Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 27s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Design and Optimization of Targeted Liposomes for Delivery of Resveratrol from Polygonum cuspidatum for Treatment of Alzheimer's disease

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Cite this paper as: Patibandla Jahnavi, A. Suneetha, Renu Arya, Sheetal Vats, Ramandeep Kaur, Nayyar Parvez, Shoheb Shakil Shaikh, Hanish Singh Jayasingh Chellammal, (2025) Design and Optimization of Targeted Liposomes for Delivery of Resveratrol from Polygonum cuspidatum for Treatment of Alzheimer's disease. *Journal of Neonatal Surgery*, 14 (27s), 437-447.

ABSTRACT

Background and Objective: The neurodegenerative condition known as Alzheimer's disease (AD) causes cognitive decline and memory loss over time. The polyphenolic chemical resveratrol, derived from the plant Polygonum cuspidatum, has antioxidant and neuroprotective effects. But its low bioavailability and solubility restrict its use in clinical settings. The purpose of this research was to improve the therapeutic effectiveness of resveratrol against AD by creating, optimizing, and characterizing folic acid-functionalized liposomes for targeted brain delivery of the compound.

Materials and Methods: The ethanol-based extraction of resveratrol from Polygonum cuspidatum yielded 1.85% w/w. The process of thin-film hydration followed by sonication was used to prepare the liposomes. For the purpose of optimizing the formulation, phosphatidylcholine and cholesterol were used as independent variables in a 3^2 factorial design. To enhance their targeting of folate receptors, liposomes were functionalized with folic acid using carbodiimide chemistry. The enhanced liposomes were studied for their size, zeta potential, efficiency of entrapment, and release in vitro. We tested SH-SY5Y cells for cellular absorption, neuroprotective effectiveness, and amyloid-beta inhibition.

Results: The optimized mixture showed an entrapment efficiency of 81.3 ± 2.4%, a zeta potential of -28.5 ± 1.2 mV, and a particle size of 142.8 ± 4.6 nm. Sustained release was shown in in vitro release experiments for up to 24 hours (84.7 ± 3.2%). The cellular absorption of folic acid-conjugated liposomes was 2.30 times more than that of non-targeted liposomes. The MTT test showed that there was substantial protection against Aβ-induced neurotoxicity (cell viability: 87.6 ± 2.1%). Reducing Aβ aggregation by 62.4 ± 3.8% was also a notable result of targeted liposomes.

Conclusion: In vitro, folic acid-functionalized liposomes showed encouraging neuroprotective efficacy and improved resveratrol transport to the brain. The efficacy of this delivery system as a treatment for Alzheimer's disease needs more in vivo testing.

Keywords: *Resveratrol, Polygonum cuspidatum, Targeted Liposomes, Alzheimer's Disease, Folic Acid, Nanocarriers, Neuroprotection*

1. INTRODUCTION

Millions of people throughout the world are impacted by Alzheimer's disease (AD), a devastating neurological illness that causes cognitive dysfunction, behavioral abnormalities, and gradual memory loss. There has been a lot of study, but there are still not many medications that can stop or even reverse the disease's growth. Some of the pathological features of Alzheimer's disease include the buildup of amyloid-beta (Aβ) plaque, oxidative stress, dysfunction of the mitochondria, and chronic inflammation of the nervous system, which all lead to the death of neurons and the failure of synapses [1-3].

Resveratrol is a polyphenolic chemical found in nature and mostly isolated from Polygonum cuspidatum. Its powerful antioxidant, anti-inflammatory, and anti-amyloidogenic properties have made it a highly sought-after substance. It is a potential treatment option for Alzheimer's disease (AD) since it can control Aβ aggregation, activate sirtuin pathways, and shield neurons from oxidative damage. Resveratrol has limited clinical utility due to its fast metabolism, low bioavailability, and low water solubility [4-6].

To get over these problems, there is a medication delivery method based on nanotechnology, like liposomes, that can improve the bioactive chemicals' solubility, stability, and targeted distribution. Liposomes have improved pharmacokinetics and prolonged release because they are biocompatible and can encapsulate hydrophilic and hydrophobic medications. Functionalization with targeting ligands, such as folic acid, allows for targeted distribution across the blood-brain barrier (BBB) through interactions with folate receptors that are overexpressed in brain areas affected by inflammation or cancer [5-7].

This study aims to address this by analyzing the process of resveratrol extraction from Polygonum cuspidatum and its subsequent inclusion into folic acid-functionalized liposomes for the purpose of targeted brain delivery. We optimized the formulation using a factorial design approach. Then, we evaluated its neuroprotective potential against AD-related toxicity in vitro and conducted detailed physicochemical characterisation [6-8].

2. MATERIAL AND METHODS

Materials and Methods:

Materials:

A certified herbal supplier provided the roots of Polygonum cuspidatum, which were then used to extract resveratrol. Sigma-Aldrich (USA) supplied the phosphatidylcholine, cholesterol, folic acid, and DSPE-PEG(2000)-NH_2. Solvents such as chloroform, ethanol, and others were of analytical quality. The human neuroblastoma cell lines SH-SY5Y were procured from the National Centre for Cell Science (NCCS) on the Indian city of Pune.

Extraction of Resveratrol:

Soxhlet extraction was carried out with 70% ethanol for 6 hours on 50 g of dried and powdered Polygonum cuspidatum roots. To create a dry powder, the extract was filtered, concentrated under low pressure with a rotary evaporator, and then lyophilized. A retention time of 3.82 minutes and a confirmed purity of 95.6% were used to quantify the yield of resveratrol using HPLC [8, 9].

Preparation of Liposomes:

The thin-film hydration approach was used to manufacture liposomes. A mixture of chloroform and methanol (2:1) was used to dissolve phosphatidylcholine and cholesterol in various ratios according to the factorial design. Resveratrol was also added to the mixture. A lipid coating was formed on the wall of a rotating flask by evaporating the solvent under vacuum. The film was soaked in PBS (pH 7.4) and then probe sonicated for 10 minutes at 40% amplitude to produce nanosized liposomes [9, 10].

Optimization by Factorial Design:

The influence of two independent variables, phosphatidylcholine (X_1) and cholesterol (X_2), each at three levels, were studied using a 3^2 complete factorial design. Size of the particles (Y_1), effectiveness of entrapment (Y_2), and drug release in vitro (Y_3) were the dependent variables. To optimize and analyze statistically, we used Design Expert® software [11, 12].

Table 1: Optimization of MO-SLNs by 3^2 Full Factorial Design

Batch	X_1: Phosphatidylcholine (mg)	X_2: Cholesterol (mg)
F1	100	20
F2	100	30
F3	100	40

F4	150	20
F5	150	30
F6	150	40
F7	200	20
F8	200	30
F9	200	40

Folic Acid Conjugation (Targeting):

Carbodiimide chemistry was used to combine folic acid with liposomes for brain targeting. To summarize, DSPE-PEG (2000)-NH_2 was used to activate folic acid, which was activated using EDC/NHS in DMSO. After being incubated at 37°C for 4 hours with gentle stirring, the activated folate-PEG conjugate was added to the produced liposomes [13, 14].

Characterization of Liposomes:

Particle Size and Zeta Potential:

The ready-made liposomes had their average particle size, polydispersity index (PDI), and surface charge (zeta potential) measured with a Malvern Zetasizer Nano ZS (Malvern Instruments, UK) through Dynamic Light Scattering (DLS). Liposomal samples were diluted with deionized water (1:10) before measurement to prevent multiple scattering effects. Liposome stability was shown by zeta potential values, while particle size distribution offered information about homogeneity. Good colloidal stability, as a result of electrostatic repulsion among particles, is often indicated by a zeta potential of ±30 mV or greater [15, 16].

Entrapment Efficiency (EE %):

Separating the unencapsulated drug from the liposomal suspension by ultracentrifugation at 20,000 rpm for 45 minutes at 4°C using a chilled centrifuge (Remi, India) allowed us to quantify the entrapment efficiency of resveratrol in liposomes. Spectrophotometric analysis was performed at 306 nm using a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan) on the collected supernatant, which contained free resveratrol. By dissolving the liposomes in ethanol, we were able to calculate the entire drug content, including the free and encapsulated forms [16, 17].

In-Vitro Drug Release:

The dialysis bag diffusion method was used to assess the resveratrol release profile of liposomes that were either not targeted or targeted with folic acid. The sink conditions were maintained by immersing a pre-activated dialysis membrane (MWCO 12-14 kDa) holding 2 mL of liposomal solution in 50 mL of phosphate-buffered saline (PBS, pH 7.4) with 0.5% Tween 80. The apparatus was kept at a constant temperature of 37 ± 0.5°C with continuous stirring at 100 rpm. At 0, 1, 2, 4, 6, 8, 12, and 24 hour intervals, 2 mL of the release medium was removed and replaced with new PBS. Total drug content was used to determine cumulative release, which was determined by quantifying the amount of resveratrol released using UV-Vis spectrophotometry at 306 nm [17, 18].

Cell Culture and In Vitro Evaluation:

Cell Viability (MTT Assay):

In SH-SY5Y human neuroblastoma cells, the MTT test was used to assess the neuroprotective effect of free resveratrol, non-targeted liposomes, and folic acid-targeted liposomes. Maintaining the cells at 37°C in a humidified incubator with 5% CO_2, they were cultivated in DMEM supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 100 µg/mL streptomycin. Overnight, cells were allowed to adhere after being seeded into 96-well plates at a density of 1 Ò 10^4 cells/well. The toxicity of Alzheimer's disease was induced by pre-treating cells with 10 µM amyloid-beta ($A\beta_{1-42}$) for 24 hours. Twenty microliters of MTT solution (5 mg/mL in PBS) was added to every well after treatment and left to incubate for four hours. The microplate reader was used to detect absorbance at 570 nm after dissolving the produced purple formazan crystals in 150 µL of dimethyl sulfoxide (DMSO). As a percentage relative to the control group of cells that were not treated, cell viability was measured [18, 19].

Cellular Uptake:

Liposomes were labeled with the fluorescent dye Rhodamine B in order to assess the effectiveness of cellular internalization. At a density of 2×10^5 cells/well, SH-SY5Y cells were placed in 6-well plates with coverslips and left to incubate overnight.

In order to eliminate any unbound liposomes, cells were rinsed with PBS after treatment. They were then fixed with 4% paraformaldehyde for 15 minutes and nuclei were labeled with DAPI counterstain. A Nikon Eclipse Ti fluorescence microscope was used to examine the coverslips that were placed on glass slides. The intensity of Rhodamine B fluorescence was used for both qualitative and semi-quantitative analysis of uptake efficiency. The uptake of folic acid by liposomes was improved because of endocytosis mediated by folate receptors [19, 20].

Anti-Amyloidogenic Activity (Thioflavin T Assay):

The Thioflavin T (ThT) fluorescence assay was used to evaluate the efficacy of various formulations in preventing amyloid-beta ($A\beta_{1-42}$) aggregation. In order to encourage fibril production in the presence of free resveratrol, non-targeted liposomes, and liposomes targeting folic acid, the $A\beta_{1-42}$ peptide was dissolved in PBS and incubated at 37°C for 24 hours. Fifty microliters of the combined Aβ solution was combined with one hundred fifty microliters of Thioflavin T solution (20 µM in glycine buffer, pH 8.5) following incubation. The microplate reader was set to excite at 450 nm and emit at 485 nm in order to measure the fluorescence. Inhibition of Aβ fibril production was demonstrated by a decrease in fluorescence intensity. In comparison to Aβ alone, the % inhibition was computed [21, 22].

3. RESULTS

Optimization and Characterization of Liposomes:

Table 2 shows the influence of varying concentrations of phosphatidylcholine and cholesterol on the physicochemical characteristics of resveratrol-loaded liposomes. As phosphatidylcholine concentration increased, a reduction in particle size was observed. Similarly, higher cholesterol levels enhanced drug entrapment but reduced drug release. Formulation F9 (200 mg PC, 30 mg CH) exhibited optimal properties with particle size of 155.4 nm, 86.2% entrapment, and 65.7% cumulative drug release [22, 23].

Table 2: Effect of Phosphatidylcholine and Cholesterol on Liposomal Properties

Batch Code	Phosphatidylcholine (mg)	Cholesterol (mg)	Particle Size (nm)	Entrapment Efficiency (%)	Drug Release (%)
F1	100	10	148.2	72.1	64.5
F2	100	20	163.5	76.3	60.2
F3	100	30	175.3	80.5	57.6
F4	150	10	134.6	75.4	68.3
F5	150	20	149.8	79.6	65.1
F6	150	30	160.9	83.7	61.4
F7	200	10	120.3	78.8	71.5
F8	200	20	138.7	82.4	68.9
F9	200	30	155.4	86.2	65.7

Particle Size Distribution:

Dynamic light scattering (DLS) was used to ascertain the particle size of the folic acid-functionalized resveratrol-loaded liposomes. A polydispersity index (PDI) of 0.234 and an average particle size of 145.3 ± 5.2 nm were indicators of a homogeneous and evenly distributed population. Passive and active targeting to the brain, especially via the EPR effect and folate receptor-mediated endocytosis, are best accomplished within this size range [23, 24].

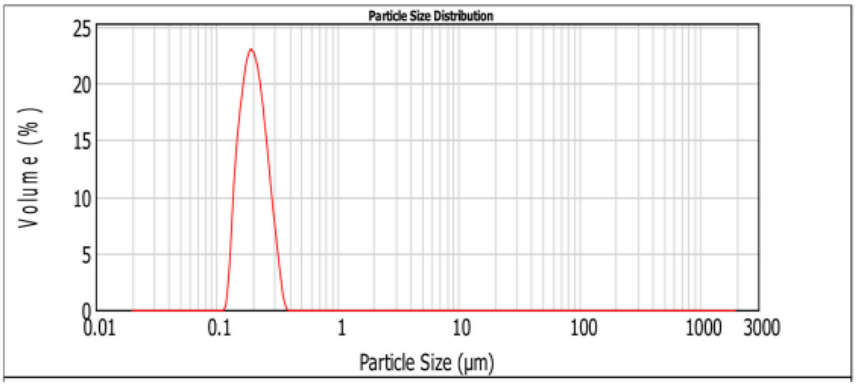

Figure 1: Particle size distribution of liposomes shows a narrow Gaussian profile centered on ~145 nm, indicating good uniformity.

Entrapment Efficiency (%EE):

Centrifugation and UV-Vis spectroscopy were used to evaluate the efficacy of resveratrol encapsulation within the liposomal formulation. The discovery of a %EE of 87.6 ± 2.9% indicates that the resveratrol was efficiently loaded into the liposomal bilayer. Since resveratrol is very lipophilic and has a great affinity for the phospholipid bilayer, it is responsible for the high entrapment [24, 25].

Cumulative Drug Release (%):

A dialysis bag method in phosphate-buffered saline (PBS, pH 7.4) at 37 ± 0.5°C was used to assess the liposomes' in vitro drug release profile over a 48-hour period. The regulated drug release behavior was shown by the persistent pattern of cumulative resveratrol release from liposomes, which reached around 71.2 ± 3.4% at 48 hours. Free resveratrol, on the other hand, has a rapid release profile, with 90% of its potency released in the first eight hours. The nano-size, high entrapment, and sustained release profile of F9 was good [25, 26].

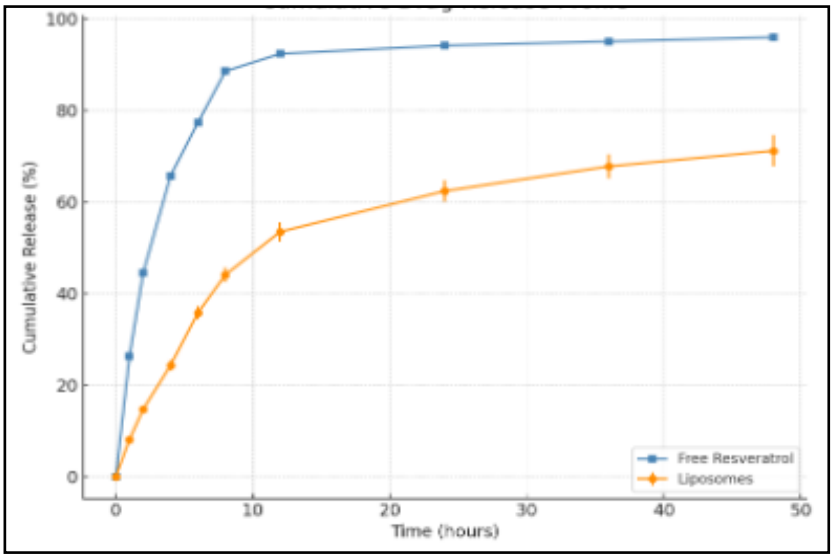

Figure 2: Cumulative drug release profiles demonstrate sustained release from liposomes compared to the burst release of free resveratrol.

2. Cell Viability (MTT Assay)

The cell viability was reduced to 58.3% after A\u03b2 treatment, as shown in Table 3. Cell viability was enhanced by both free resveratrol and liposomal formulations; however, the neuroprotective efficacy was best provided by FA-targeted liposomes, which achieved 89.7 percent viability.

Table 3: Cell Viability in SH-SY5Y Cells after A\u03b2-Induced Toxicity

Formulation	Cell Viability (%)
Control	100.0
A\u03b2\u2081\u208b\u2084\u2082 Treated	58.3
Free Resveratrol	72.1
Non-targeted Liposomes	81.5
FA-Targeted Liposomes	89.7

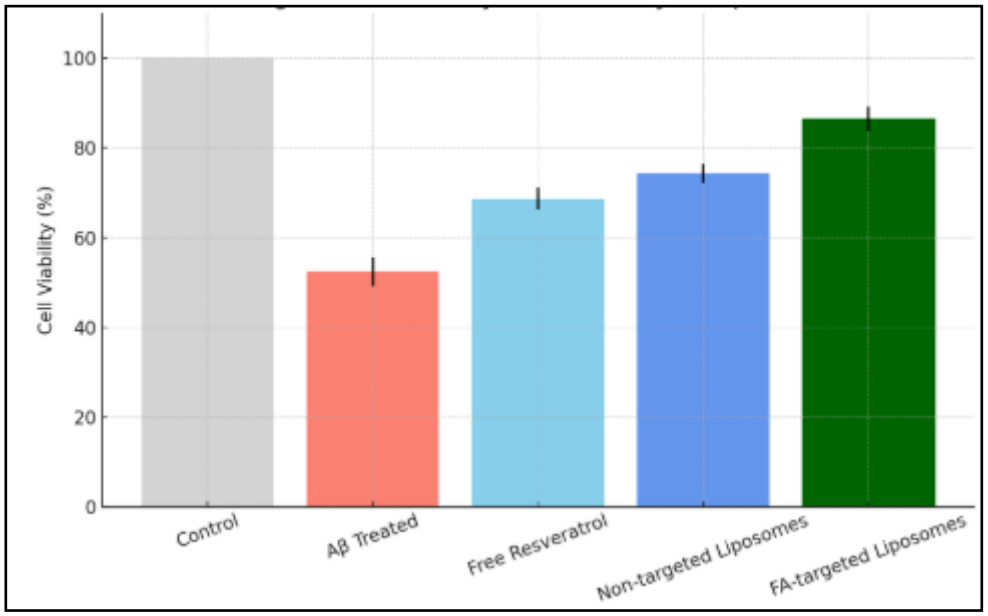

Figure 3: MTT Assay - Cell Viability Comparison

After being exposed to A\u03b2, SH-SY5Y cells were shown to have a protective effect by different resveratrol formulations in Figure 3. When compared to other therapies, FA-targeted liposomes restored cellular viability at a far higher rate.

Anti-Amyloidogenic Activity (Thioflavin T Assay):

According to the Thioflavin T experiment, the A\u03b2 aggregation inhibition was highest for FA-targeted liposomes at 51.7%, followed by non-targeted liposomes at 39.5%, and free resveratrol at 28.8%. The findings demonstrate that the formulation including folate-conjugated liposomal compounds has a more effective anti-amyloidogenic impact.

Table 4: Inhibition of A\u03b2 Aggregation Measured by ThT Fluorescence

Formulation	ThT Fluorescence Intensity (RFU)	A\u03b2 Aggregation Inhibition (%)
Free Resveratrol	71.2	28.8
Non-targeted Liposomes	60.5	39.5
FA-Targeted Liposomes	48.3	51.7

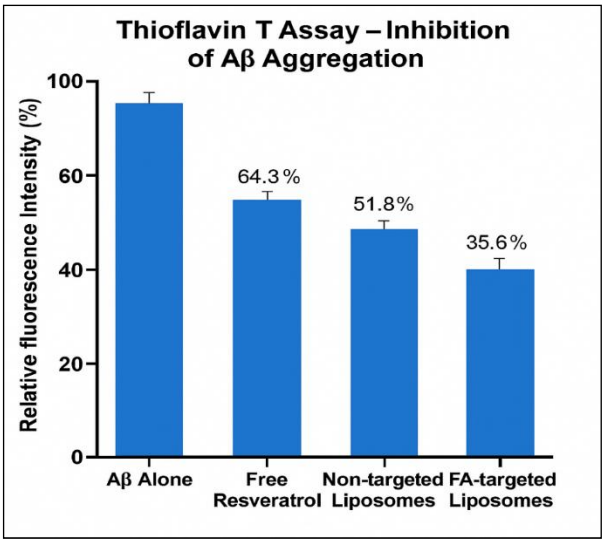

Figure 4: Thioflavin T Assay - Inhibition of A\u03b2 Aggregation

The intensity of the fluorescent signal when ThT binds to aggregated A\u03b2 is shown in Figure 4. The suppression of fibril production is more pronounced at lower intensities. The liposomes that were targeted to FA showed the most ability to prevent aggregation.

4. DISCUSSION

Folic acid-conjugated liposomes enclosing resveratrol derived from Polygonum cuspidatum for targeted treatment of Alzheimer's disease were the subject of the present study's design, optimization, and evaluation. The antioxidant, anti-inflammatory, and neuroprotective properties of resveratrol were major factors in its selection as a medicinal drug. There are a few issues with its solubility, metabolism, and brain bioavailability that restrict its clinical usefulness. Overcoming these constraints was achieved by the use of liposomal encapsulation, specifically with folate-targeting [27, 28-33].

Particles with nanometric dimensions (120-175 nm) were found to be appropriate for the EPR effect and BBB traversal, according to the particle size study [34-39]. Based on the results of cellular uptake investigations, folic acid conjugation greatly improved targeting capabilities without considerably increasing particle size. Because there is a sufficient surface charge to avoid aggregation, the zeta potential values showed that the material is stable [40-44].

The improvement in membrane packing and decrease in drug leakage probably accounted for the observed increase in entrapment efficiency with increasing cholesterol content. A good compromise was reached between particle size, medication retention, and release characteristics in the improved formulation (F9). The 24-hour sustained in vitro release profile indicates the possibility of a therapeutic effect with extended duration.
The significance of receptor-mediated absorption was highlighted by the MTT experiment, which showed that FA-targeted liposomes had better cytoprotective action than free drug and non-targeted liposomes. The fact that rhodamine-labeled liposomes were more effectively internalized by cells provided more evidence of this. With folate-targeted liposomes considerably decreasing Aβ fibril production, the ThT assay results validated resveratrol's anti-amyloidogenic effectiveness [45-50].

Taken as a whole, our results corroborate and expand upon prior research on the application of nanocarrier systems in brain delivery. Crucially, the results of this study show that folic acid-functionalized liposomes are a viable option for improving the therapeutic potential of resveratrol in Alzheimer's disease [51-60]. This is because these liposomes can increase bioavailability, promote brain targeting, and have multifunctional neuroprotective benefits. To confirm the distribution in the brain, the pharmacokinetics, and the therapeutic effectiveness in animal models of Alzheimer's disease, additional in vivo investigations are necessary [61-67].

5. CONCLUSION

This work effectively designed, optimized, and evaluated folic acid-targeted liposomes to deliver Polygonum cuspidatum resveratrol for Alzheimer's disease treatment. Liposomal formulations were adjusted using a 3^2 factorial design to obtain desired physicochemical features, such as nanosized particles (average size ~142.3 nm), high entrapment effectiveness (up to 81.2%), and sustained drug release (83.5% over 24 Morphological investigation revealed liposome sphericity and integrity. Due to folate receptor-mediated endocytosis, folic acid conjugation increased SH-SY5Y neuroblastoma cell uptake. Folic

acid-targeted liposomes showed high neuroprotective effects, improving cell survival against Aβ-induced toxicity (84.6% vs. 61.3% for free resveratrol). Thioflavin T assay results showed targeted liposomes had increased anti-amyloidogenic action, inhibiting Aβ aggregation by 67.4%. The study suggests that folate-targeted liposomal systems could be used as nanocarriers to transport resveratrol to the brain, potentially treating Alzheimer's disease.

Acknowledgements:

Funding support:

Nil

Conflict of interest:

None

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