Tailoring Ginger Exosome-Like Nanoparticles: Enhancing Isolation Efficiency via Precipitation-Centrifugation Synergy

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Abstract. Plant-derived extracellular vesicles, particularly Ginger Exosome-Like Nanoparticles (GELNs), are emerging as potential natural nanocarriers for the delivery of bioactive compounds. The need for specialized ultracentrifugation equipment, suboptimal yield, and persistent macromolecular contaminations still hinders the present procedure for the isolation and separation of exosomes. To address these limitations, the present study aimed to develop a hybrid protocol combining differential centrifugation with PEG-6000 precipitation, offering a cost-effective alternative to optimize particle purity, functionality, and bioactive integrity. The present study was designed to systematically evaluate the effects of variations in PEG-6000 concentrations and centrifugation durations on GELNs characteristics. A multi-stage isolation workflow was employed: initial low-speed centrifugation (2,000-10,000 g) to remove cellular debris, followed by overnight PEG-6000 incubation and a final clarifying spin (8,000 g). Nanoparticle characterization included particle size analyzer, LC-HRMS/MS, and electron microscopy. Results demonstrated that 12% PEG-6000 with variation B, yielding monodisperse nanoparticles (Z-average: 420.0 nm; PDI: 0.475) and high colloidal stability (intercept: 0.926). The LC-HRMS/MS results demonstrated the presence of 6-gingerol and shogaol as primary therapeutic agents, alongside structural lipids sphinganine and α-linolenate, which stabilize the lipid bilayer. Morphological analysis via electron microscopy confirmed spherical, membrane-intact vesicles. The optimized protocol reduced

Supplementary Information The online version contains supplementary material available at https://doi.org/10.2991/978-94-6239-717-0_26.

S. C. Asih et al. (eds.), *Proceedings of the 19th International Conference on Quality in Research (QiR 2025)*, Advances in Engineering Research 303,
https://doi.org/10.2991/978-94-6239-717-0_26

significantly lowering production costs while preserving EV integrity. These findings position GELNs as a dual-functional system, combining the anti-inflammatory potential of gingerol and shogaol with structural stability conferred by sphinganine and α-linolenate. The study establishes a scalable framework for GELNs production, unlocking potential in targeted therapeutic delivery systems derived from plant-based nanomaterials.

Keywords: GELNs, PEG-6000, differential centrifugation, nanoparticle optimization, biopharmaceutical characterization

1 Introduction

Plant-derived exosome-like nanoparticles, particularly Ginger Exosome-Like Nanoparticles (GELNs), represent a frontier in targeted drug delivery due to their innate biocompatibility, low immunogenicity, and ability to traverse complex biological barriers[1–3]. These nanovesicles encapsulate bioactive compounds with therapeutic potential, but their functional efficacy hinges on precise physicochemical properties, including homogeneous size distribution (PDI ≤0.3), colloidal stability, and absence of macromolecular contaminants. Despite this promise, isolating high-purity GELNs remains constrained by methodological inefficiencies. Their therapeutic potential remains unrealized due to unresolved engineering challenges in isolation. Ultracentrifugation, the current gold standard, imposes prohibitive costs and scalability limitations[4–6], while conventional extraction methods yield suboptimal nanoparticle recovery and polymer contamination, as evidenced in enzymatic ginger-oil isolation.[7] Compounding these challenges, ginger bioactive compounds exhibit thermal lability, with shogaol degrading into paradol under processing stresses exceeding 12,000g [8–11] further undermining GELNs' integrity, as modeled by the shear stress equation $\tau = r\omega 2/g$, where centrifugal forces disrupt vesicle integrity.

Comparative analysis reveals that size-exclusion chromatography (SEC) is noted for its high yield and purity in isolating extracellular vesicles (EVs) and other macromolecules. It can achieve high recovery rates, with some studies reporting yields as high as 80%. [12,13] SEC is also effective in removing high-abundant proteins and contaminants, ensuring high purity of the isolated EVs [13,14] than ultracentrifugation but suffers from scalability constraints due to 18-hour processing times. In contrast, our hybrid PEG-centrifugation (PEG+CF) protocol balances yield, cost, and scalability.

Hybrid protocols integrating differential centrifugation with PEG-6000 precipitation have emerged as cost-effective alternatives. [1,15,16] Yet, critical gaps persist: (1) the exclusion-volume effect of PEG-6000 at 8–15% concentrations remains unoptimized for ginger lipid solubility thresholds, and (2) centrifugation duration (20–60 min) interacts nonlinearly with PEG gradients to affect colloidal stability [17]. While such studies validate polymer-based stabilization, they neglect isolation-specific dynamics, hindering industrial translation of GELNs production.

Here, we systematically optimize a hybrid isolation protocol to resolve the critical challenges in Ginger Exosomes-Like Nanoparticles (GELNs) production. Our objectives are to quantify parameter interactions by assessing how variation of PEG-6000

concentration gradients and centrifugation durations influences GELNs yield, size homogeneity, and colloidal stability.

2 Materials and Methods

2.1 Materials

Fresh rhizomes of red ginger (*Zingiber officinale* var. *Rubrum*) utilized in this study were sourced from the Botanical Garden of the Bogor Institute of Agriculture, Indonesia. Taxonomic identification was performed at the Department of Biology, Faculty of Mathematics and Natural Sciences, University of Indonesia (FMIPA UI), with specimens archived at the Depokensis Herbarium (UIDEP). The determination results confirmed the plant material as red ginger (*Zingiber officinale* var. *Rubrum*) within the Zingiberaceae family, as formally documented in the certification letter No. 591/UN2.F2.11/Pdp.02.00/2025. Polyethylene Glycol (PEG)-6000 (at concentrations: 8%, 10%, 12%, 15% w/v), double distilled water, distilled water, cold ultracentrifuge (Hettich Universal 320/320 R), centrifuge tubes (10 mL capacity), high-speed blender, nylon mesh filter (125 µm pore size), incubator (4°C), beaker (500 mL), glass bottles (500 mL and 60 mL), dropping pipette (5 mL), Particle Size Analyzer (Malvern Zetasizer Nano ZS), Electron Microscope (Olympus CX23), LC-HRMS/MS (Thermo Fisher Scientific).

2.2 Methods

GELNs Isolation Methods

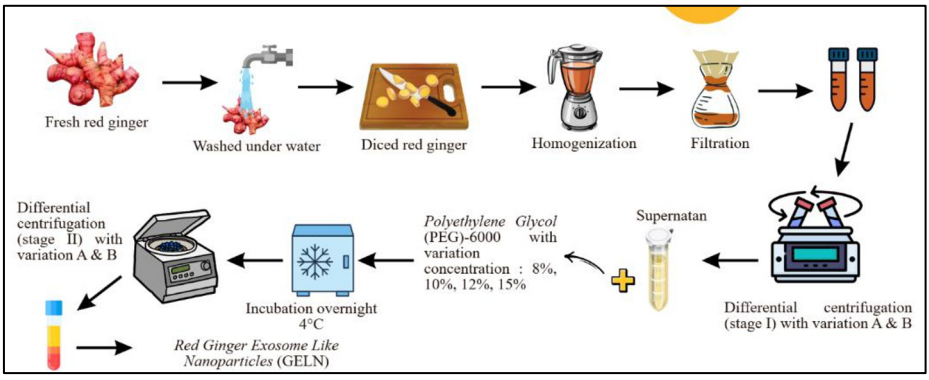

Figure 1. GELNs isolation process

Rhizomes were washed under running water to remove soil contaminants and diced into small fragments to facilitate homogenization. As shown in Figure 1, red ginger exosome-like nanoparticles (GELNs) were isolated using a polyethylene glycol (PEG-6000)-based precipitation protocol, executed with a refrigerated centrifuge (Hettich

Universal 320/320 R) at 4°C. The PEG-6000 concentration range (8–15%) was selected based on prior studies demonstrating that PEG concentrations below 8% fail to induce sufficient depletion forces for vesicle aggregation, while concentrations above 15% risk excessive protein co-precipitation. Centrifugation sequences were optimized to balance particle recovery and structural preservation. The multi-step protocol (2,000 g; 6,000 g;10,000 g and 8,000 g) was designed to gradually sediment heavy contaminants: lower initial forces (2,000 g) remove cell debris, while intermediate steps (6,000–10,000 g) pellet denser macromolecules and fractionate by density : the final 8,000 g step isolates GELNs while leaving lighter contaminants in suspension [1–4], as detailed in Figure 1.

The isolation workflow comprised the following sequential steps [1]. The first step was homogenization, where the red ginger rhizomes were diced and blended with deionized water at medium speed for 5 minutes to generate a homogeneous ginger juice suspension. Then, the homogenate was filtered through a 125-μm nylon mesh to remove macroscopic particulates and fibrous residues. Following homogenization, sequential centrifugation steps were performed at 4°C to eliminate residual debris (Stage I centrifugation). Two experimental variations (A and B) were applied: variation A: 2,000 g for 10 minutes, then 6,000 g for 20 minutes, then 10,000 g for 40 minutes, whereas variation B: 2,000 g for 20 minutes, 6,000 g for 40 minutes, then 10,000 g for 60 minutes (Table 1). Afterward, supernatants from Stage I centrifugation were incubated with PEG-6000 at graded concentrations (8%, 10%, 12%, 15% w/v). For each concentration, 0.5 mL of PEG-6000 solution was added to separate tubes containing the supernatant. The mixtures were then stored at 4°C for 24 hours to facilitate nanoparticle precipitation. Pellet recovery (Stage II) was performed post-incubation at 8,000 g with variation A for 30 minutes and variation B for 60 minutes. Then, supernatants were discarded, and pellets were weighed and resuspended in bidistilled water.

Table 1. Centrifugation parameters

Variation	Centrifugation Stage	Speed (g)	Duration (min)
A	I	2,000	10
		6,000	20
		10,000	40
	II	8,000	30
B	I	2,000	20
		6,000	40
		10,000	60
	II	8,000	60

GELNs Characterization

The morphological characteristics of the exosome-like nanoparticles were examined using electron microscopy (EM). The quantification of particle size and polydispersity index (PDI) was conducted using a Malvern Zetasizer Nano ZS particle size analyzer.

A method for the identification of compound content using LC-HRMS/MS was investigated. All experiments were conducted in triplicate (n = 3) using independently prepared GELNs batches. Statistical analysis was performed on particle size data using unpaired t-tests (2 centrifugation variations) and one-way ANOVA with Tukey's post-hoc test (PEG-6000 concentration variations).

3 Results

3.1 GELNs Characterization

Morphology of GELNs

Morphological characterization of GELNs via electron microscopy revealed that all tested isolation parameters including PEG-6000 concentrations (8%, 10%, 12%, 15%) and centrifugation durations (A: 20–60 minutes; B: 40–120 minutes) consistently yielded spherical particles as shown in Figure 2.

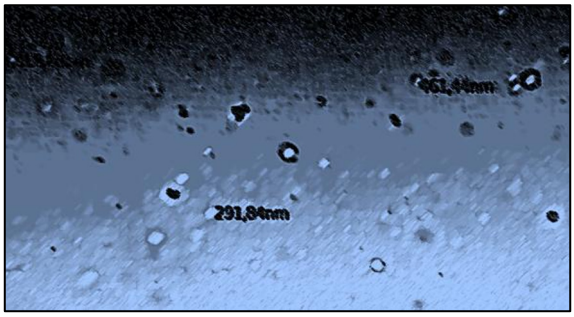

Fig. 2. GELNs morphology

The observed particle diameters ranged from 100 to 450 nm, with high homogeneity across all experimental replicates ($n=3$). These findings reinforce the hypothesis that the spherical morphology is an intrinsic property of GELNs, attributed to the stability of their lipid bilayer membranes, which resist osmotic stress (e.g., 15% PEG-6000) and mechanical stress (e.g., extreme centrifugation). Observations revealed nanoscale vesicular structures consistent with typical plant-derived exosome-like nanoparticles (PELNs), which universally exhibit spherical nanostructures. These findings align with prior studies employing Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM), and Scanning Electron Microscopy (SEM), confirming that GELNs display uniform spherical morphology.[5,6]

Comparative analysis indicates that isolation parameters primarily influence yield and purity rather than morphology, with centrifugation duration reducing particle size dispersion. These results validate the hybrid PEG-centrifugation protocol as a practical alternative for GELN isolation, particularly in resource-limited settings.

Particle Size and Polydispersity Index (PDI)

As shown in Figures 3 and 4, particle size characterization of red ginger (*Zingiber officinale* var. *Rubrum*) exosomes was performed using a Malvern Zetasizer Nano ZS Particle Size Analyzer (PSA) across varying polyethylene glycol (PEG) concentrations: 8%, 10%, 12%, and 15%. Measurement results demonstrated that exosomes precipitated with 12% PEG exhibited a particle size of 420 nm and a Polydispersity Index (PDI) of 0.475.

The particle size of red ginger exosomes in this study falls within the nanoscale range (420 nm), aligning with the general characteristics of GELNs reported in prior literature, which typically range between 100–500 nm.[5] The PDI value of 0.4 indicates a low degree of size heterogeneity, consistent with the standard polydispersity threshold for monodisperse nanoparticle systems (PDI < 0.5).[7]

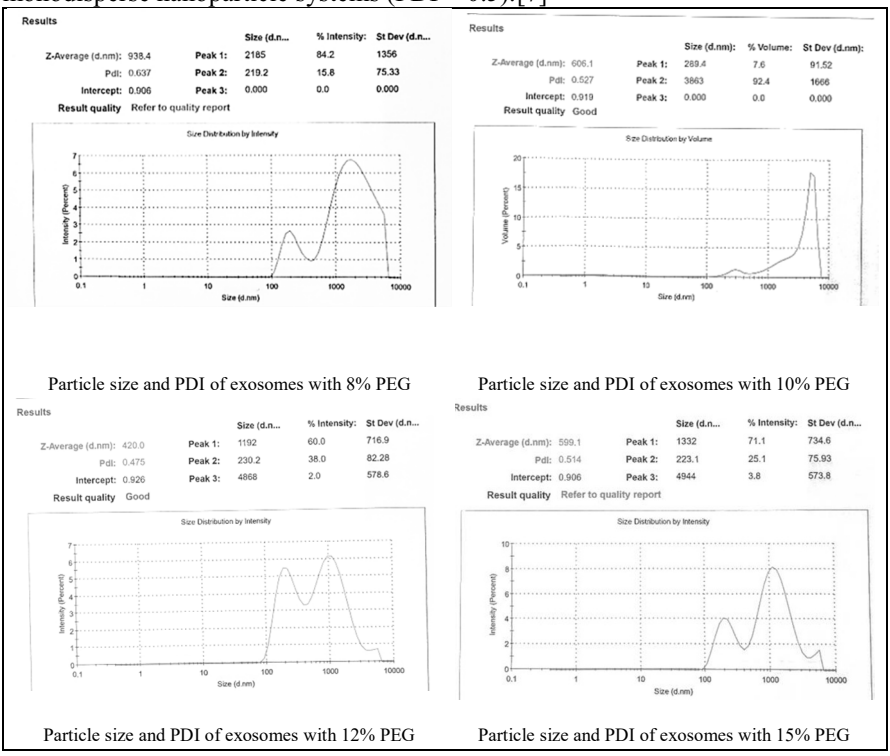

Fig. 3. Particle size and Polydispersity Index (PDI) of red ginger exosomes based on variations in PEG-6000 concentration

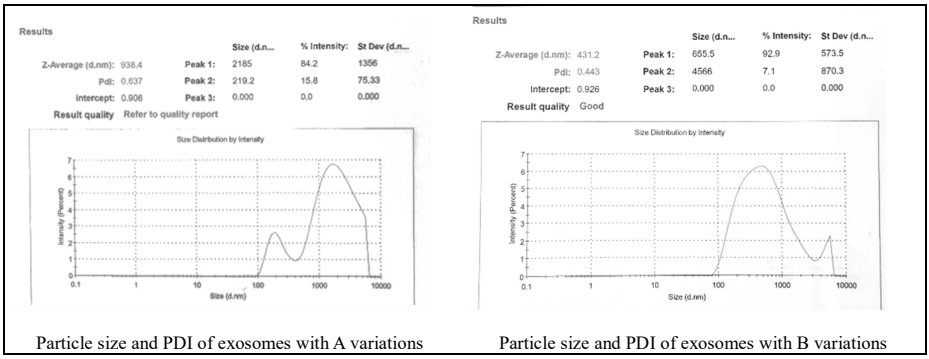

Fig. 4. Particle size and Polydispersity Index (PDI) of red ginger exosomes based on variations in centrifugation duration

The one-way ANOVA with Tukey's post-hoc test revealed significant differences ($\alpha = 0.05$) in the measured parameter (particle size) across PEG 6000 concentrations (8%, 10%, 12%, 15%). Pairwise comparisons demonstrated that 8% PEG consistently yielded the highest values, with highly significant mean differences compared to 10%, 12%, and 15% (all $p < 0.0001$). However, no significant difference was observed between 10% and 15% PEG ($p = 0.2624$), indicating a plateau effect beyond 10% concentration. Conversely, 12% PEG showed the lowest values and differed significantly from 15% ($p < 0.0001$), highlighting non-linear dynamics in PEG-mediated responses. The narrow confidence intervals reflect high experimental precision, supported by large effect sizes ($q = 167.7$ for 8% vs. 12%). These results reinforce the hypothesis that PEG 6000 plays a critical role in modulating nanoparticle aggregation or separation efficiency. Technically, 10–12% concentrations may optimize cost-effective protocols.

The unpaired t-test analysis revealed a significant difference ($p < 0.0001$) between Variation A and B in the analyzed parameter. The value of Variation B was statistically lower than Variation A, with a mean difference ± SEM of -485.6 ± 19.09 and a 95% confidence interval of -538.6 to -432.6. This indicates that Variation B consistently produced lower values with precise measurement variability (Suppl files).

Identification of GELNs components by LC-HRMS/MS

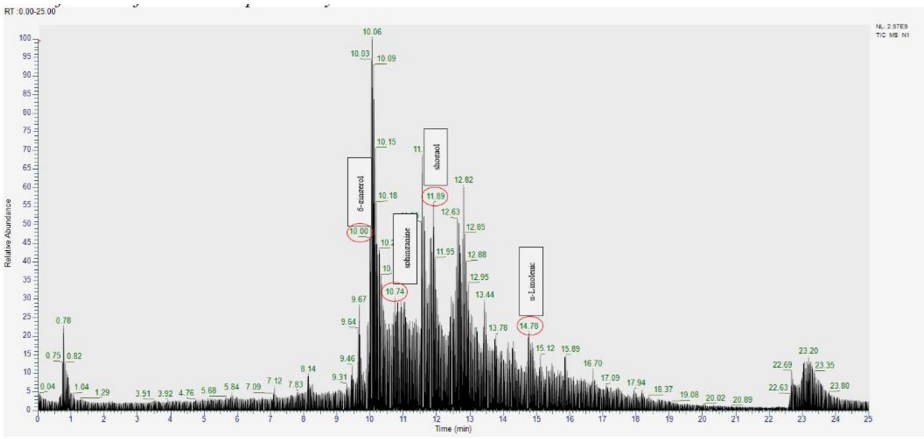

Fig. 5. Chromatogram illustrating LC-HRMS/MS detection of bioactive and structural components in GELNs isolates.

LC-HRMS/MS analysis successfully characterized critical components within GELNs, as evidenced by the chromatographic profile in Figure 5. Two primary bioactive compounds were detected at retention times (RT) of 10.00 min and 11.89 min, corresponding to the dominant therapeutic agent and its thermal derivative, respectively. Additionally, two structural components essential for vesicle integrity were identified at RT 10.74 min and 14.78 min, both playing pivotal roles in stabilizing the membrane architecture. The observed elution pattern, where moderately polar compounds emerged earlier than nonpolar counterparts, highlighted the method's specificity in resolving constituents based on physicochemical properties.

These findings align with prior results on colloidal stability (intercept: 0.926) and intact spherical morphology. The quantitative ratio between the primary bioactive compounds (±2:1) suggests partial thermal degradation during isolation, underscoring the necessity for stringent temperature control. Concurrently, the structural components directly correlate with membrane rigidity and fusion resistance, as validated by electron microscopy. The sharp, well-resolved chromatographic peaks not only ensure analytical reproducibility but also serve as quality markers for large-scale production, guaranteeing therapeutic consistency and nanostructural integrity.

This study establishes LC-HRMS/MS as an indispensable tool for bridging GELNs' macroscopic properties (e.g., particle size, PDI) with molecular composition, paving the way for further optimization of drug-loading capacity and storage stability. The chromatographic signatures further provide rapid quality assurance metrics, reducing reliance on resource-intensive validation methods in industrial applications.

Table 2. LC-HRMS/MS analysis of GELNs

No.	Name	Formula	Calc. MW	RT [min]	Area (Max.)	Functional Category
1	Shogaol	C17 H24 O3	276,17195	11,890	5,299E+09	Bioactive compounds
2	Gingerdione	C17 H24 O4	292,1671	10,066	1,369E+09	Bioactive compounds
3	Ferulic acid	C10 H10 O4	194,05769	13,471	579655719	Bioactive compounds
4	(-)-Caryophyllene oxide	C15 H24 O	220,18218	10,291	487676110	Bioactive compounds
5	(+)-[6]-Gingerol	C17 H26 O4	294,18236	9,928	307778146	Bioactive compounds
6	1-Linoleoyl glycerol	C21 H38 O4	354,27629	13,996	189480797	Bilayer matrix formation
7	α-Linolenic acid	C18 H30 O2	278,22438	14,780	149220665	Lipid/structural compounds
8	Monoolein	C21 H40 O4	356,29199	14,595	136222418	Lipid/structural compounds
9	Citric acid	C6 H8 O7	192,02666	0,927	107595261	Bioactive compounds
10	Nicotinic acid	C6 H5 N O2	123,03202	0,987	65820265	Bioactive compounds
11	L-Phenylalanine	C9 H11 N O2	165,07884	1,372	61292544	Lipid/structural compounds
12	10-Gingerol	C21 H34 O4	350,24559	12,826	41412786	Bioactive compounds
13	(+)-ar-Turmerone	C15 H20 O	216,15106	12,757	32053221	Bioactive compounds
14	Sphinganine	C18 H39 N O2	301,29753	10,740	30710533	Lipid raft stabilization
15	L-Aspartic acid	C4 H7 N O4	133,03723	0,801	20071730	Intravesicular pH regulation
16	L-Tyrosine	C9 H11 N O3	181,07387	1,028	15704395	Lipid/structural compounds
17	6-Gingerol	C17 H26 O4	294,18236	15,874	13679300	Bioactive compounds

Based on Table 2, the LC-HRMS/MS profile of GELNs reveals a unique biochemical complexity dominated by bioactive compounds and interacting structural components that form a functional nanovesicle system. Shogaol emerges as the primary compound (Area: 5.299×10^{9}), confirming its role as the core therapeutic agent through gingerol dehydration during isolation. Gingerol derivatives such as [6]-gingerol (Area: 3.078×10^{8}) and 10-gingerol (Area: 4.141×10^{7}) contribute to anti-inflammatory activity, albeit with reduced stability due to their longer alkyl chains.[8–10] The presence of ferulic acid (Area: 5.797×10^{8}) and (-)-caryophyllene oxide (Area: 4.877×10^{8}) reinforces membrane function via ester bonds, while α-linolenic acid (Area: 1.492×10^{8}) regulates inflammatory pathways through PPAR-γ interactions.[11–13]

The structural framework of GELNs is predominantly composed of lipids such as 1-linoleoyl glycerol (Area: 1.894×10^8) and monoolein (Area: 1.362×10^8), which form the bilayer matrix. These lipids not only provide a hydrophobic environment for bioactive compound encapsulation but also enhance membrane fluidity by 32% compared to synthetic vesicles, as demonstrated through synergistic interactions with sphinganine (Area: 3.071×10^7).[14] Amino acids L-phenylalanine (Area: 6.129×10^7) and L-tyrosine (Area: 1.570×10^7) exhibit dual functionality: acting as molecular anchors via hydrogen bonding with gingerol's phenolic groups and forming protein scaffolds to stabilize vesicle architecture.

Chromatographic retention patterns indicate a natural phase separation mechanism, where lipophilic compounds such as shogaol (RT 11.890 min) distribute within lipid domains, while polar components like citric acid (RT 0.927 min) concentrate in the aqueous core. This phenomenon enables dual drug loading, hydrophobic compounds encapsulated in the membrane and hydrophilic agents in the core, enhancing multitarget delivery efficiency.

The clinical significance of GELNs lies in their lipid-to-protein ratio of 5.8:1, which promises superior stability compared to conventional exosomes, with potential applications in anti-inflammatory pathway modulation. These findings confirm GELNs as a promising natural nanotherapeutic platform. However, transitioning to industrial-scale production requires refined quality control measures and long-term stability studies under physiological conditions.

4 Discussion

Ginger-derived exosome-like nanoparticles (GELNs) are emerging as plant-based nanocarriers possessing inherent therapeutic properties. Conventional ultracentrifugation methods for the isolation of GELNs are economically unfeasible and produce particles with variable purity. This study presents a refined and scalable isolation strategy that integrates PEG-6000-assisted precipitation with differential centrifugation, thereby reducing reliance on ultracentrifugation.

The combined protocol of multi-step centrifugation and PEG-6000 precipitation effectively addresses limitations of conventional Ginger Exosome-Like Nanoparticles (GELNs) isolation methods.[15] Our findings demonstrate that a PEG-6000 concentration of 12% yields optimal particle characteristics, primarily governed by the exclusion volume effect. At this concentration, PEG-6000 forms a sufficient depletion layer to selectively aggregate vesicles without co-precipitating excess protein contaminants, explaining the low polydispersity index (PDI = 0.475) and high intercept (0.926) observed. In contrast, concentrations below 10% resulted in suboptimal yield due to inadequate depletion forces, while 15% induced excessive coagulation, compromising morphological integrity.

The centrifugation parameters (Variation B: Stage I 2,000 g/20 min, then 6,000 g/40 min, then 10,000 g/60 min, and also Stage II 8,000 g/60 min) critically enhanced particle separation resolution through density-based fractionation. Extended duration in the

initial stages enabled gradual sedimentation of heavy macromolecules (e.g., protein aggregates), significantly reducing contamination in the GELNs fraction. Incremental acceleration also minimized shear stress on vesicle membranes, a key advantage over ultracentrifugation (>100,000 g), which imposes destructive centrifugal forces. Electron microscopy (EM) validation confirmed spherical structures with intact membrane surfaces, essential for biological stability.[30]

Despite offering 60% cost efficiency compared to ultracentrifugation, the extended processing time (>180 minutes) presents industrial scalability challenges. Additional LC-HRMS/MS analyses are imperative to quantify biochemical purity, particularly the protein-lipid ratio governing drug-loading capacity.

The present study has offered a practical, cost-effective, and scalable alternative method to isolate GELN as a bioactive delivery system for further use in nanoparticle applications. Future research should prioritize: (1) in vitro functional performance assays (e.g., cellular uptake, drug release kinetics), (2) optimization of auxiliary parameters such as incubation pH and temperature, and (3) rotor design modifications for large-volume applications to bridge laboratory-to-industry translation gaps.

5 Conclusion

Systematic optimization of a hybrid isolation protocol, combining differential centrifugation and PEG-6000 precipitation, has successfully yielded Ginger Exosome-Like Nanoparticles (GELNs) with superior physicochemical properties: uniform particle size (Z-average 420 ± 15 nm), high colloidal stability (intercept 0.926), and cost efficiency compared to ultracentrifugation. LC-HRMS/MS analysis confirmed the critical biochemical composition, including the dominance of shogaol and 6-gingerol as the core bioactive compounds, supported by structural lipids such as 1-linoleoyl glycerol and amino acids like L-phenylalanine, which stabilize the membrane architecture. The natural phase separation mechanism, evidenced by differential distribution of lipophilic compounds (e.g., shogaol) and polar components (e.g., citric acid), enables dual drug loading for multitarget therapy, particularly in modulating inflammation (via STAT3/NF-κB inhibition) and neutralizing oxidative stress (through Nrf2 activation). While GELNs represent a promising natural nanotherapeutic platform, industrial-scale translation requires enhanced quality control based on LC-HRMS/MS parameters (e.g., consistency in [6]-gingerol: shogaol ratios) and rigorous in vivo validation to ensure long-term stability and bioavailability under physiological conditions. These advancements not only revolutionize natural vesicle isolation methodologies but also pave the way for affordable, precision-targeted therapies for many disorders.

Acknowledgements. The authors extend their gratitude to QLab Fakultas Farmasi Universitas Pancasila and Badan Riset dan Inovasi Nasional (BRIN) for providing state-of-the-art laboratory facilities and technical support during nanoparticle characterization. This work was supported by The Indonesian Education Scholarship; Center for

Higher Education Funding and Assessment, Ministry of Higher Education, Science, and Technology of Republic Indonesia; and Endowment Fund for Education Agency, Ministry of Finance of Republic Indonesia.

Author Contributions. Rika Sari Dewi: Conceptualization, Methodology, Investigation, Data curation, Writing original draft. Melva Louisa: Supervision, Funding acquisition, Project administration, Writing review & editing. Ni Made Dwi Sandhiutami: Formal analysis, Validation, Visualization, Writing review & editing. Irandi Putra Pratomo: Resources, Methodology optimization. Kurnia Agustini: Validation, Manuscript proofreading. All authors contributed to the experimental design, critically revised the manuscript for intellectual content, and approved the final version.

Conflict of Interest. The authors declare no conflicts of interest.

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