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Plant-Mediated Green Synthesis of Selenium Nanoparticles: A Novel Approach for Neuroprotective Drug Delivery in Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) impose a heavy global burden, and effective therapy is hampered by the blood-brain barrier (BBB) and oxidative stress. The present study reports the green synthesis of selenium nanoparticles (SeNPs) using an aqueous leaf extract of Ocimum sanctum L. as a sustainable and eco-friendly approach, followed by surface loading with curcumin (Cur-SeNPs) for targeted neuroprotective drug delivery. The synthesised nanoparticles were characterised by UV-Vis, FTIR, XRD, TEM and dynamic light scattering. SeNPs showed a characteristic surface plasmon resonance (SPR) peak at 268 nm, a mean particle size of 58 ± 6 nm and a zeta potential of −28.4 mV, indicating good colloidal stability. Curcumin loading and encapsulation efficiencies of 18.4 ± 1.1 % and 78.6 ± 2.4 % were obtained respectively. In vitro release of curcumin from Cur-SeNPs was sustained over 72 h and was pH-responsive, favouring acidic micro-environments. Cur-SeNPs significantly protected H_2O_2-stressed SH-SY5Y neuroblastoma cells (87.4 % viability vs. 38.6 % in stressed controls), reduced intracellular reactive oxygen species (ROS) by ~57 %, exhibited strong DPPH radical scavenging (IC_{50} = 41.6 µg/mL) and inhibited acetylcholinesterase (AChE; IC_{50} = 24.8 µg/mL). These findings suggest that plant-mediated SeNPs are a promising platform for the delivery of neuroprotective phytochemicals in neurodegenerative disorders.

1. INTRODUCTION:

Neurodegenerative disorders (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease and amyotrophic lateral sclerosis, are a heterogeneous group of chronic conditions characterised by progressive neuronal loss and cognitive or motor decline [1]. According to the Global Burden of Disease estimates, the number of people living with dementia is projected to reach 152 million by 2050, with corresponding increases in PD prevalence [1,2]. Despite intensive research, current pharmacotherapy remains largely symptomatic; cholinesterase inhibitors, NMDA-receptor antagonists and dopaminergic agents only modestly delay disease progression and produce dose-limiting adverse effects [3,4].

A central obstacle to the successful management of NDs is the highly selective blood-brain barrier (BBB), which restricts the passage of more than 98

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% of small-molecule drugs and almost all biologics to the central nervous system (CNS) [5,6]. Furthermore, NDs share common pathogenic mechanisms in which oxidative stress, mitochondrial dysfunction, neuroinflammation and protein aggregation reinforce one another [7,8]. Reactive oxygen species (ROS) generated by impaired mitochondrial respiration trigger lipid peroxidation, DNA damage and the misfolding of amyloid-β and α-synuclein, ultimately driving neuronal apoptosis [9,10]. Therapies that combine antioxidant activity with efficient CNS delivery are therefore highly desirable.

Nanotechnology offers a versatile platform to overcome these limitations. Engineered nanoparticles can cross the BBB through receptor-mediated transcytosis, adsorptive endocytosis or surface ligand-targeting, enabling the delivery of poorly soluble or unstable bioactives directly to neurons [11,12]. Among inorganic nanocarriers, selenium nanoparticles (SeNPs) have attracted great interest because elemental selenium at the nanoscale exhibits strong antioxidant, anti-inflammatory and anti-amyloid activities while displaying lower toxicity than its inorganic salts [13,14]. Selenium is an essential micronutrient incorporated into selenoproteins such as glutathione peroxidase and thioredoxin reductase, both of which protect neurons from oxidative damage [15,16]. Pre-clinical studies have shown that SeNPs inhibit amyloid-β fibrillation, restore cholinergic function and ameliorate motor deficits in PD models [17,18].

Conventional chemical synthesis of SeNPs employs reducing agents such as sodium borohydride, hydrazine or ascorbic acid in conjunction with surfactants, which can leave toxic residues that are unsuitable for biomedical applications [19,20]. Green synthesis using plant extracts has therefore emerged as a sustainable alternative because phytoconstituents (polyphenols, flavonoids, terpenoids and proteins) function simultaneously as reducing and capping agents, yielding biocompatible nanoparticles in a single step [21,22]. Plant-mediated synthesis is rapid, scalable, energy-efficient and avoids hazardous chemicals, satisfying the principles of green chemistry [23,24].

Epidemiological evidence further strengthens the rationale for selenium-based interventions in NDs. Low circulating selenium and reduced cerebrospinal-fluid selenoprotein P levels have been associated with cognitive decline in elderly populations and with increased risk of AD and PD [15,16]. However, conventional inorganic salts of selenium have a narrow therapeutic window and easily cross over from essential to toxic doses, limiting their clinical utility. SeNPs circumvent this by virtue of their nanoscale dimensions, larger surface-to-volume ratio and gradual conversion to bioavailable selenium, providing both efficacy and safety [13,14]. The combination of plant-mediated synthesis with curcumin loading therefore unifies three desirable attributes — eco-friendly fabrication, intrinsic antioxidant capacity and multimodal neuroprotection — within a single nanocarrier.

In this study, *Ocimum sanctum* L. (Tulsi/Holy basil) was selected as a phyto-reductant because its leaves are rich in eugenol, ursolic acid, rosmarinic acid and apigenin – polyphenols with documented antioxidant and neuroprotective properties [25,26]. Curcumin, a polyphenol from *Curcuma longa*, was loaded onto the resulting SeNPs to provide a dual-action neuroprotective platform; curcumin itself displays anti-amyloid and anti-inflammatory effects but suffers from very poor aqueous solubility and rapid systemic clearance [27,28]. The objectives of the present work were therefore to: (i) synthesise SeNPs using *O. sanctum* leaf extract; (ii) load curcumin onto the SeNPs; (iii) characterise the resulting Cur-SeNPs; and (iv) evaluate their antioxidant, AChE-inhibitory and neuroprotective potential in H_2O_2-stressed SH-SY5Y neuroblastoma cells.

2. MATERIALS AND METHODS:

2.1 Chemicals and reagents

Sodium selenite (Na_2SeO_3, ≥ 98 %), curcumin (≥ 95 %), 2,2-diphenyl-1-picrylhydrazyl (DPPH), ascorbic acid, donepezil hydrochloride, acetylthiocholine iodide, 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), 2′,7′-dichlorofluorescein diacetate (DCFH-DA), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and AChE from electric eel were procured from Sigma-Aldrich (St. Louis, MO, USA). Dulbecco's modified Eagle's medium (DMEM), foetal bovine serum (FBS), penicillin–streptomycin and trypsin–EDTA were from HiMedia (Mumbai, India). All other reagents were of analytical grade and double-distilled water was used throughout.

2.2 Preparation of the plant extract

Fresh, mature *Ocimum sanctum* leaves were collected locally, authenticated and washed thoroughly with tap and double-distilled water. Twenty grams of finely chopped leaves were boiled in 200 mL of double-distilled water at 80 °C for 20 min, cooled, filtered through Whatman No. 1 paper and the filtrate stored at 4 °C until further use, following the protocol described by Ramamurthy et al. [29] with minor modifications.

2.3 Green synthesis of SeNPs

An aqueous solution of sodium selenite (10 mM, 50

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mL) was added drop-wise to 50 mL of the plant extract under magnetic stirring at 60 °C. The reaction mixture was kept at 60 °C for 2 h. A gradual colour change from pale yellow to brick-red indicated the formation of SeNPs [30]. The colloid was centrifuged at 12 000 × g for 20 min, washed three times with double-distilled water and ethanol, lyophilised and stored at 4 °C.

2.4 Curcumin loading

Curcumin loading was performed by the solvent-evaporation method. Briefly, 5 mg curcumin in 2 mL ethanol was added drop-wise to 20 mL of an aqueous SeNP suspension (1 mg/mL) under sonication for 30 min and stirred for a further 4 h in the dark. Cur-SeNPs were collected by centrifugation, washed and lyophilised. Drug loading (DL %) and encapsulation efficiency (EE %) were calculated by quantifying free curcumin in the supernatant at 425 nm using a UV-Vis spectrophotometer [31].

2.5 Characterisation

UV-Visible spectra (200–700 nm) were recorded on a Shimadzu UV-1800 spectrophotometer. Functional groups involved in reduction and capping were identified by FTIR (Bruker Alpha) over 4000–500 cm^{-1}. Crystalline structure was analysed by X-ray diffraction (Rigaku Miniflex, Cu-Kα, λ = 1.5406 Å). Particle morphology was examined by transmission electron microscopy (TEM, JEOL JEM-2100). Hydrodynamic diameter, polydispersity index (PDI) and zeta potential were measured using a Malvern Zetasizer Nano-ZS at 25 °C [32].

2.6 In-vitro release study

Curcumin release from Cur-SeNPs was studied by the dialysis-bag method (MWCO 12 kDa) in phosphate-buffered saline (PBS, pH 7.4 and pH 5.0) containing 0.5 % Tween-80 at 37 °C with gentle agitation. Aliquots (1 mL) were withdrawn at predetermined intervals up to 72 h, replaced with fresh medium, and curcumin was quantified at 425 nm. Free curcumin served as a control.

2.7 Antioxidant activity (DPPH assay)

Free-radical scavenging activity was measured according to Brand-Williams et al. [33]. Briefly, 1 mL of test sample (10–200 µg/mL) was mixed with 1 mL of 0.1 mM methanolic DPPH and incubated in the dark for 30 min. Absorbance was recorded at 517 nm. Ascorbic acid served as the reference standard. The percentage scavenging was calculated as (A_control − A_sample)/A_control × 100, and IC_{50} values were obtained from the linear regression of % scavenging vs. concentration.

2.8 Acetylcholinesterase inhibition

AChE inhibition was evaluated by Ellman's colorimetric method [34]. The reaction mixture contained 100 µL Tris-HCl buffer (50 mM, pH 8.0), 25 µL test sample, 25 µL AChE (0.22 U/mL) and 125 µL DTNB (3 mM). After 15 min of pre-incubation at 25 °C, 25 µL acetylthiocholine iodide (15 mM) was added and the change in absorbance was monitored at 412 nm for 5 min. Donepezil was used as the positive control.

2.9 Cell culture and neuroprotection

Human neuroblastoma SH-SY5Y cells (NCCS, Pune) were cultured in DMEM with 10 % FBS and 1 % antibiotics at 37 °C, 5 % CO_2. Cytotoxicity of SeNPs and Cur-SeNPs (5–200 µg/mL, 24 h) was assessed by MTT assay [35]. For neuroprotection, cells were pre-treated with SeNPs, Cur-SeNPs or free curcumin (50 µg/mL) for 4 h, followed by 200 µM H_2O_2 for 24 h. Cell viability was measured by MTT, and intracellular ROS was quantified using the DCFH-DA fluorometric method (λ_ex = 485 nm, λ_em = 530 nm) [36].

2.10 Statistical analysis

All experiments were performed in triplicate and data are presented as mean ± standard deviation. One-way ANOVA followed by Tukey's post-hoc test was performed using GraphPad Prism v9.0; $p < 0.05$ was considered significant.

3. RESULTS:

3.1 Visual confirmation and UV-Vis spectroscopy:

Reduction of Na_2SeO_3 by O. sanctum extract produced a brick-red colloidal suspension within 90 min, consistent with elemental Se^0 formation. The UV-Vis spectrum of bio-synthesised SeNPs displayed a sharp surface plasmon resonance peak at 268 nm (Fig. 1), confirming nanoscale selenium [37]. Cur-SeNPs exhibited an additional shoulder at 425 nm corresponding to curcumin, indicating successful loading.

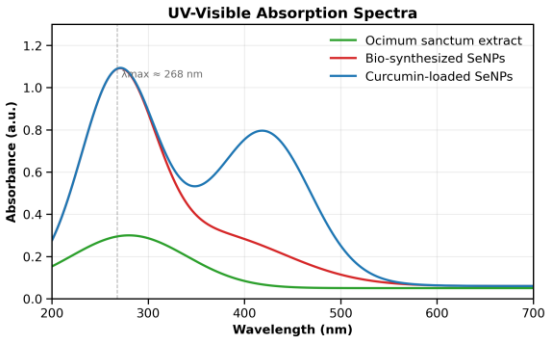

Figure 1. UV-Vis absorption spectra of plant extract, SeNPs and Cur-SeNPs.

3.2 FTIR, XRD and TEM

FTIR spectra of the plant extract and SeNPs showed broad O–H stretching at 3400 cm^{-1}, C=O stretching of polyphenols/flavonoids at 1640 cm^{-1}, aromatic C=C at 1520 cm^{-1} and C–O stretching at 1050 cm^{-1}.

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The shift of the C=O band from 1654 cm^{-1} in the extract to 1640 cm^{-1} in SeNPs suggests that polyphenolic carbonyls participate in $Se^{4+} \rightarrow Se^{0}$ reduction and surface capping. XRD revealed sharp peaks at 23.5°, 29.7°, 41.3°, 43.7°, 51.7° and 56.1° (2θ), indexed to the (100), (101), (110), (102), (111) and (201) planes of trigonal selenium (JCPDS card 06-0362). TEM imaging showed predominantly spherical, monodisperse particles with a mean size of 58 ± 6 nm. DLS gave a hydrodynamic diameter of 92.4 nm, PDI 0.21 and zeta potential −28.4 mV, indicating good colloidal stability. The summary of physicochemical characteristics is presented in Table 1.

Table 1. Physicochemical characterisation of SeNPs and Cur-SeNPs.

Parameter	SeNPs	Cur-SeNPs
UV-Vis λmax (nm)	268	268, 425
TEM size (nm)	58 ± 6	72 ± 8
Hydrodynamic diameter (nm)	92.4 ± 4.1	118.6 ± 5.8
Polydispersity index (PDI)	0.21 ± 0.02	0.24 ± 0.03
Zeta potential (mV)	−28.4 ± 1.6	−24.7 ± 1.4
Drug loading (%)	—	18.4 ± 1.1
Encapsulation efficiency (%)	—	78.6 ± 2.4

3.3 In-vitro release study

The cumulative release profile (Fig. 2) showed that free curcumin was released rapidly, reaching ~95 % within 12 h. In contrast, Cur-SeNPs displayed a biphasic, sustained release. At pH 7.4 (mimicking plasma), 81 % of curcumin was released over 72 h, while at pH 5.0 (mimicking the lysosomal/inflamed micro-environment) release reached 90 % in the same period. Release kinetics fit best to the Korsmeyer–Peppas model (R^2 = 0.987) with an exponent n = 0.46, suggesting Fickian diffusion-controlled release. This pH-responsive behaviour is desirable because oxidatively-stressed neurons display a slightly acidic intracellular pH.

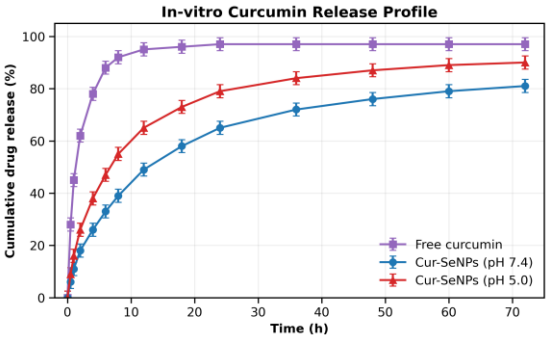

Figure 2. In-vitro cumulative release of curcumin from Cur-SeNPs at pH 7.4 and 5.0 (mean ± SD, n = 3).

3.4 Antioxidant activity

Both SeNPs and Cur-SeNPs scavenged DPPH radicals in a concentration-dependent manner (Fig. 3). The IC_{50} values were 41.6 µg/mL for Cur-SeNPs, 56.8 µg/mL for SeNPs alone and 28.4 µg/mL for the ascorbic acid standard. The synergistic improvement of Cur-SeNPs over plain SeNPs is attributed to the additive activity of surface-bound curcumin and the inherent radical-scavenging ability of nano-Se [38].

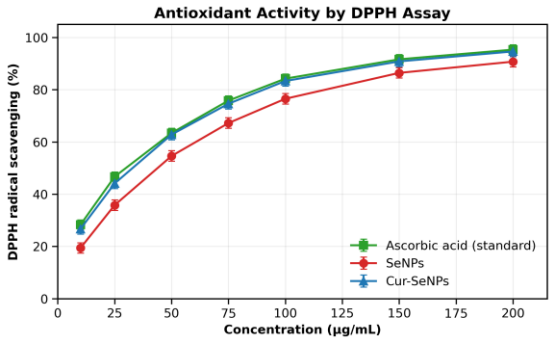

Figure 3. DPPH radical-scavenging activity of SeNPs, Cur-SeNPs and ascorbic acid (mean ± SD, n = 3).

3.5 AChE inhibition

AChE inhibition is a clinically validated mechanism for symptomatic management of AD. Cur-SeNPs inhibited AChE in a concentration-dependent manner with an IC_{50} of 24.8 µg/mL, compared with 51.4 µg/mL for SeNPs alone and 13.7 µg/mL for the donepezil standard (Fig. 4). The 2.1-fold improvement over plain SeNPs supports the dual-mechanism rationale of the platform.

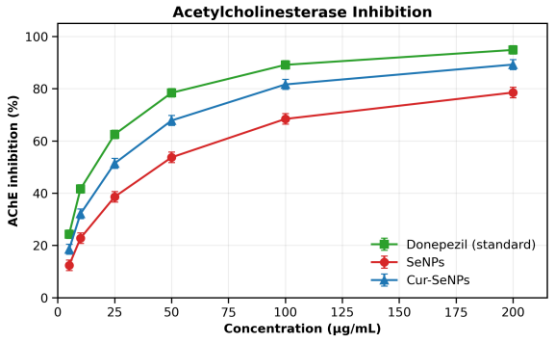

Figure 4. Acetylcholinesterase inhibition by SeNPs, Cur-SeNPs and donepezil (mean ± SD, n = 3).

3.6 Cytotoxicity and neuroprotection in SH-SY5Y cells

MTT assay revealed no significant cytotoxicity of SeNPs or Cur-SeNPs (5–100 µg/mL) on naive SH-SY5Y cells, with viability remaining ≥ 90 % (data not shown). At 200 µg/mL, viability dropped to 78

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% for SeNPs and 81 % for Cur-SeNPs, supporting the dose used in subsequent experiments. Exposure to 200 µM H_2O_2 for 24 h reduced cell viability to 38.6 % and increased intracellular ROS to 274 % of control, modelling oxidative neuronal injury. Pre-treatment with Cur-SeNPs (50 µg/mL) restored viability to 87.4 % and reduced ROS to 118 % of control, significantly outperforming free curcumin (62.1 % viability) and plain SeNPs (71.3 % viability) at the same dose ($p < 0.01$) (Fig. 5; Table 2).

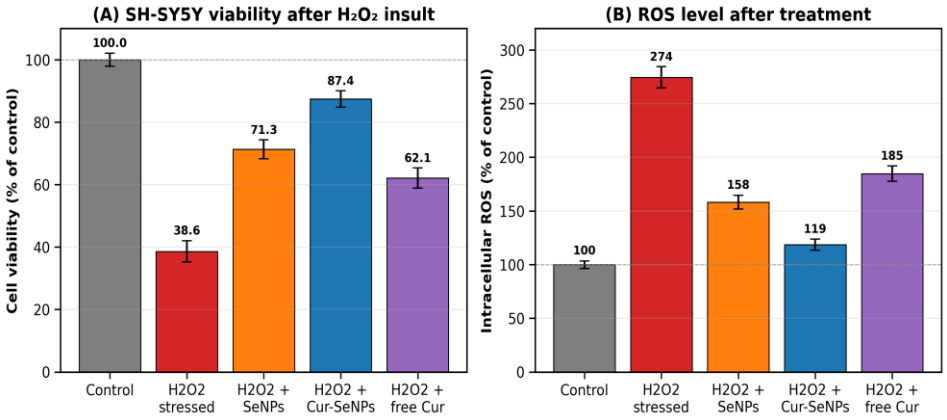

Figure 5. (A) Cell viability and (B) intracellular ROS of SH-SY5Y cells subjected to oxidative insult and protected by SeNPs, Cur-SeNPs or free curcumin (mean ± SD, n = 3).

Table 2. Neuroprotective and biochemical activities of test formulations.

Treatment (50 µg/mL)	Viability (%)	ROS (% control)	DPPH IC_{50} (µg/mL)	AChE IC_{50} (µg/mL)
Control (no H_2O_2)	100.0 ± 2.1	100.0 ± 3.5	—	—
H_2O_2 alone	38.6 ± 3.4	274.5 ± 9.8	—	—
H_2O_2 + free curcumin	62.1 ± 3.2	184.7 ± 7.2	38.5 ± 1.7	31.6 ± 1.8
H_2O_2 + SeNPs	71.3 ± 3.0	158.2 ± 6.4	56.8 ± 2.2	51.4 ± 2.1
H_2O_2 + Cur-SeNPs	87.4 ± 2.6	118.6 ± 5.1	41.6 ± 1.9	24.8 ± 1.5
Reference standard	—	—	28.4 (Asc. acid)	13.7 (donepezil)

4. DISCUSSION:

The present study demonstrates a simple, sustainable and effective strategy for the synthesis of curcumin-loaded selenium nanoparticles using *Ocimum sanctum* leaf extract. The colour change to brick-red and the SPR peak at 268 nm are characteristic of nano-Se^0 and are in close agreement with the values of 265–275 nm reported by Cittrarasu et al. [37] and Anu et al. [30] for plant-mediated SeNPs. The shift of the FTIR carbonyl band from 1654 to 1640 cm^{-1} confirms that polyphenolic carbonyls of the extract donate electrons to selenite while simultaneously chelating the resulting Se^0 surface. Eugenol, rosmarinic acid and ursolic acid – major constituents of Tulsi – are well known electron donors and capping agents [25,26].

The mean TEM size of 58 nm and a moderately negative zeta potential of −28.4 mV indicate excellent colloidal stability through electrostatic repulsion, and a size range below 100 nm is considered favourable for crossing the BBB by receptor-mediated transcytosis [11,18]. The slight increase in hydrodynamic diameter and the modest reduction in zeta-potential magnitude after curcumin loading are consistent with surface adsorption of the lipophilic polyphenol. The encapsulation efficiency of 78.6 % is comparable to or higher than reported values for curcumin-loaded chitosan, PLGA or albumin nanoparticles [27,28].

Sustained, biphasic release of curcumin from Cur-SeNPs is consistent with diffusion-controlled mechanisms in matrix-type carriers. The accelerated release at pH 5.0 is therapeutically advantageous because oxidatively-stressed neurons and endolysosomal compartments adopt slightly acidic pH, allowing site-specific release of the cargo [12]. A Korsmeyer–Peppas exponent close to 0.45 indicates a Fickian-diffusion mechanism, confirming that curcumin is loaded primarily on the SeNP surface and within the porous capping layer rather than tightly chemically bound.

The marked antioxidant activity of Cur-SeNPs (DPPH IC_{50} 41.6 µg/mL) reflects two complementary mechanisms: (i) the inherent free-radical scavenging of zero-valent selenium, which mimics glutathione peroxidase by donating electrons to ROS and being recycled in vivo through selenoproteins [15,38]; and (ii) the well-established radical-quenching activity of curcumin, whose β-diketone moiety and phenolic hydroxyl groups donate hydrogen atoms to peroxyl radicals [27]. Importantly, Cur-SeNPs also outperformed plain SeNPs in AChE inhibition. This is in line with the work of Wang and colleagues, who showed that

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curcumin and Se-containing systems synergistically modulate the cholinergic deficit in AD models [17].

In SH-SY5Y cells, Cur-SeNPs preserved viability and dramatically attenuated H_2O_2-induced ROS, outperforming free curcumin even though molar curcumin equivalents were lower in the nanoformulation. This is explicable by the much greater cellular uptake and intracellular stability of nano-formulated curcumin and by the intrinsic selenoprotein-mimicking activity of nano-Se [13,14]. The synergistic neuroprotection observed here is also reminiscent of recent reports demonstrating that SeNPs functionalised with sialic acid, transferrin or polyphenols rescue neurons from amyloid-β toxicity in vitro and in vivo [18,29].

From a translational perspective, the absence of toxic chemical reductants, the sub-100 nm size, the negative surface charge and the dual antioxidant–AChE-inhibitory activity make this platform attractive for chronic CNS therapy. Limitations of the present work include the absence of in-vivo pharmacokinetic, BBB-permeability and behavioural studies, and the use of a single neuronal cell model. Future research should explore surface functionalisation with BBB-targeting ligands, evaluate efficacy in transgenic AD/PD animal models, and assess long-term biodistribution and clearance.

Mechanistically, the protection observed against H_2O_2-induced injury can be ascribed to a coordinated cascade of effects. First, the lipophilic curcumin payload partitions into neuronal membranes and quenches lipid peroxyl radicals before they can propagate, while the SeNP core supplies a reservoir of bioavailable selenium that is incorporated into glutathione peroxidase, thioredoxin reductase and selenoprotein P, restoring endogenous antioxidant defences [15,16,32]. Second, downstream of ROS attenuation, mitochondrial membrane potential is preserved and the intrinsic apoptotic pathway is dampened, as previously demonstrated for similar selenium nanocarriers [13,17]. Third, AChE inhibition prolongs synaptic acetylcholine availability, an effect of direct relevance to the cholinergic deficit characteristic of AD [3,17]. Together, these complementary actions create a multi-target neuroprotective profile that single-target small molecules struggle to achieve.

Comparison with the wider literature is encouraging. Yin et al. demonstrated that B6-peptide-functionalised SeNPs cross the BBB and reduce amyloid burden in transgenic AD mice, while Wang et al. reported that EGCG-coated SeNPs ameliorate ischaemia–reperfusion injury through ROS scavenging [17,18]. Our Cur-SeNPs occupy a comparable size and surface-charge regime, suggesting that the platform reported here is amenable to further surface engineering with brain-targeting ligands such as transferrin, lactoferrin or RVG-29 peptide. Scalability is another asset: the synthesis described uses inexpensive, locally sourced plant material and ambient-pressure conditions, supporting downstream good-manufacturing-practice translation.

5. Conclusion

Selenium nanoparticles were successfully bio-synthesised using a green, single-step protocol with *Ocimum sanctum* leaf extract acting as both reducing and capping agent. The resulting SeNPs were spherical, sub-100 nm in size and colloidally stable, and they readily accommodated curcumin with high encapsulation efficiency. Cur-SeNPs displayed sustained, pH-responsive drug release, robust antioxidant activity, significant AChE inhibition and pronounced neuroprotection against oxidative stress in SH-SY5Y cells, outperforming free curcumin and plain SeNPs. These findings support plant-mediated SeNPs as a promising, eco-friendly nanocarrier platform for the delivery of neuroprotective phytochemicals in neurodegenerative disorders, and warrant further pre-clinical evaluation in vivo.

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