plot highlights the dominant process parameters controlling the predicted outcome and supports prioritizing precursor selection and pH control for optimization. The dominance of precursor type reflects its direct influence on carbon structure, functional group incorporation, and defect density, which

govern nanoparticle reactivity and biological interactions. Similarly, pH affects surface charge, ionization state, and nucleation behavior, thereby influencing particle stability and cytotoxic response.

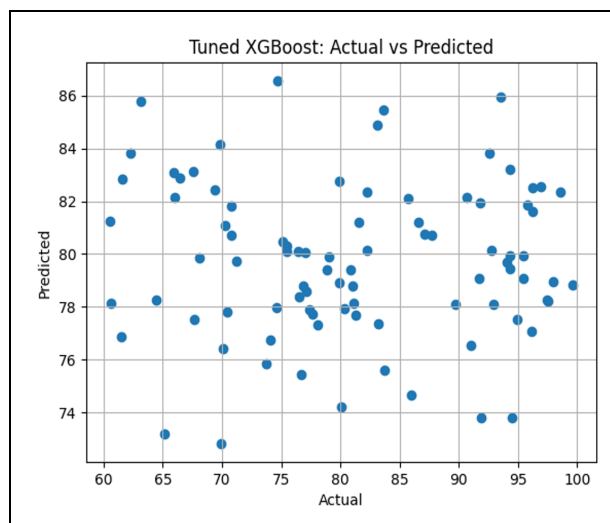


Fig. 3: Actual versus predicted values obtained from the tuned XGBoost regression model

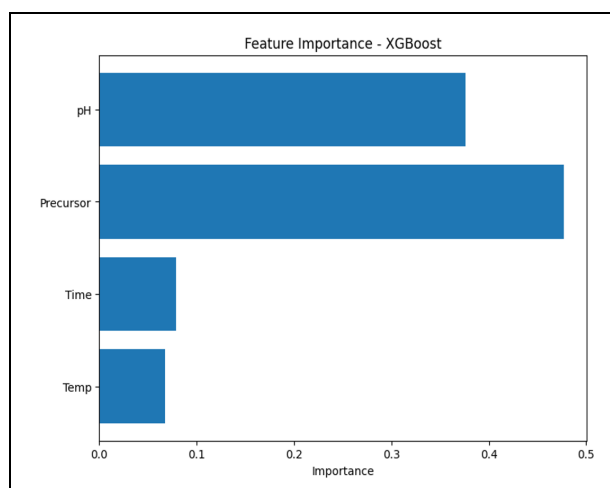


Fig. 4: XGBoost feature-importance ranking of input variables

Figure 5 illustrates the cytocompatibility of *Terminalia arjuna* bark powder and its derived Graphene Quantum Dots (GQD-TA) was evaluated using SH-SY5Y neuronal cells. The TA bark powder showed cell viability of 95, showing minimal intrinsic cytotoxicity. GQD-TA nanoparticles demonstrated high biocompatibility across all tested concentrations. At 50 $\mu\text{g/ml}$, the highest viability of 98 was observed, followed by 96 at 100 $\mu\text{g/ml}$. A gradual reduction was noted at higher concentrations, with 92 at 250 $\mu\text{g/ml}$ and 88 at 500 $\mu\text{g/ml}$; however, viability remained well above the cytotoxic threshold. The standard antioxidant (ascorbic acid) showed a viability of 99, confirming assay reliability. Overall, the results indicate that GQD-TA

nanoparticles maintain excellent cellular compatibility at elevated doses, supporting potential for biomedical and neuroprotective applications.

Table 2. CCD–RSM design matrix with experimental and predicted yields

Std	Run	Factor 1	Factor 2	Factor 3	Factor 4	Response 1
		A:A	B:B	C:C	D:D	Yield (%)
						6.12
29	1	0	0	0	0	5.5
5	2	-1	-1	1	-1	12.4
30	3	0	0	0	0	15.98
18	4	2	0	0	0	6.25
4	5	1	1	-1	-1	15.08
24	6	0	0	0	2	11.43
16	7	1	1	1	1	6.13
22	8	0	0	2	0	11.01
17	9	-2	0	0	0	5.32
12	10	1	1	-1	1	10.92
14	11	1	-1	1	1	7.28
27	12	0	0	0	0	10.92
9	13	-1	-1	-1	1	7.36
28	14	0	0	0	0	12.9
2	15	1	-1	-1	-1	15.57
11	16	-1	1	-1	1	10.53
26	17	0	0	0	0	12.05
13	18	-1	-1	1	1	12.35
21	19	0	0	-2	0	11.02
6	20	1	-1	1	-1	10.12
15	21	-1	1	1	1	12.95
10	22	1	-1	-1	1	9.45
1	23	-1	-1	-1	-1	11.75
3	24	-1	1	-1	-1	9.55
23	25	0	0	0	-2	7.45
7	26	-1	1	1	-1	12.75
8	27	1	1	1	-1	13.83
25	28	0	0	0	0	10.13
19	29	0	-2	0	0	10.39
20	30	0	2	0	0	6.13

Graphene nanomaterials illustrated in green, like Ag5-g-C₃N₄, and tGC₃N₄, show elevated cell survival akin, signifying less cytotoxicity and potential applicability in nanomedicine. Conversely, specific ZnO, TiO₂, and TiO₂-based composites exhibit reduced viability, indicating relatively elevated cytotoxic effects.

Numerous graphene nanoparticles exhibited significant biocompatibility, highlighting their

appropriateness for biomedical applications and their selection for production. Graphene Quantum Dots obtained from Terminalia arjuna bark and urea were selected, and process parameters were improved utilizing the central composite design to improve nanoparticle yield. The ML-identified importance of precursor and pH is consistent with experimental observations, where precursor composition influenced GQD structure and pH affected synthesis efficiency and stability, ultimately impacting yield and biocompatibility.

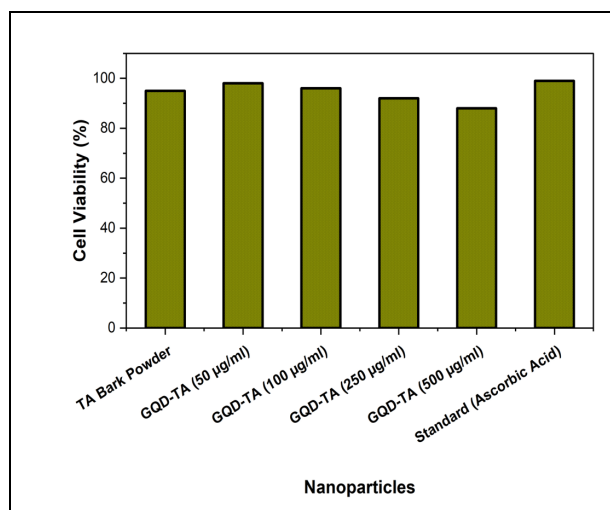


Fig. 5: Predicted cytotoxicity profiles of evaluated nanomaterials

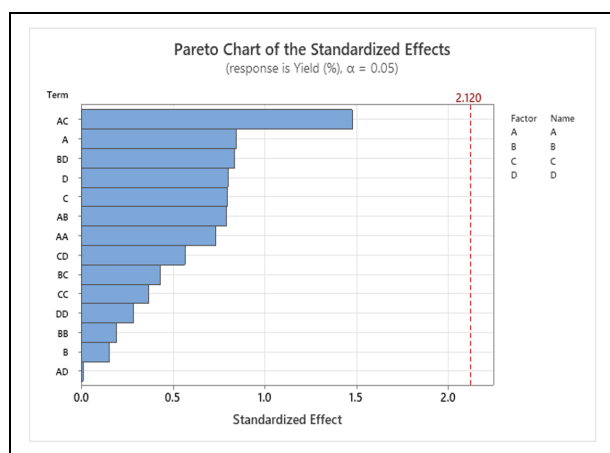


Fig. 6: Effect of linear, interaction and quadratic terms on GQDN-TA yield

3.3 Statistical Significance of Evaluated Variables

Fig. 6 presents the Pareto chart of the standardized effects for nanoparticle yield at a significance level of $\alpha = 0.05$. The interaction term AC exhibits the highest standardized effect, followed by the main effects A, BD, and D, indicating their comparatively stronger influence on yield. However, none of the factors cross the critical reference line

(2.120), suggesting that the individual and interaction terms are statistically insignificant at the 95% confidence level. Quadratic and secondary interaction terms show relatively lower contributions. These findings were further examined using ANOVA and regression analysis to confirm model adequacy and reliability. Although the Pareto chart indicates that individual standardized effects do not cross the significance threshold, ANOVA evaluates the collective contribution of variables. The significant model p-value ($p < 0.05$) confirms that the factors jointly influence the response, even if individual effects appear statistically weak in isolation.

3.4 Statistical Validation via ANOVA and Regression

The central composite design results were evaluated by ANOVA to assess statistical adequacy of developed regression model for GQD yield. An overall model was found to be significant ($F = 2.55$, $p = 0.0380$), confirming that the selected factors collectively influence the yield. Among the main effects, temperature (A) ($p = 0.0121$) and precursor wt% (C) ($p = 0.0375$) were statistically significant contributors, whereas time (B) and pH (D) showed comparatively lower influence within the studied range. Interaction terms were statistically insignificant ($p > 0.05$), indicating limited combined effects between variables. The lack-of-fit was not significant ($p = 0.9969$), confirming good model adequacy. These results validate the reliability of the regression model for predicting GQD yield under the examined experimental conditions.

Table 3. ANOVA results for factors influencing GQD yield

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2422.22	10	242.22	2.55	0.0380	significant
A-Temperature	730.41	1	730.41	7.69	0.0121	
B-Time	222.04	1	222.04	2.34	0.1428	
C-Precursor wt%	475.26	1	475.26	5.00	0.0375	
D-pH	210.04	1	210.04	2.21	0.1535	
AB	0.3025	1	0.3025	0.0032	0.9556	
AC	179.56	1	179.56	1.89	0.1852	
AD	246.49	1	246.49	2.59	0.1237	
BC	48.30	1	48.30	0.5084	0.4845	
BD	172.92	1	172.92	1.82	0.1932	
CD	136.89	1	136.89	1.44	0.2448	
Residual	1805.16	19	95.01			
Lack of Fit	561.70	14	40.12	0.1613	0.9969	not significant
Pure Error	1243.45	5	248.69			
Cor Total	4227.37	29				

All (AB, AC, AD, BC, BD, CD) shows p-values greater than 0.05, showing that combined factor effects were not statistically same. The lack-of-fit is also insignificant ($p = 0.9969$), confirming good agreement among predicted and experimental values and validating

model adequacy. The analysis demonstrates that yield optimization primarily depends on temperature and precursor concentration, while interaction and curvature effects are comparatively minimal under the evaluated conditions.

Figure 7 presents the XGBoost predicted versus actual yield plot, where the dashed red line represents the ideal 1:1 agreement line. The data points are reasonably distributed around this reference line, indicating acceptable predictive alignment between experimental and model-estimated yields. Minor deviations are observed at certain yield levels, reflecting localized prediction errors. Overall, the scatter distribution suggests that the XGBoost model captures the general trend of yield variation with moderate accuracy and satisfactory generalization performance across the dataset.

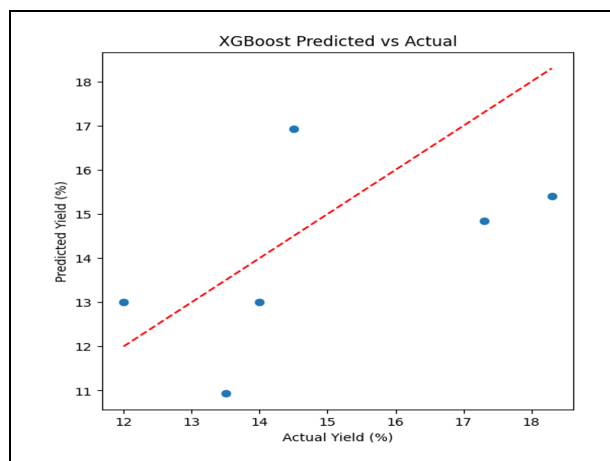


Fig. 7. Comparison of actual and XGBoost-predicted nanoparticle yield (%)

3.5 Yield Evaluation

Fig. 8 presents three-dimensional RSM surface plots illustrating interaction effects of synthesis parameters at GQD yield. In Fig. 8(a), the combined influence of reaction time (B) and precursor wt% (C) shows gradual raise at yield with increasing precursor concentration, while reaction time exhibits a comparatively mild effect within the studied range. In Fig. 8(b), the interaction between temperature (A) and pH (D) indicates that higher temperature contributes positively to yield enhancement, whereas pH demonstrates a relatively moderate influence. The nearly planar surface profiles suggest limited curvature and weak interaction effects, consistent with the ANOVA results showing dominant main effects and statistically insignificant interaction terms.

Figures 9 present the 3D surface plots illustrating the interaction effects on precursor wt% with reaction time and pH on GQD yield. The surfaces exhibit a gradual increase in yield with increasing precursor

concentration, while reaction time and pH show comparatively moderate influence within the investigated range. The nearly planar response surfaces and smooth contour profiles indicate weak interaction and minimal quadratic effects, suggesting that yield variation is primarily governed by main factor contributions rather than strong synergistic interactions.

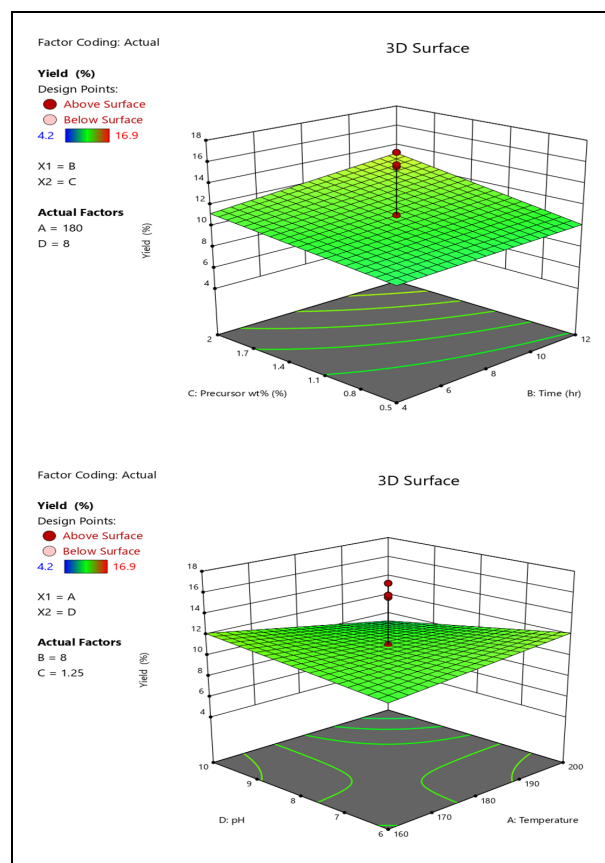


Fig. 8: 3D RSM surface plots showing interaction effects of synthesis parameters on GQD yield (%)

Figures 10 present the 3D RSM surface plots illustrating combined effects of temperature, time, precursor wt%, and pH at GQD yield. Across all interaction profiles, yield generally increases with higher temperature and precursor concentration, while time and pH exhibit comparatively moderate influences within the studied domain. The response surfaces appear nearly planar with gentle gradients, indicating weak interaction and limited curvature effects, consistent with ANOVA findings. These graphical analyses aided in identifying favorable synthesis conditions, after which GQD-TA nanoparticles were synthesized using the optimized hydrothermal method.

3.6 Characterization of Graphene- nanoparticles (GQDN-TA)

The yield of manufactured nanoparticles, as per specified 27-run CCD matrix at Table 2, were

documented followed by the characterisation of the nanoparticles.

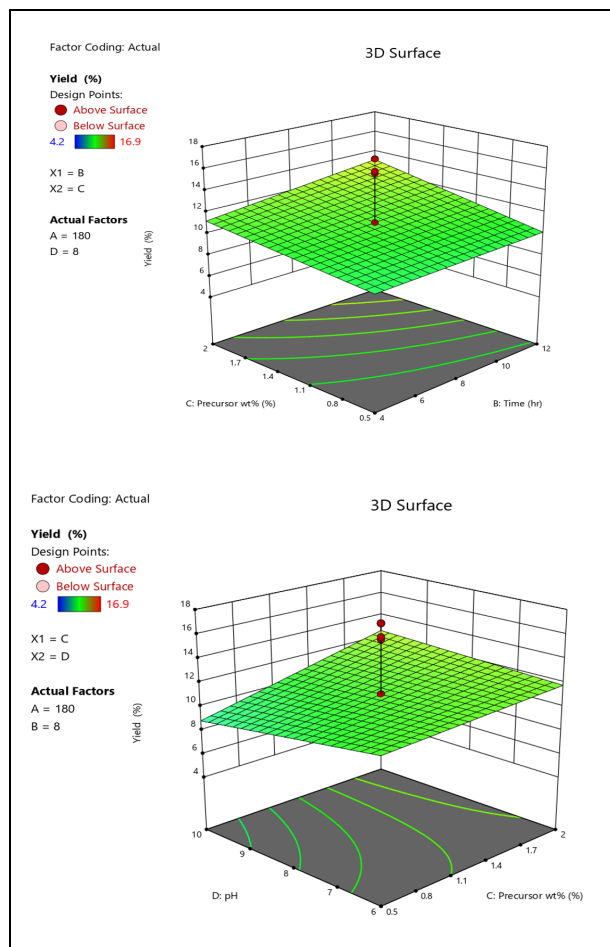


Fig. 9: 3D RSM surface plots showing interaction effects of precursor wt% with reaction time and pH on GQD yield (%)

3.6.1 Ultraviolet–visible Absorption Spectroscopy Results

The UV–Vis absorption spectrum of GQD-TA (Figure 11) exhibits strong absorption at UV region ($\approx 220\text{--}350\text{ nm}$), followed by gradual decrease in intensity extending into the visible region up to $\sim 700\text{ nm}$. An intense UV absorption band were attributed $\pi\text{--}\pi^*$ of conjugated aromatic sp^2 carbon, while broad tail toward the visible region suggests $\text{n--}\pi^*$ transitions with surface functional groups like C=O and C–N. Observed absorption edge around $410\text{--}420\text{ nm}$ to estimated optical bandgap approximately $2.4\text{--}2.5\text{ eV}$ ($E_g = 1240/\lambda$), confirming semiconducting nature of the synthesized GQDs. The absence of distinct plasmonic peaks in the higher wavelength region further verifies their non-metallic, carbon-based quantum dot characteristics. The UV–Vis absorption peak observed for GQD-TA was comparable with previously reported plant-derived graphene quantum dots exhibiting characteristic $\pi\text{--}\pi^*$ transitions within the $260\text{--}320\text{ nm}$ region (Kadyan *et al.* 2024).

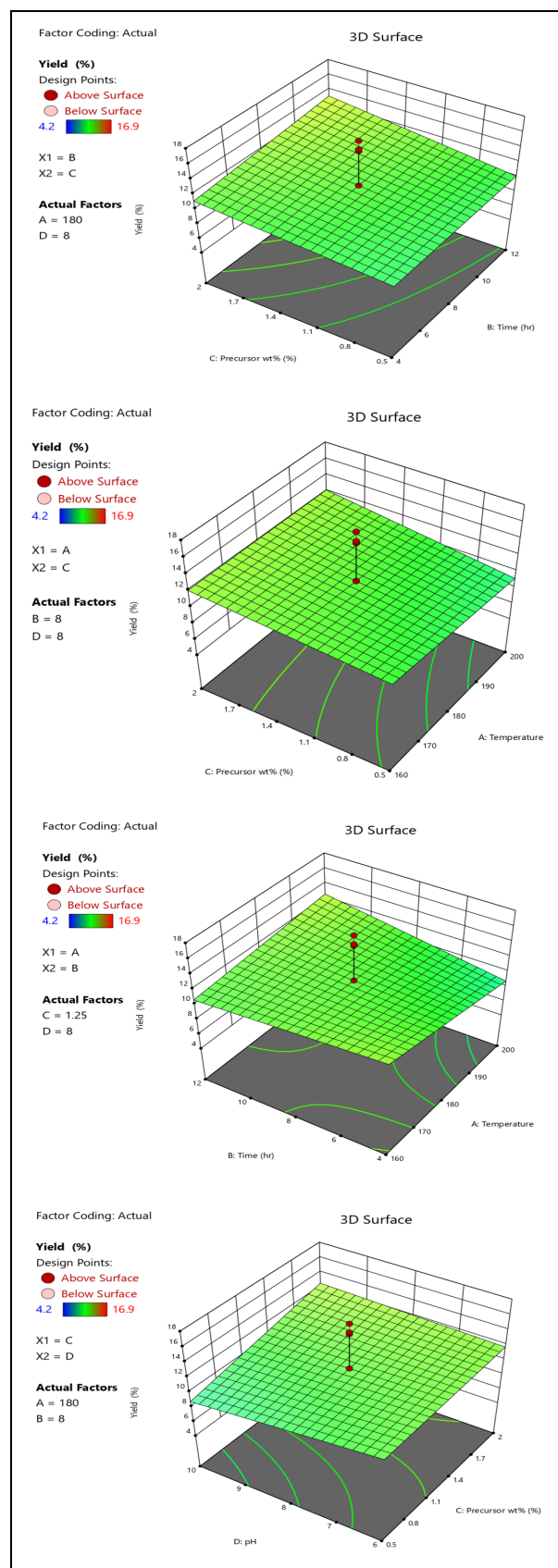


Fig. 10: 3D central composite design response surfaces illustrating interaction effects on RSM yield

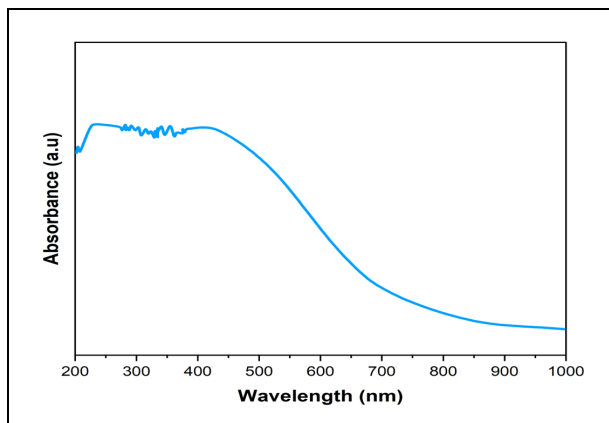


Fig. 11: Optical absorption profile of GQDN-TA with π - π and n - π transitions

3.6.2 X-Ray Diffraction

The XRD of GQDN-TA shows peaks of $2\theta = 23.53^\circ$ and 34.25° , indicative of graphitic carbon structures. A minor deviation at 25° indicates structural diversity, corroborating the production of stacked Graphene Quantum Dots. The XRD pattern of GQDN-TA confirmed the formation of graphitic nanoscale structures, similar to previously reported green-synthesized nanomaterials using *Terminalia arjuna* extract. The observed diffraction behavior indicated successful crystalline carbon domain formation (Singh *et al.* 2026)

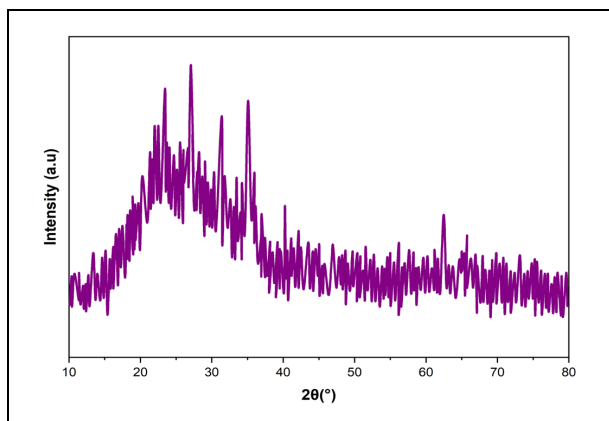


Fig. 12: XRD pattern revealing crystalline features of GQDN-TA nanoparticles

3.6.3 Fourier Transform Infrared Spectroscopy Results

The FTIR spectrum (Fig. 13) of GQDN-TA exhibits distinctive bands indicative of graphitic carbon nitride structures. The peaks at 1623 cm^{-1} C–N and C=N stretching, affirming inclusion of aromatic heptazine frameworks, whereas broad band about 3357 cm^{-1} signifies N–H/O–H groups, showing surface functionalization. The functions authenticate GQD production and furnish active locations for ROS scavenging by electron donation and proton-transfer

pathways, hence enhancing antioxidant capability. The FTIR spectrum of GQDN-TA confirmed the presence of oxygen-containing functional groups responsible for phytochemical-mediated stabilization. Similar surface functionalization has been reported for *Terminalia arjuna*-derived nanomaterials (Shivaputrappa *et al.* 2026).

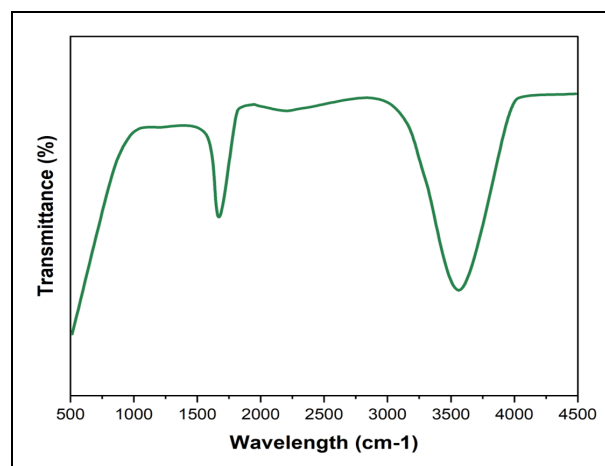


Fig. 13: FTIR spectrum confirming functional groups in GQDN-TA nanoparticles

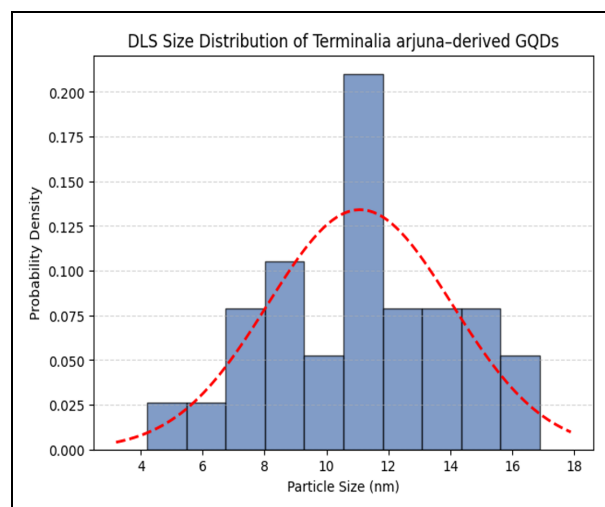


Fig. 14: DLS and zeta potential analysis of GQDN-TA nanoparticles

3.6.4 Dynamic Light Scattering

The DLS size distribution profile of *Terminalia arjuna*-derived GQDs (Fig. 14) reveals a predominantly narrow particle size range centered around approximately 10–12 nm, with average diameter near 11 nm. The histogram and fitted distribution curve indicate a relatively symmetric, near-normal distribution without pronounced secondary peaks, suggesting minimal aggregation and good size uniformity. Most particles fall within the 8–15 nm range, confirming controlled nucleation and growth during green synthesis. The absence of broad tails or multimodal features supports a

fairly monodisperse dispersion, which is favorable for consistent optical behavior, antioxidant performance, and potential biomedical applications. The DLS analysis of GQD-TA revealed nanoscale particle distribution with good colloidal stability, comparable to previously reported *Terminalia arjuna*-derived nanomaterials. Similar hydrodynamic size behavior confirmed effective green synthesis and nanoparticle stabilization (Suganthi *et al.* 2018)

3.6.5 SEM- EDS

SEM micrographs (Figs. 15a–c) reveal that GQD-TA exhibits a heterogeneous and moderately aggregated morphology composed predominantly of quasi-spherical microdomains with rough and irregular surface textures. Figure 15(a) shows a well-defined spherical structure with a textured outer layer, while Fig. 15(b) illustrates fragmented and clustered particles distributed across the substrate, indicating partial agglomeration. In Fig. 15(c), a larger spherical entity

with surface flakes and adhered nanofragments is observed, confirming structural exfoliation and layered carbon architecture. The particle dimensions range approximately between 40–100 nm, with representative sizes around ~43 nm and ~71–72 nm, consistent with effective carbonization and exfoliation during hydrothermal synthesis. The visible surface irregularities, nanoscale voids, and interparticle spacing suggest enhanced surface area and active sites, which are favorable for electron transfer, radical scavenging, and catalytic interactions. The porous and defect-rich morphology supports quantum confinement-induced photoluminescence behavior and validates the suitability of GQD-TA for antioxidant, bioimaging, and therapeutic applications. SEM analysis of GQD-TA revealed homogeneous nanoscale morphology with effective particle distribution, similar to previously reported *Terminalia arjuna*-based materials. The observed structural uniformity indicated successful green synthesis and surface stabilization (Shahzad *et al.* 2025)

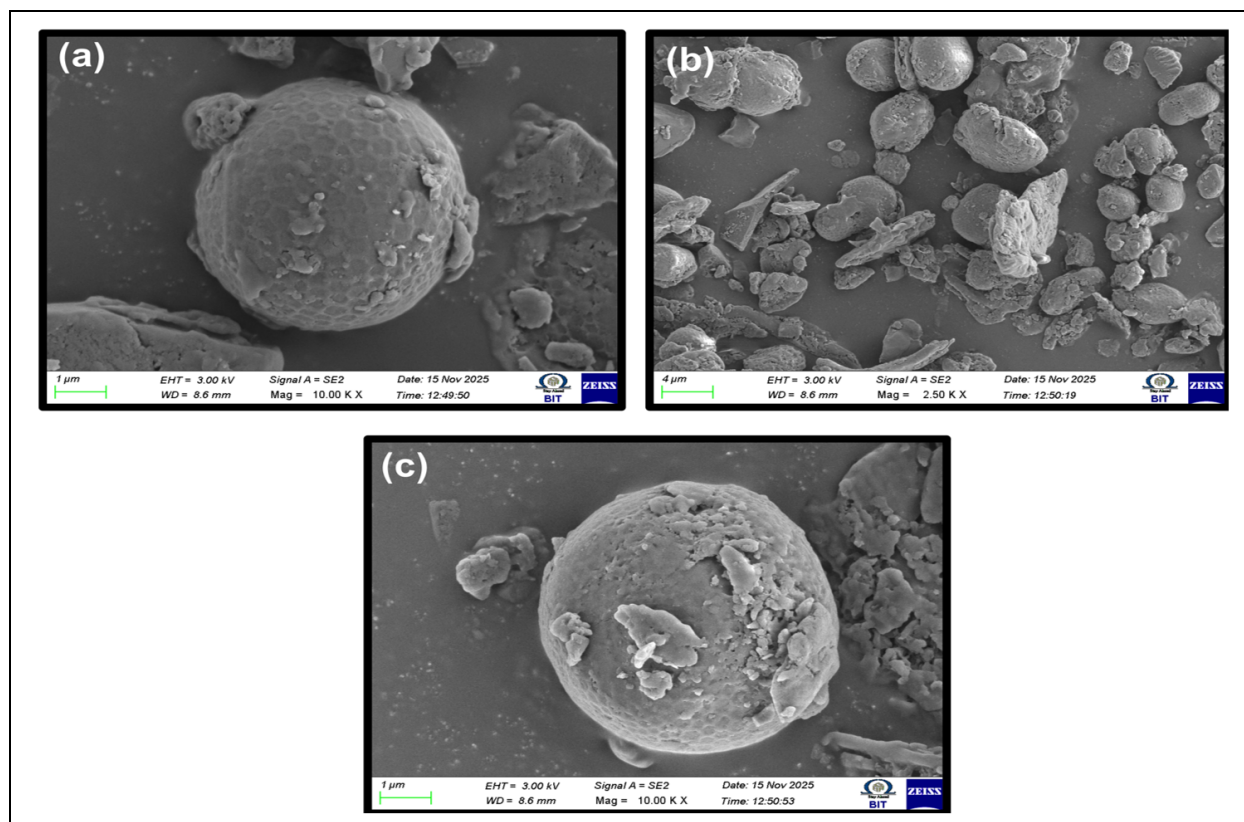


Fig. 15: SEM micrographs of *Terminalia arjuna*-derived g-C₃N₄ at various magnifications

Figure 16 presents the EDS spectrum of GQD-TA, confirming that carbon (67.85 wt%, 73.29 at%), nitrogen (15.24 wt%, 19.02 at%), and oxygen (11.03 wt%, 6.94 at%) are the dominant elements in the synthesized nanoparticles. The high carbon content verifies the graphitic backbone of the quantum dots, while the substantial nitrogen fraction confirms successful N-incorporation into the carbon framework,

which can enhance electronic conductivity and surface reactivity. The inclusion of oxygen suggests surface functional groups like hydroxyl and carbonyl moieties that improve hydrophilicity and dispersion stability. Minor traces of Si (2.05 wt%), S (1.58 wt%), K (0.78 wt%), Ca (0.57 wt%), and Fe (0.9 wt%) are detected, likely originating from precursor residues or environmental background. Importantly, no significant

heavy-metal impurities are observed, confirming the predominantly carbonaceous and non-metallic nature of GQD-TA. Overall, the EDS results validate the successful formation of nitrogen-functionalized graphene quantum dots with appropriate elemental composition for antioxidant and biomedical applications.

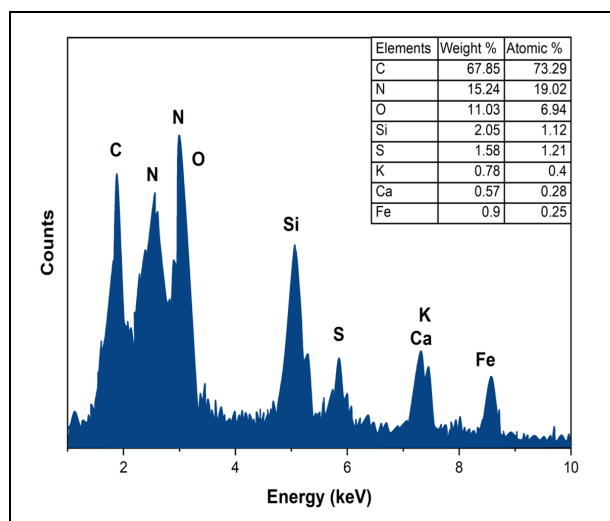


Fig. 16: EDS spectrum and elemental composition of GQD-N-TA NPs

3.7 DPPH Assay for Antioxidant Activity Evaluation

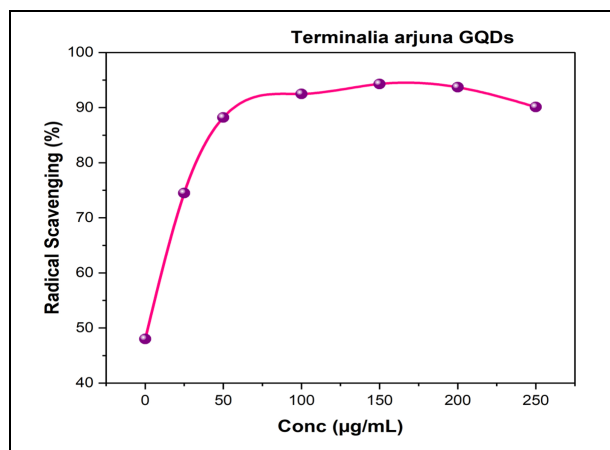


Fig. 17: Dose-dependent radical scavenging activity of AA and GQD-N-TA

The DPPH radical scavenging activity of GQD-TA produced from *Terminalia arjuna* was compared to that of ascorbic acid (AA). GQD-TA demonstrated limited efficacy at 15.62 µg/mL (45.70%), which significantly increased to 87.79% at 31.25 µg/mL and 92.11% at 111 µg/mL, equivalent to AA. The IC₅₀ value, defined as the concentration required to achieve 50% radical scavenging, was estimated to be approximately ~10–15 µg/mL, indicating considerable antioxidant efficiency. AA exhibited dose-dependent efficacy

ranging from 73.68% to 99.06%, hence affirming its robust antioxidant capabilities (Fig. 17).

The DPPH radical scavenging activity of *Terminalia arjuna*-derived GQDs (GQD-TA) is shown in Fig. 17, demonstrating a clear concentration-dependent antioxidant response. Radical scavenging increases sharply from approximately 48% at low concentration to nearly 88% at 50 µg/mL, reaching a maximum of about 94–95% around 150 µg/mL. Beyond this concentration, a slight decline is observed at higher doses (200–250 µg/mL), possibly due to aggregation or optical interference effects. The overall trend confirms strong free-radical neutralization capability, indicating effective electron-donating behavior of surface-functionalized GQDs synthesized by the green route. The observed scavenging efficiency (~94–95%) is comparable to or higher than many reported carbon-based nanomaterials, highlighting the antioxidant potential of GQD-TA (Krunić *et al.* 2021).

3.8 MTT-based Cell Viability Assessment in SH-SY5Y Cells

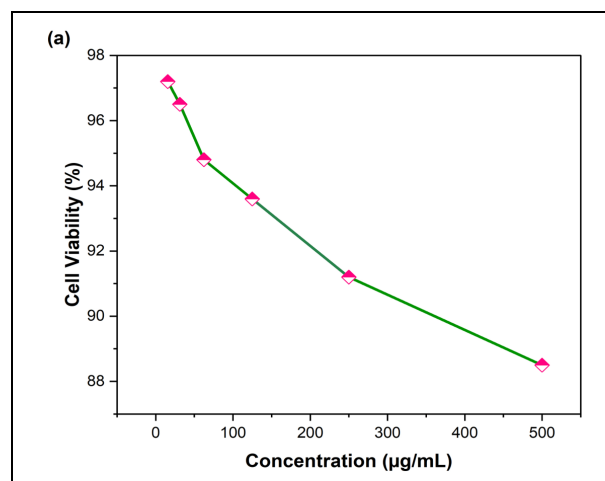


Fig. 18: Cell viability assessment of SH-SY5Y cells

The MTT assay was conducted to assess the cytocompatibility of GQD-TA in SH-SY5Y cells. Cell viability was determined by comparing treated samples to untreated controls, which were defined as 100% viable. High viability was sustained across doses from 15.62 to 500 µg/mL. At 15.62 µg/mL, viability was 97.2%, slightly declining to 96.5% at 31.25 µg/mL. The progressive decrease were noted with rising concentration: 94.8% (62.5 µg/mL), 93.6% (125 µg/mL), 91.2% (250 µg/mL), and 88.5% (500 µg/mL). The data demonstrate a slight, concentration-dependent decrease in viability, indicating dose-responsive cellular effects while preserving overall biocompatibility. The cytocompatibility of GQD-TA can be attributed to its surface functional groups (–OH, –NH, –COOH), which enhance biocompatibility, reduce oxidative stress, and promote cellular interactions while minimizing

membrane damage. Overall, the strong agreement between machine learning predictions and experimental findings demonstrates the effectiveness of the integrated nano-QSAR and CCD-RSM framework in designing biocompatible and high-performance graphene quantum dots.

4. CONCLUSION

A data-driven nano-QSAR framework integrated with machine learning and central composite design enabled the rational development of green-synthesized graphene quantum dots (GQD-TA) derived from *Terminalia arjuna* bark. Among the evaluated regression models, tuned XGBoost demonstrated reliable cytotoxicity prediction performance ($R^2 = 0.78$, RMSE = 6.82), facilitating computational screening prior to experimental validation. Subsequent statistical optimization confirmed the significance of synthesis parameters ($F = 2.55$, $p = 0.0380$), with temperature and precursor concentration exerting dominant effects on nanoparticle yield. The optimized GQD-TA exhibited a narrow size distribution (~11 nm), nitrogen-functionalized carbon composition, and antioxidant activity, achieving up to 94–95% DPPH radical scavenging. In vitro cytocompatibility assessment in SH-SY5Y neuronal cells revealed sustained cell viability of 88.5% at 500 µg/mL, confirming low cytotoxicity across the investigated concentration range. The combined computational–statistical–experimental strategy demonstrates a sustainable and predictive platform for designing neurocompatible antioxidant nanomaterials, advancing translational prospects in oxidative stress-related neurological applications. Future work should focus on in vivo validation and clinical translation to further establish the therapeutic safety and efficacy of GQD-TA. Additionally, integration of advanced biological datasets with machine learning frameworks may further enhance predictive accuracy and accelerate the development of personalized nanomedicine strategies. This integrated approach minimizes experimental trial-and-error by enabling informed material selection through predictive modeling.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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