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Physicochemical Stability and Bio-Functionality of Liposome-Encapsulated Macadamia Husk Phenolic Extract

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Abstract

Macadamia husks are an underutilized by-product of nut processing and a rich source of phenolic compounds with strong antioxidant activity. However, their instability during processing, storage, and gastrointestinal digestion limits their application in food systems. This study aimed to encapsulate macadamia husk phenolic-rich extract (MHPE) in liposomes to improve stability, enable controlled release, and assess cytotoxicity for functional food applications. MHPE was encapsulated in soy lecithin liposomes using high-shear mixing followed by high-pressure homogenisation. Liposomes were characterized by particle size, polydispersity index (PDI), ζ-potential, encapsulation efficiency, and morphology. Cytotoxicity was evaluated using Caco-2 cells, and phenolic release was assessed under simulated gastrointestinal conditions. MHPE-loaded liposomes exhibited nano-sized particles (77–78 nm), low PDI (0.21), and high negative ζ-potential (−43.11 to −47.01 mV) during two months of storage at 4 °C. Transmission electron microscopy confirmed predominantly spherical vesicles with sizes consistent with dynamic light scattering measurements. Encapsulation efficiency remained high (81.50% initially; 73.60% after 28 days). Both free and extract-loaded liposomes were non-cytotoxic to Caco-2 cells. Encapsulated MHPE showed slower phenolic release compared with the free extract. Overall, liposomal encapsulation effectively enhanced the stability and controlled release of macadamia husk phenolics, supporting their potential use as functional food and nutraceutical ingredients.

Keywords: macadamia husk; phenolic extract; encapsulation; liposome; cytotoxicity; antioxidants

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1. Introduction

Nuts are nutrient-dense foods that contain high levels of unsaturated fats, plant protein, dietary fibre, vitamins, minerals, and various bioactive phytochemicals [1–6]. Regular nut consumption has been associated with multiple health benefits, including improved lipid profiles, reduced oxidative stress, better glycemic control, and a lower risk of cardiovascular disease and other chronic conditions [5,7,8]. Macadamia nuts are particularly rich in monounsaturated fatty acids, especially oleic acid, and contain essential micronutrients such as magnesium, potassium, and vitamin E, along with phenolic compounds that contribute to their antioxidant capacity [9–13]. Their lipid profile, characterized by a high proportion of unsaturated fats and low levels of saturated fatty acids, has been

linked to beneficial effects on cardiovascular health, including reductions in total and LDL cholesterol [14–16]. In addition, nuts and their by-products (such as husk, shell, leaf, and flower, among others) have been identified as rich sources of phenolic compounds with diverse health-promoting properties [2,17–19]. Therefore, incorporating these phenolic compounds from nut co-products into the human diet is strongly encouraged, as they may serve as cost-effective natural antioxidants for application in functional foods and nutraceutical products.

Macadamia is a commercially valuable nut crop cultivated in tropical and subtropical regions worldwide. The expanding global production of macadamia nuts has resulted in substantial quantities of agri-industrial by-products, particularly macadamia husk, which remains largely underutilized [12,20]. Recent studies have demonstrated that macadamia green husk is a rich source of phenolic compounds, such as phenolic acids, flavonoids, and proanthocyanidins, which exhibit strong antioxidant activity [21–24]. The reported total phenolic content (TPC) value for macadamia husk extract is approximately 168 mg of gallic acid equivalents (GAE)/g dry weight (DW), depending on extraction conditions [25,26]. Comparable or higher values have been reported for other nut husks, such as walnut husk (85–220 mg GAE/g extract) [27–29], pistachio green hull (~20–49 mg GAE/g) [30,31], while almond is generally reported in approximately 342 mg of catechin equivalents/g extract [32]. These by-products are dominated by phenolic acids, flavonoids, and tannin-type compounds, highlighting their potential as sources of natural antioxidants. Despite this potential, the application of macadamia husk phenolics as functional food ingredients is limited.

Phenolic compounds are well known for their antioxidant and health-promoting properties and are increasingly incorporated into food systems as natural preservatives and functional ingredients [2,33–35]. However, their practical use is limited by susceptibility to degradation under processing, storage, and gastrointestinal conditions, including exposure to various environmental conditions such as heat, light, oxygen, enzymes, and pH variations [36–39]. In addition, many polyphenols exhibit low intestinal bioavailability, reducing their bio-functionality [40,41]. Notably, macadamia husk phenolics are dominated by simple phenolics and flavonoids [21], which are chemically unstable and decompose rapidly or undergo auto-oxidation when exposed to environmental factors [42]. This compositional profile differs from lipid-rich kernels or protein-rich nut meals and makes the husk phenolics particularly suitable for encapsulation to preserve their functional properties.

Encapsulation is an effective strategy to overcome the instability of phenolic compounds by enhancing their protection, stability, and delivery in food systems [43,44]. Among encapsulation techniques, liposomes (phospholipid-based vesicles) are particularly attractive for food applications due to their biocompatibility, biodegradability, non-toxicity, and ability to encapsulate both hydrophilic and lipophilic compounds [45,46]. Furthermore, phospholipids contribute to improved phenolic stability by reducing their susceptibility to oxidative reactions, light and pH-dependent deterioration [47,48]. While liposomal systems have been widely applied to stabilize phenolic compounds and phenolic-rich extracts from various plant and agri-food by-products [49–54], their application to macadamia husk phenolic extract remains unexplored. Although macadamia husk phenolic extract has previously been encapsulated in nano-emulsion systems [55], such systems differ fundamentally from phospholipid-based carriers in structure, interfacial composition, and gastrointestinal behaviour.

In the existing literature, liposome preparation for phenolic or lipophilic compounds is predominantly performed using organic solvent-assisted techniques, most commonly the thin-film hydration method, where lipids are first dissolved in organic solvents and subsequently rehydrated with an aqueous phase after solvent removal [56–59]. Although

ethanol is generally regarded as safe (GRAS) for food applications, these approaches still rely on organic solvents at the lipid dissolution stage. This study employed an aqueous macadamia husk phenolic extract, from which ethanol had been removed prior to liposome preparation, and developed an organic solvent-free liposomal system, in which liposome formation occurred entirely in water without the use of organic solvents at any stage of lipid dissolution or film formation. We hypothesize that an organic solvent-free, aqueous soy lecithin liposomal system can efficiently encapsulate macadamia husk phenolic extract, resulting in physically stable nano-sized vesicles that protect phenolic compounds, enable sustained gastrointestinal release, and maintain cellular safety, thereby enhancing their suitability for functional food applications.

In this context, the present study aims to explore the potential of encapsulating phenolic-rich extracts derived from New Zealand-grown macadamia husk within soy lecithin liposomes. Specifically, it seeks to examine how liposomal systems can be optimized to achieve stable and efficient encapsulation of these phenolic compounds. By investigating the factors influencing colloidal stability, encapsulation capacity, and potential for sustained delivery, this research provides both practical and theoretical insights that can guide the design of robust liposomal delivery systems for plant-derived phenolic extracts and other bioactive mixtures.

2. Materials and Methods

2.1. Materials and Chemicals

Commercial soy lecithin (Fast Easy Bread—Pure Liquid Soy Lecithin (Food Grade)) was purchased from the local market. Folin–Ciocâlteu reagent, sodium carbonate, and 2,2-Diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma-Aldrich, Auckland, New Zealand. WST-1 cell proliferation reagent was purchased from Abcam. Caco-2 cells were procured from ATCC (American Tissue Culture Collection, #HTB-37, Manassas, VA, USA). Minimum essential medium (MEM), fetal bovine serum (FBS), TrypLE, and antibiotics were procured from Gibco, Invitrogen, Waltham, MA, USA.

2.2. Preparation of Phenolic Extract from Macadamia Husk

Fresh macadamia green husks were freeze-dried and ground into a fine powder. Phenolic compounds were extracted from the ground macadamia husk (5%, w/v) with 50% aqueous ethanol. The extraction process began with solvent maceration at room temperature to facilitate diffusion of the solvent into the sample matrix and promote solute release [60]. Our preliminary results revealed that a mixture of ethanol: water (1:1 v/v) gave the highest extraction of phenolic compounds; thus, this mixture was used as the solvent for the preparation of phenolic extracts in this study. After the maceration process, ultrasound probe-assisted extraction was performed using a high-intensity ultrasonic device equipped with a sonication probe (50 Hz and 250 W, QSonica, Newtown, CT, USA). The extraction process was carried out with modifications according to the method specified by Zhang et al. [21]. The sample mixture was sonicated for three cycles, each lasting three minutes (total of nine minutes) to minimize excessive heat buildup during extraction, with the temperature increasing gradually from ambient conditions to approximately 55 °C. The extracted mixture was centrifuged, and the clear supernatant was collected and stored at 4 °C until further use and analysis.

2.3. Phenolic Content and Antioxidant Capacity

Macadamia husk extract was characterized in terms of its total phenolic content (TPC) and antioxidant properties. The TPC of macadamia husk extract was assessed by the Folin–Ciocalteu assay [61]. According to this method, TPC was determined in a 96-well

transparent plate, following the procedure reported by Rashidinejad and Ahmmed [62], with slight modifications. Briefly, the crude extract was diluted 1:10 with distilled water to ensure the absorbance reading fell within the gallic acid standard curve range (0–1000 µg/mL). The Folin–Ciocâlteu (FC) working solution was prepared by diluting the reagent 1:10 (*v*/*v*) with distilled water. 20 µL samples of the diluted extract or standard solution were loaded onto the plate and mixed with 100 µL of the FC reagent. After 6 min, 80 µL of 7.5% (*w*/*v*) sodium carbonate (Na_2CO_3) solution was added, and the plate was incubated in the dark for 30 min. Absorbance was measured at 765 nm using a UV–Vis microplate reader (Synergy™ 2, BioTek® Instruments, Inc., Winooski, VT, USA). The results were presented in milligrams of gallic acid equivalents per gram of dry extract (mg GAE/g), calculated using the gallic acid standard curve.

2.4. DPPH Free Radical Scavenging Activity

The antioxidant potential of the extract was measured using the 2,2-Diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay. The effective concentration (EC_{50}) was determined as the concentration required to quench 50% of the DPPH radicals. The assay is based on the stable free radical of DPPH, which exhibits a strong absorbance at 517 nm. Upon accepting an electron or a hydrogen atom, the radical is reduced and loses its absorbance, resulting in a visible colour change from purple to yellow. DPPH radical scavenging activity was measured using a modified version of the method described by Sembiring et al. [63]. A 10 mM stock solution of DPPH was freshly prepared in absolute ethanol each day and diluted to a 0.1 mM working solution, which was allowed to equilibrate for 2 h before use. In a 96-well plate, 5 µL of different concentrations of extract (or ethanol as a blank) was mixed with 195 µL of the DPPH working solution. The mixture was allowed to incubate in the dark at room temperature for 30 min. Absorbance was then measured at 517 nm using a UV–Vis microplate reader (Synergy™ 2, BioTek® Instruments, Inc., Winooski, VT, USA). The radical scavenging activity was expressed as the percentage of DPPH radical scavenging activity (%RSA), determined using the following Equation (1):

$$\%\text{RSA} = \frac{\text{Absorbance of the control} - \text{Absorbance of the sample}}{\text{Absorbance of the control}} \times 100\% \quad (1)$$

2.5. Preparation of Liposome Loaded with Macadamia Husk Extract

Liposomes were prepared from soy lecithin dispersions according to Rashidinejad et al. [49] with slight modifications. A phospholipid concentration of 1% (*w*/*v*) was selected based on literature evidence and preliminary screening trials, which demonstrated that this level provides stable dispersions and high encapsulation efficiency without causing excessive viscosity or aggregation [49,53,64,65]. Briefly, 20 mL of aqueous extract was used for the preparation of 100 mL of liposome suspension, resulting in 5 mL of liposome dispersion containing 1 mL equivalent amount of crude extract. 1% (*w*/*v*) soy lecithin was dispersed in aqueous extract solution. The dispersion was kept at 25 °C overnight to ease the swelling of the phosphatidylcholine (and other lipids) in lecithin. Subsequently, the obtained dispersion was first blended using an Ultra-Turrax (Black line, Todtnau, Germany) at 24,000 rpm for 5 min, and then the coarse liposome dispersion was passed through a high-pressure homogenizer (Microfluidiser Processor M-110P, Microfluidics, Newton, MA, USA) five times at a homogenisation pressure of 200 MPa. The homogenisation chamber was cooled during homogenisation with ice to prevent the heating of samples. Empty liposomes prepared in distilled water without the extract were used as a control. The final formulation was selected after preliminary trials evaluating different phospholipid concentrations and processing conditions to obtain stable dispersions.

2.6. Characterization of Liposomes

Measurements of Particle Size, Polydispersity Index, and Zeta Potential

Liposomes were characterized in terms of their particle size (z-average), polydispersity index (PDI), and zeta potential (ζ-potential) using the dynamic light scattering (DLS) technique (Malvern Zetasizer Pro ZS, Malvern Analytical Limited, Worcestershire, UK). Before measuring the mean particle diameter, an aliquot of liposomal suspension was diluted with water (1:10, v/v) to minimize multiple scattering effects. The instrument reports the mean particle diameter as z-average and provides PDI as an estimate of the width of the size distribution, with values ranging from 0 (monodisperse) to 1 (polydisperse). The ζ-potential of the liposomes was determined by DLS using undiluted samples, allowing accurate assessment of the surface electrostatic charge and providing insights into the colloidal stability of the formulations. All measurements were carried out at 25 °C with a scattering angle of 173 °C, refractive index of 1.45, and absorbance at 0.001. All measurements were performed in triplicate.

The size of liposomes with or without extract was further confirmed by transmission electron microscopy (TEM). TEM analysis was employed to observe the morphology of liposomes with a negative staining method according to the protocol of Rashidinejad et al. [49]. Briefly, the liposome suspension was diluted 10-fold with distilled water to reduce the concentration of the particles. A drop of a water-diluted liposome sample (20 µL) was placed on a 200-mesh nickel grid (TABB Laboratories Equipment, Berks, UK). The surplus was removed by filter paper. Then, the sample was negatively stained with one drop of 2% (w/v) aqueous solution of uranyl acetate. The surplus solution was removed after 5 min. The sample was air-dried at room temperature prior to imaging the vesicles using a TEM, operating at an acceleration voltage of 200 KV (FEI Tecnai G2 Biotwin TEM, Thermo Fisher Scientific, Hillsboro, OR, USA).

2.7. Determination of Encapsulation Efficiency

Encapsulation efficiency (EE) is defined as the ratio of encapsulated compound to the total amount added to the liposomal dispersion. To determine the percentage of EE (EE%), free (non-encapsulated) phenolics were removed from the liposomal suspensions by centrifuging at 4000× g rpm for 15 min using an Amicon® Ultra 10 KDa molecular weight cutoff (Amicon®/MWCO, Anaheim, CA, USA) ultra-centrifugal membrane filter. The %EE was determined by calculating the difference between the ratio of initial TPC in the dispersion and the total non-encapsulated phenolics (TPC) in the filtrate of the liposome dispersion after ultrafiltration, according to Barekat et al. [66], with some modifications. The Folin–Ciocâlteu method was used to measure the total phenolic content as described in Section 2.3. The EE% values obtained using centrifugation and the Folin–Ciocalteu assay should be considered apparent EE, as incomplete separation, possible leakage during centrifugation, and the non-specific nature of the assay may introduce methodological bias. Although this assay is widely used to estimate total phenolic content, it is not entirely specific to phenolic compounds and can respond to other reducing substances present in the system, such as proteins, sugars, or lipid-associated components [67]. The percentage of EE was calculated according to the following Equation (2).

$$\text{EE\%} = \frac{\text{TPC in the dispersion} - \text{TPC in the supernatant after ultrafiltration}}{\text{TPC in the dispersion}} \times 100\% \quad (2)$$

2.8. Stability Study of the Liposomes

The stability of liposomes with or without phenolic extract was evaluated by observing the changes in mean particle diameter, PDI, and ζ-potential of all formulations at 14-day intervals over a period of 60 days. Encapsulation efficiency (EE%) was calculated over

four weeks at seven-day intervals. All formulations were stored at 4 °C, and the above-mentioned measurements were made using the DLS technique (Section Measurements of Particle Size, Polydispersity Index, and Zeta Potential). Storage at 4 °C was chosen to simulate typical refrigerated conditions used for many foods, such as beverages, yoghurt or dairy-based drinks.

2.9. Cell Viability Assay

Cell viability of macadamia husk phenolic extract (MHPE) was determined using the WST-1 cell proliferation assay reagent (Abcam, Cat. No. ab155902, Cambridge, UK), according to the manufacturer's instructions. Briefly, Caco-2 cells were cultured in minimum essential media (MEM) supplemented with 10% (*v*/*v*) sterile fetal bovine serum (FBS), 1% (*v*/*v*) nonessential amino acids (NEAA), and 1% (*v*/*v*) PenStrep GlutaMax antibiotics (Penicillin 10,000 U/mL, Streptomycin 10,000 µg/mL, and GlutaMax 200 mM). The cells were incubated at 37 °C in a humid atmosphere with 5% CO_2. The culture media was changed every 72 h. Cell confluence was estimated by visual inspection using an optical microscope. After Caco-2 cells reached 80% confluence in 75 cm^2 culture flasks, cells were washed twice with sterile PBS (pH 7.4) and subsequently dissociated from the surface using TrypLE reagent (Thermos Fisher, Waltham, MA, USA). Cells were plated on a clear, flat-bottom 96-well plate with a density of 5×10^4 cells/well in 100-µL of complete growth media/well in Corning Costar® 96-well and incubated at 37 °C overnight.

The next day, the growth media were removed, and the cells were gently washed with PBS. Cells were separately treated with freshly prepared free extract (1–100 µg/mL) or 2-fold serial diluted MHPE-loaded liposome suspension in growth media and incubated at 37 °C for 48 h. For each treatment, 100 µL of the corresponding concentration or dilution was added to wells containing cells, and control cells were incubated with growth medium alone. After 48 h of treatment, 10 µL of WST-1 reagent was added to each well and incubated at 37 °C for 1 h. The absorbance values were measured at 450 nm with a 630 nm reference using a microplate reader. The results were expressed as percent cell viability by using Equation (3). The cells, treated with only media, were considered 100% viable. All assays were performed in triplicate, and results are shown as pooled means (n = 9).

$$\text{Cell viability } (\%) = \frac{\text{absorbance at 450 nm for treated cells}}{\text{absorbanceat 450 nm for the control}} \times 100\% \quad (3)$$

2.10. Release of Phenolics from Liposomes

The release behaviour of phenolics from the extract-loaded liposomes in simulated gastrointestinal conditions was studied. To simulate oral conditions, 5 mL of simulated salivary fluid (SSF, pH 7.0) containing α-amylase (30 U/mL) (Sigma-Aldrich, St. Louis, MO, USA) was added to 5 mL of liposomes containing extract (1 mL equivalent amount of crude extract). The mixture was adjusted to pH 7.0 and placed in a water bath, and shaken at 100 rpm for 2 min at 37 °C. Subsequently, simulated gastric fluid (SGF, 8 mL) containing pepsin (2000 U/mL gastric phase) was added to an equal volume of oral bolus, and HCl (6.0 M) was used to adjust the pH to 3.0. The mixture was incubated at 37 °C under continuous agitation at 100 rpm for 120 min. For the intestinal phase, the gastric chyme (8 mL) was mixed with simulated intestinal fluid (SIF, 8 mL) containing bile salts (10 mM), and pancreatin (2000 U lipase activity/mL intestinal phase, NaOH (1.0 M) to adjust the pH to 7.0, and the mixture was incubated at 37 °C under continuous agitation at 100 rpm for 120 min. In this study, phenolic content was determined at the end of each digestion phase to evaluate bioaccessibility and stability. For the determination of TPC, 2 mL aliquots of the digesta were collected after 2 min of the oral phase, at which point the amylase activity was immediately stopped by the addition of HCl.

During the gastric and intestinal phases, samples were collected, and the enzymatic reactions were quenched by adding the appropriate enzyme inhibitors (pepstatin for gastric samples and protease inhibitor for intestinal samples). All samples were subsequently placed on ice to prevent further enzymatic activity before analysis. The phenol content was determined by the Folin–Ciocâlteu method as described in Section 2.3. For comparison, the free extract was also tested. All assays were performed in triplicate.

2.11. Statistical Analysis

All analytical procedures were performed in triplicate (n = 3) to ensure reliability and reproducibility of the data. The results are presented as mean values accompanied by the standard deviation (±SD). Statistical analysis was undertaken using MiniTab software, Version 21.3.1. A one-way analysis of variance (ANOVA) was employed to assess differences among groups, followed by Tukey's post hoc test to identify specific pairwise comparisons. A p-value of less than 0.05 was considered indicative of statistical significance. The EC_{50} indicates the concentration of extract required to scavenge 50% of DPPH free radicals, and IC_{50} represents the concentration that reduces the viability of Caco-2 cells by 50%.

3. Results and Discussion

3.1. Phenolic Content of Macadamia Husk Extract

A 50% aqueous ethanolic extract of macadamia husk was obtained and characterized for TPC, antioxidant properties, and cytotoxicity. The extract showed a considerable value for TPC of 49.92 ± 0.011 mg GAE/g dry sample, confirming macadamia husk as a phenolic-rich by-product. Different values of TPC for macadamia husk extract were reported in various studies, e.g., 18.23 mg GAE/g dry material [21], 45 mg GAE/g dry weight (DW) sample [68], 86 mg GAE/g DW [24] and 14.3 mg GAE/g extract [69]. The differences regarding the phenolic content between our findings and those reported in the literature may be attributed to differences in agro-climatic conditions, extraction solvents, and techniques [26].

3.2. DPPH Free Radical Scavenging Activity of Macadamia Husk Extract

Antioxidant activity of macadamia husk extract, evaluated using the DPPH free radical scavenging assay, showed a strong, concentration-dependent response (Figure 1). The extract exhibited an EC_{50} of 8.87 µg/mL, indicating high radical scavenging efficiency. DPPH inhibition increased sharply with increasing extract concentration, reaching approximately 75% at 10 µg/mL and exceeding 90% at concentrations ≥ 25 µg/mL. At the highest tested concentration (100 µg/mL), the extract achieved 92.99 ± 0.06% of free radical scavenging activity, confirming strong antioxidant potential even at low concentrations. Several studies have reported the values of DPPH radical scavenging activity of the macadamia husk [23,69] expressed as the concentration required to inhibit 50% of radicals (IC_{50}; µg/mL) [55]. A comparable high DPPH radical scavenging activity (~95.8 ± 0.6%) has been reported for macadamia husk extracts [69]. However, the IC_{50} value (64 µg/mL) reported in the literature for macadamia husk ethanolic extract [55] is substantially higher than that obtained in the present study, indicating a markedly stronger antioxidant capacity of the extract produced under the current extraction conditions. The DPPH assay was selected in this study as a widely accepted and reliable method for evaluating the radical scavenging activity of polyphenolic compounds. However, chemical-based antioxidant assays do not fully reflect physiological antioxidant effects. Therefore, future studies will focus on cellular antioxidant activity to better assess the biological relevance of the extract.

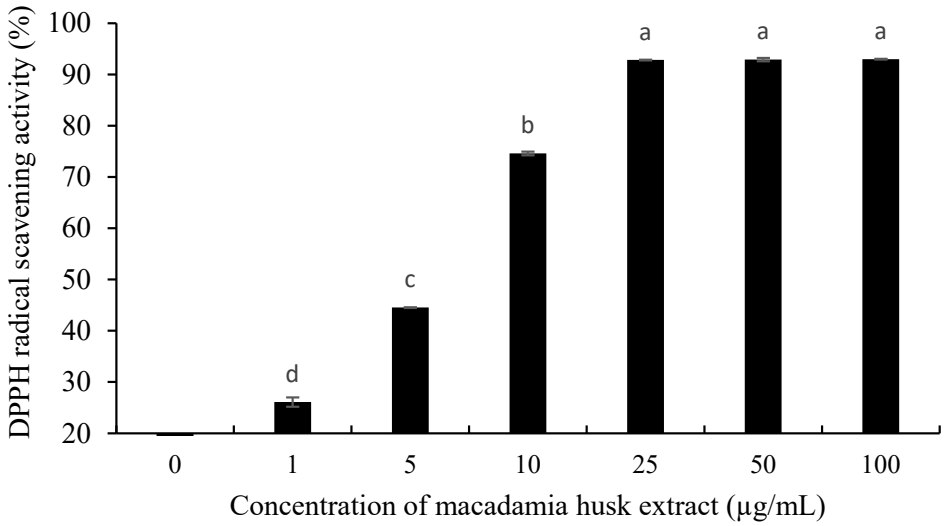


Figure 1. DPPH free radical-scavenging activity of macadamia husk extract at concentrations ranging from 0 to 100 µg/mL, expressed as µg of dried sample per mL of assay solution. Values are expressed as mean ± SD (n = 3). Different letters above the bars indicate statistically significant differences between treatments ($p < 0.05$).

3.3. Characterization of Liposomes Loaded with Macadamia Husk Extract

The mean particle diameter, PDI, and ζ-potential of samples were measured to characterize liposomes, and the results are presented in Table 1. Determining the particle size of lipid vesicles is essential, as smaller diameters can enhance the occlusive effect [70,71], while particle size more broadly influences the stability, encapsulation capacity, appearance, texture of the system, and cellular uptake [72–74]. Empty liposomes exhibited a mean diameter of approximately 111 nm and a PDI value of <0.27, while the addition of macadamia husk extract reduced the mean particle size to ~77 nm with a PDI < 0.21 (Table 1). The mean particle size observed for liposomes prepared by microfluidization is consistent with the findings of Akgün et al. [75] and others, demonstrating small mean liposome diameter (<150) could be achieved by the microfluidization processing technique [76]. All liposomes exhibited negative surface charges, whether they contained extract or not, ranging between −43.11 and −62.55 mV.

Table 1. Characteristics of fresh liposomes, mean particle size, PDI, zeta potential, and encapsulation efficiency of liposomes with and without macadamia husk extract.

Liposomes	Particle Size (nm)	PDI	ζ-Potential (mV)	EE%
Empty liposomes	$111.46^{a} \pm 0.75$	$0.27^{a} \pm 0.011$	$-62.55^{a} \pm 1.00$	-
Extract-loaded liposomes	$77.58^{b} \pm 0.34$	$0.21^{b} \pm 0.001$	$-43.11^{b} \pm 1.62$	81.50 ± 0.22

Note: Values are presented as mean values ± standard deviation (n = 3). Different superscript letters within the same column indicate significant differences ($p < 0.05$) between empty and extract-loaded liposomes.

When compared with other plant extract-loaded liposomal systems reported in the literature, the MHPE-loaded liposomes demonstrated competitive performance. For example, liposomes containing grape seed extract have been reported to exhibit particle sizes below 100 nm with encapsulation efficiencies above 80% [65], while olive leaf extract liposomes typically show encapsulation efficiencies ranging from approximately 30–76% depending on formulation conditions [77–79]. Trucillo et al. [80] reported that the encapsulation efficiency of total phenolics from olive pomace ranged between 25 and 55%, depending on the

processing conditions and the phospholipid-to-phenolic ratio. In comparison, the MHPE-loaded liposomes in the present study achieved a particle size of approximately 78 nm and an encapsulation efficiency of about 81.5%, together with good colloidal stability. These results demonstrate that the developed MHPE liposomal system performs comparably to or better than previously reported systems for phenolic-rich plant extracts.

The incorporation of macadamia husk extract into the liposomes caused a reduction in the particle size. This may be attributed to interactions between the phenolic compounds and the phospholipids, which can promote tighter packing within the lipid bilayer [81]. The encapsulation technique employed in this study is suitable for both hydrophilic and lipophilic bioactive compounds due to the amphiphilic nature of liposomes, whereby hydrophilic compounds are entrapped in the aqueous core, and lipophilic compounds are incorporated into the hydrophobic region of the lipid bilayer [82,83]. The observed decrease in size may therefore be related to the formation of stabilizing interactions, potentially including covalent or non-covalent bonds, between the phenolics and the lipid components.

Studies have shown that liposome size is strongly influenced by their formulation and the characteristics of the encapsulated material [64,84]. Our results are in agreement with several reports in the literature. Jovanović et al. [85] and Micheletto et al. [86] reported the reduction in particle size at the incorporation of rosehip (*Rosa canina* L.) extract and yerba mate (*Ilex paraguariensis*) extract, respectively. The size reduction was also reported for olive leaf phenolic compounds [77,78] and liposomes loaded with extract from wild thyme (*Thymus serpyllum* L.) polyphenols [87]. Furthermore, other scientific findings, such as those published by Lopez-Pinto et al. [88], have shown that residual ethanol can affect the particle size of liposomes, thus causing a change in the net charge and contributing to electrostatic stabilization. In this study, the macadamia husk extract used for encapsulation was initially obtained using 50% (*v*/*v*) aqueous ethanol; following extraction, the ethanol fraction was removed under reduced pressure using a SpeedVac(Thermo Fisher Scientific, Waltham, MA, USA), and the concentrated extract was subsequently reconstituted with water to restore the original solvent ratio. Residual ethanol may have contributed to the observed reduction in liposome size. Furthermore, the encapsulation of polyphenols may decrease the number of lipid compounds involved in liposome membrane formation [89,90], resulting in the formation of smaller particles.

The PDI values for both empty and extract-loaded liposomes were low, demonstrating that the formulations possessed a highly uniform particle size distribution and suggesting successful formation of stable nanoscale vesicles. In this study, the soy lecithin liposomal formulations showed smaller PDI values (<0.27). These values indicate a lower tendency for aggregation and demonstrate good homogeneity of these colloidal systems. The PDI values obtained are in agreement with the literature, wherein the PDI of soy lecithin liposomes with hibiscus extract was ~0.25 [64]. Liposomal dispersity is strongly affected by lipid composition [86], concentration [64], preparation method, and mixing time. Similarly, Trucillo et al. [80] observed that increasing the concentration of bioactive compounds in liposomes resulted in larger vesicle sizes and higher PDI values with the increasing content of olive pomace extract-loaded liposomes.

The zeta potential reflects the overall surface charge of the vesicles within the dispersion medium and is therefore an important indicator of colloidal stability. This charge of the particles functions as an electrical barrier that prevents the coalescence of the particles, thereby contributing to the stability of the suspension [91,92]. The zeta potential of liposomes prepared without extract was measured at −62.55 mV, whereas for those prepared with extract was −43.1 mV (Table 1). These highly negative ζ-potential values may be related to the presence of phosphatidic acid, an anionic phospholipid commonly found in crude soybean lecithin. Furthermore, empty liposomes showed a higher surface

charge than the extract-loaded liposomes. This effect is likely due to interactions between the phenolic extract and the phospholipid components of the liposomes [93,94]. Phenolic compounds can participate in electrostatic or hydrogen-bonding interactions with the negatively charged phosphate groups of phosphatidylcholines. As a result, the incorporation of the extract may partially neutralize the surface charge, leading to a reduction in the overall negative ζ-potential of the extract-loaded liposomes. In general, colloidal systems with a ζ-potential greater than ±30 mV indicate monodisperse formulations and exhibit enhanced electrostatic stability, as the strong repulsive forces between particles help prevent aggregation [89,95–97]. In this study, the measured ζ-potential values indicate that electrostatic repulsion between liposomal vesicles plays an important role in maintaining colloidal stability. The results obtained for ζ-potential are in agreement with studies by Micheletto et al. [86] and Gibis et al. [98], where the encapsulation of liposomes containing grape seed extract was studied.

3.4. Stability of Liposome Formulations

The physicochemical characteristics and stability of MHPE-loaded liposomes were evaluated, including encapsulation efficiency, particle size, polydispersity index (PDI), and ζ-potential during storage. The encapsulation efficiency (EE%) of MHPE in the liposomes was 81.50%, as reported in Table 1. The outcome suggests that the encapsulation was highly efficient, resulting in negligible loss of phenolics during the liposome formulation. The stability of samples was evaluated by measuring EE% at different storage intervals, up to 4 weeks. Liposomes loaded with MHPE remained stable throughout the study period. The %EE decreased from 81.50% on day 0 to 73.60% on day 28 during storage at 4 °C (Table 2). In addition, the liposomes exhibited good visual stability, with no sedimentation observed over the storage period. The changes in encapsulation efficiency and particle size indicate alterations in liposomal membrane integrity, which may result in gradual phenolic leakage.

Table 2. Changes in encapsulation efficiency of liposomes with macadamia husk extract.

	Encapsulation Efficiency (EE%)				
Liposomes	**EE%—Day 0**	**EE%—Week 1**	**EE%—Week 2**	**EE%—Week 3**	**EE%—Week 4**
Extract-loaded liposomes	81.50 ± 0.22	79.36 ± 1.00	78.59 ± 0.65	74.41 ± 0.71	73.60 ± 0.14

Note: Values are presented as mean values ± standard deviation (n = 3).

Physical stability is a critical parameter because it reflects the ability of liposomes to maintain their structural integrity, size distribution, and encapsulation characteristics during storage. Instability can lead to aggregation, fusion, or leakage of encapsulated compounds, ultimately reducing the effectiveness of the delivery system. Comparing extract-loaded liposomes with unloaded formulations allows assessment of whether the incorporated phenolic extract influences vesicle stability, either by enhancing membrane rigidity or promoting destabilization. A two-month physical stability study was conducted for liposome dispersions with and without the extract, and the measured size, PDI, and ζ-potential ranges are summarized in Table 2. Samples were stored at 4 °C to minimize oxidation and lipid hydrolysis. Extract-loaded liposomes exhibited slightly greater stability compared with unloaded liposomes, which may be attributed to interactions between the phenolic compounds and the lipid bilayer that can enhance membrane rigidity. Zhang et al. [99] reported similar findings, suggesting that bioactive compounds can incorporate into the lipid bilayer and reduce lipid mobility, thereby enhancing vesicle stability and maintaining stable particle sizes.

The physical stability of the liposomes was monitored at 14-day intervals over a 60-day storage period, with particle size, PDI, and ζ-potential (Figure 2). Entrapment efficiency (EE%) was also measured for four weeks (Table 2). The particle sizes of all liposomes did not change drastically during 60 days of storage at 4 °C. As shown in Figure 2a, the empty liposomes increased from 111.47 ± 0.75 nm on day 0 to 135.87 ± 0.61 nm by day 60, indicating a gradual enlargement of vesicles, likely due to slow aggregation or fusion over time. In contrast, extract-loaded liposomes showed minimal variation, with particle size remaining relatively stable between 77.59 ± 0.34 and 79.02 ± 0.44 nm throughout the study, demonstrating strong structural integrity. In all samples, the PDI values showed slight change throughout the 60-day storage at 4 °C, suggesting that the dispersions retained good homogeneity (Figure 2b).

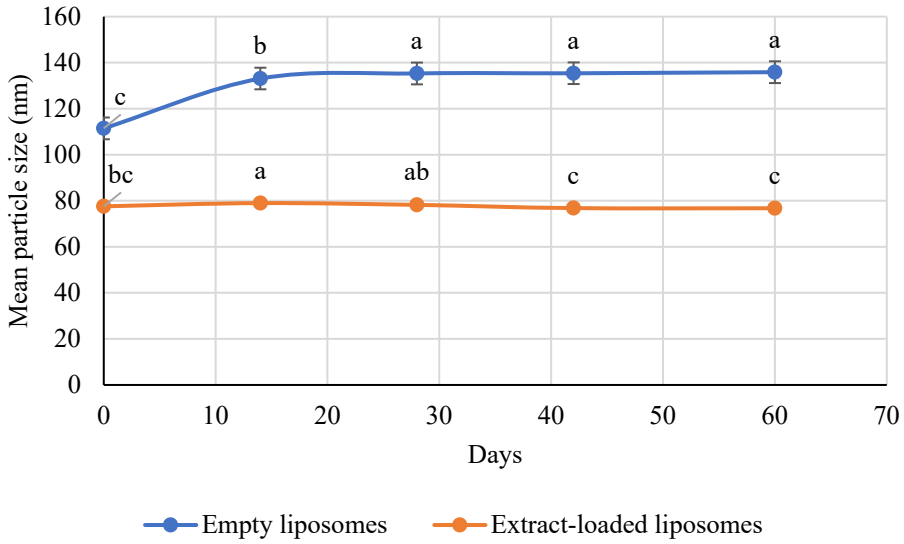
For empty liposomes, the zeta potential decreased from −62.55 ± 1.00 mV to −57.54 ± 0.73 mV, whereas for extract-loaded liposomes, the zeta potential increased from −43.11 ± 1.62 mV to −47.01 ± 1.33 mV. Zeta potential of extract-loaded liposomes increased to −51.92 ± 0.37 by the 28 day and then decreased at −47.76 ± 1.27 mV on the 42 days, followed by a reduction to −47.01 ± 1.33 mV on the 60th day. The observed changes in ζ-potential during the 60-day storage period are likely attributable to multiple, interrelated factors that influence the stability and retention of surface charge in liposomal systems. Over time, lipids within the bilayer may undergo molecular rearrangement or oxidative degradation of phospholipids, leading to altered surface charge distribution. Additionally, gradual adsorption or desorption of ions from the surrounding medium can modify the electrical double layer, thereby shifting the measured ζ-potential. In extract-loaded liposomes, interactions between phenolic compounds and the polar headgroups of the lipids may further contribute to charge stabilization. Overall, the stability of particle size, PDI, and ζ-potential over the 60 days confirms that the liposomal formulations, particularly those containing the extract, maintained robust physical stability suitable for long-term storage and controlled-release applications.

3.5. Morphology of Manufactured Liposomes

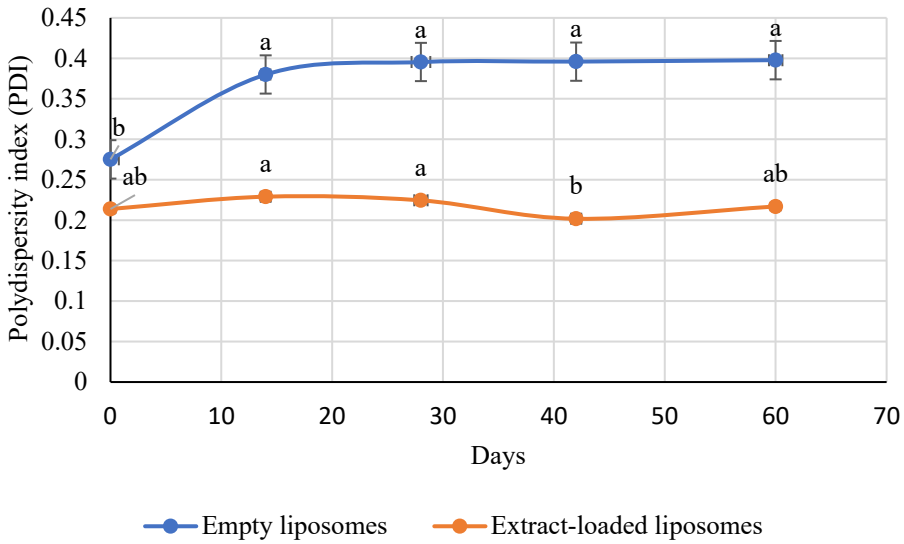
TEM imaging was used to confirm the morphology and microstructure of liposomes. The existence of spherical vesicles was observed in both free and extract-loaded liposomes, which is consistent with the typical structure of phospholipid-based liposomes presented in Figure 3. According to the TEM images, no major differences in sizes were observed in the formulation compared to the sizes measured by DLS. Empty liposomes show dense vesicles appear uniformly distributed, dispersed vesicles, and most exhibit well-defined, intact spherical structures (Figure 3a). The absence of large aggregates suggests good colloidal stability and effective liposome formation under the preparation conditions. The high packing density indicates a predominance of small unilamellar vesicles (SUVs), which are common in soy lecithin systems produced by high-energy methods such as sonication or homogenisation [64,100].

Extract-loaded liposomes show a more heterogeneous population of vesicles, including both small unilamellar vesicles and larger multilamellar structures (Figure 3b). Some degree of clustering is visible, which may reflect partial aggregation or fusion events, possibly due to sample handling or differences in lipid organization. Overall, the TEM images confirm successful formation of liposomes from soy lecithin, showing typical spherical morphology with size variability dependent on formulation or processing conditions.

(**a**)



(**b**)



(**c**)

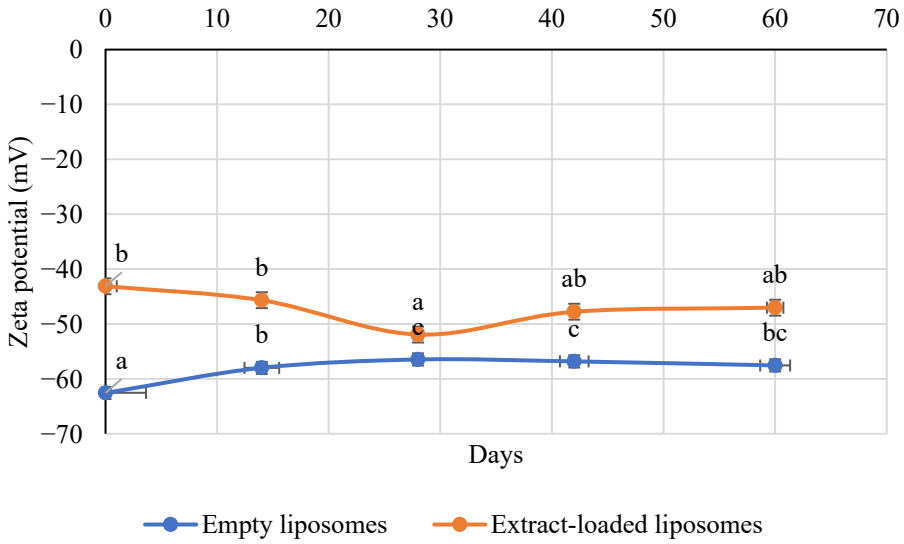


Figure 2. Mean particle size (**a**), polydispersity index (**b**), and zeta potential (**c**) of liposomes with and without macadamia husk extract during storage at 4 °C. Values are expressed as mean ± SD (n = 3). Different letters indicate significant ($p < 0.05$) differences among the same liposomes for different storage times.

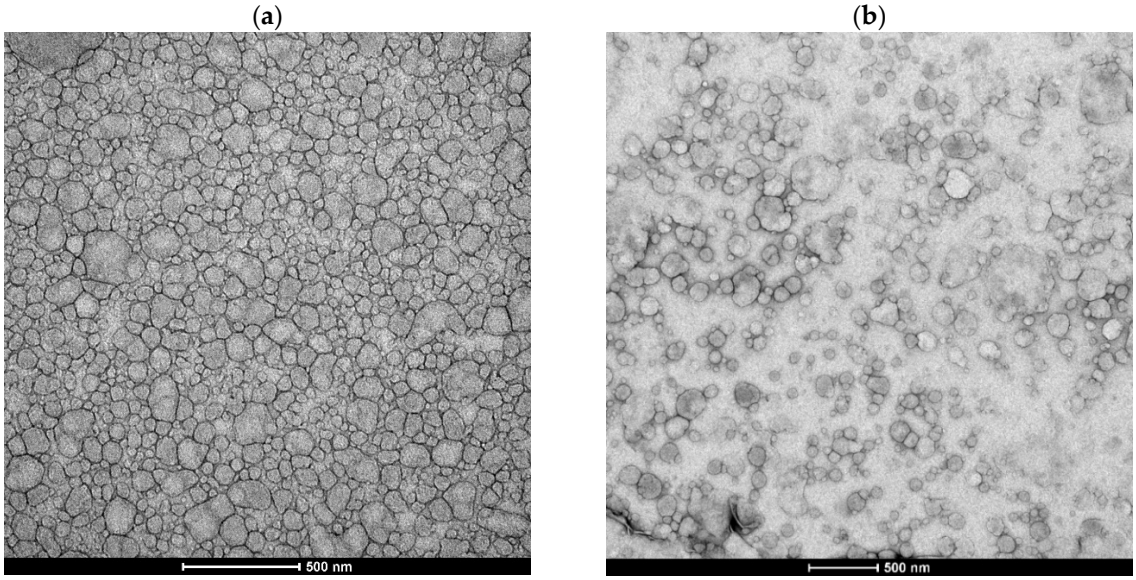


Figure 3. Transmission electron microscopy (TEM) images of liposomes without macadamia husk phenolic extract (MHPE) (**a**) and with MHPE (**b**), obtained at a scale of 500 nm, with magnification of 43,000× and 26,500×, respectively.

3.6. Cell Viability of Macadamia Husk Extract

The cytotoxicity of free macadamia husk phenolic extract (MHPE) and MHPE-loaded liposomes was evaluated in Caco-2 intestinal epithelial cells using a WST-1 cell viability assay (Figure 4). Exposure to free MHPE at concentrations ranging from 1 to 100 μg/mL for 48 h did not result in a significant reduction in cell viability (Figure 4a). Cell viability remained comparable to, or slightly higher than, the untreated control at lower concentrations (1–25 μg/mL), suggesting that MHPE does not adversely affect mitochondrial metabolic activity within this concentration range. No IC_{50} value could be determined, as cell viability did not decrease by 50% at any tested concentration. These findings suggest that the phenolic compounds present in the extract do not exert harmful effects on cellular metabolic activity at concentrations that are suitable for potential food or nutraceutical applications.

The cytotoxicity of liposomal formulations was evaluated across a lower concentration range (1.5–50 μg/mL), reflecting their enhanced cellular interaction and bioavailability (Figure 4b). Liposome concentrations between 1.5 and 6.25 μg/mL did not significantly affect cell viability compared with the control ($p > 0.05$), indicating good biocompatibility at low doses. However, a statistically significant reduction in viability was observed at concentrations $\geq$ 12.5 μg/mL, with approximately 65% viability at 25 μg/mL and a pronounced decrease (~15%) at 50 μg/mL. Similar concentration-dependent viability responses have been observed for liposomal and lipid-based nanocarriers in intestinal epithelial models, where cell viability remains high at lower lipid concentrations but declines as carrier concentration increases, reflecting enhanced cellular interactions and uptake at elevated doses [101]. Nonetheless, an empty liposome control at equivalent phospholipid concentrations was not included in the present study, which limits a definitive distinction between the effects of the lipid carrier and those of the encapsulated extract.

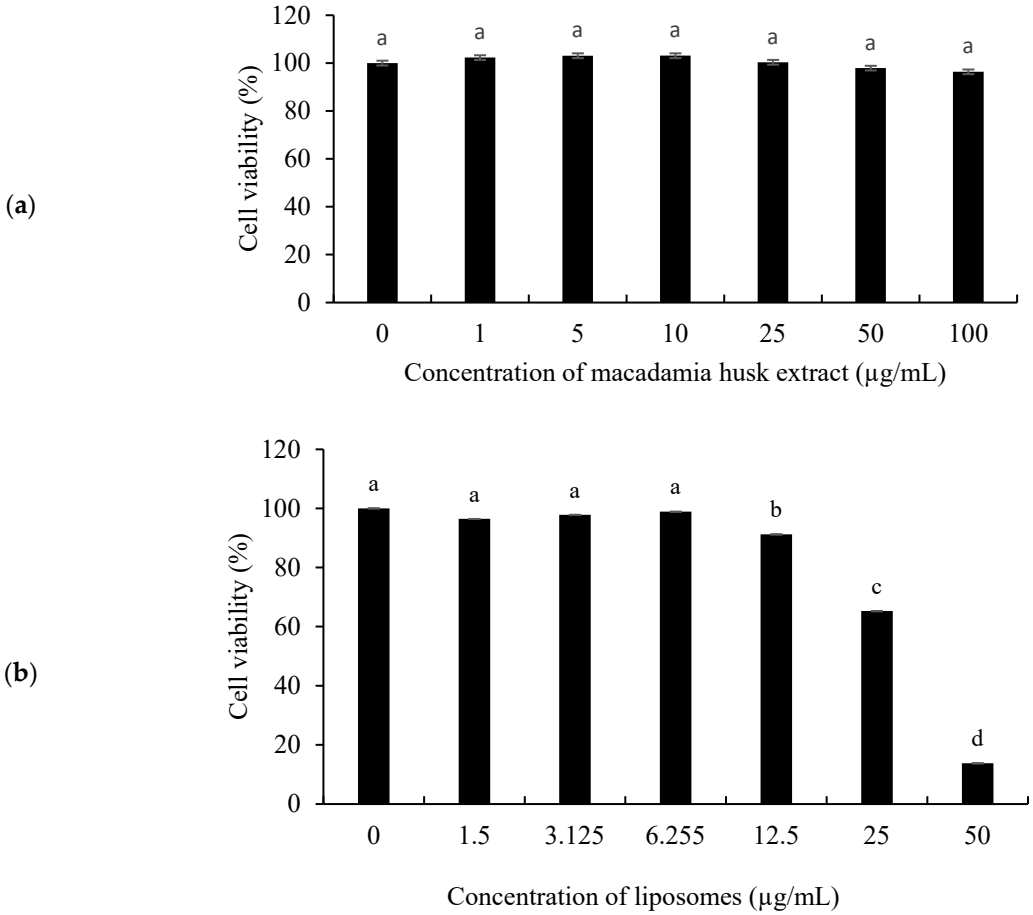


Figure 4. Viability of Caco-2 cells treated with free extract (**a**) and liposomes (**b**) at different concentrations. Values are expressed as mean ± SD of nine independent experiments (n = 9). Different letters above the bars indicate statistically significant differences ($p < 0.05$) between treatments.

Importantly, the observed cytotoxicity at higher liposome concentrations does not necessarily reflect the toxicity of the encapsulated phenolics but rather highlights a formulation-dependent effect related to vesicle concentration and surface interactions with intestinal epithelial cells [102]. Several studies have demonstrated that empty or phenolic-free liposomes exhibit minimal cytotoxicity toward intestinal cell models (e.g., Caco-2 cells) across a range of phospholipid concentrations relevant to oral delivery, with noticeable effects only at substantially higher vesicle loads that exceed typical dietary or nutraceutical exposure levels [101]. At concentrations relevant for food delivery, liposomal systems are typically present at substantially lower levels than those inducing cytotoxic effects in vitro. Therefore, these results emphasize the importance of dosage optimization when designing liposomal delivery systems for food applications. Collectively, the findings demonstrate that free MHPE is non-cytotoxic across a broad concentration range, while MHPE-loaded liposomes exhibit acceptable biocompatibility at low concentrations, supporting their potential use as safe and effective carriers for phenolic compounds in functional foods.

3.7. In Vitro Release of Phenolics from Liposomes

The release of phenolics from the liposomes loaded with macadamia husk extract and free extracts was studied in simulated in vitro digestion, and the phenolics released in oral, gastric, and intestinal phases were quantified by the Folin–Ciocâlteu assay (Section 2.3). The results indicate that phenolic release from encapsulated macadamia husk extract (MHPE) was significantly lower than that of the free extract during the oral and gastric phases (Figure 5). In contrast, a substantial increase in TPC was observed in the intestinal phase

for both treatments, with no significant difference between the encapsulated and free extracts ($p > 0.05$). In the oral phase, both samples exhibited relatively low TPC values. The non-encapsulated extract showed approximately 1.4 mg GAE/mL, whereas the liposomal formulation released approximately 0.8 mg GAE/mL. This indicates that only a small proportion of phenolics is released during the short oral digestion, and liposomes likely protect part of the phenolic content from immediate dilution or enzymatic action.

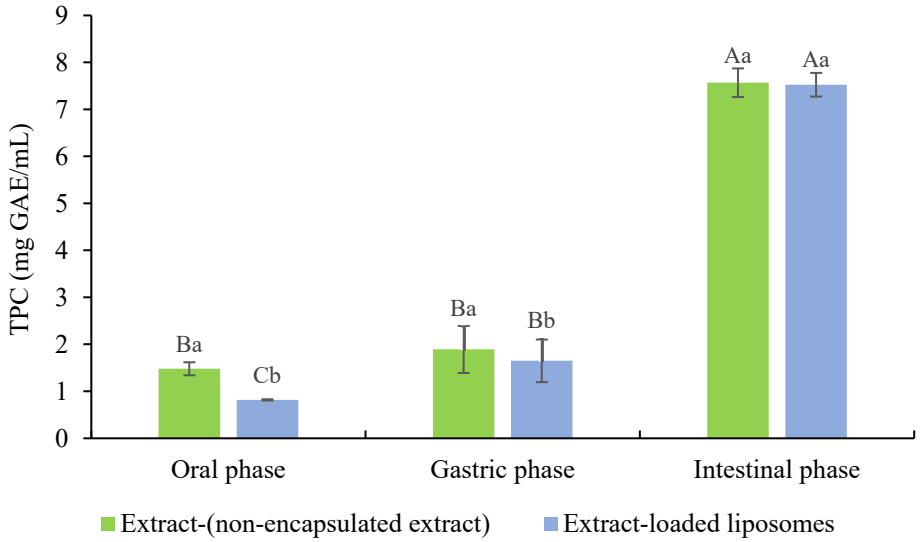


Figure 5. Total phenol content (TPC) released from extract (non-encapsulated extract) and extract-loaded liposomes during the oral, gastric, and intestinal phases of simulated gastrointestinal digestion. Values are expressed as mean ± SD ($n = 3$). Different uppercase letters indicate significant differences ($p < 0.05$) for the phenolic content among the digestion phases, while lowercase letters represent differences between the free extract and encapsulated extract for the released phenolics.

During the gastric phase, the TPC increased moderately for both samples. The free extract reached approximately 2.0 mg GAE/mL, while the extract-loaded liposomes released about 1.6 mg GAE/mL. This suggests that acidic conditions and pepsin activity promote further solubilisation of phenolic compounds. The slightly lower TPC observed in liposomes reflects partial retention of phenolics within the vesicles, indicating that the lipid bilayer protects against early release in acidic environments. A significant increase in TPC was observed during the intestinal phase for both samples. The non-encapsulated extract achieved approximately 7.5 mg GAE/mL, and the liposomal formulation showed a comparable release of around 7.4 mg GAE/mL. This sharp rise reflects the major release of phenolics in the intestinal condition, driven by bile salts and pancreatic enzymes, which is known to further disrupt lipid-based carriers, leading to extensive liposome breakdown and complete solubilisation of encapsulated compounds [103,104]. Consequently, both non-encapsulated and liposomal extracts exhibited similarly high TPC values under intestinal conditions. Some studies on phenolic-rich extracts (e.g., grape pomace) report that encapsulated forms show altered release patterns during digestion compared to free extracts, but during the intestinal phase, recovered TPC can become comparable or even improved relative to the free extract. For example, microencapsulated grape pomace extracts showed increases in total phenolic compound content through simulated digestion and enhanced bioaccessibility in the intestinal stage compared with free extract [105]. Likewise, study on red pepper bioactives found that although a much greater percentage of phenolics was released from the free extract in both gastric and intestinal fluids, the encapsulated extract still released a high fraction of phenolics during intestinal digestion suggesting that, at that stage, the difference between free and encapsulated phenolic content becomes smaller (i.e., phenolics are highly bioaccessible from both forms in the intestinal phase) [106].

These observations support the present findings and suggest that intestinal digestion conditions promote extensive phenolic solubilisation from both free and encapsulated forms, leading to similarly high TPC values. Importantly, while TPC values were comparable, liposomal systems may still enhance phenolic bioaccessibility and absorption, which cannot be fully captured by the Folin–Ciocâlteu assay. The Folin–Ciocâlteu method quantifies total reducing phenolics released into the digestion medium but does not reflect differences in bioaccessibility, permeability, or cellular uptake, where liposomal delivery systems may offer significant advantages. Overall, the in vitro digestion results indicate that liposomal encapsulation delayed the early release of phenolics during the oral and gastric phases and released efficiently in the intestinal phase, enhancing potential bioaccessibility.

The primary advantage of encapsulation lies in its ability to enhance the stability of phenolic compounds, reduce premature degradation, and enable controlled release during gastrointestinal digestion, thereby potentially improving bioaccessibility. The present findings suggest that liposomal delivery of MHPE represents a promising strategy for preserving phenolic integrity during gastrointestinal transit while facilitating sustained release at the intestinal site of absorption. However, conclusions drawn from in vitro digestion models alone should be interpreted with caution, as the Folin–Ciocâlteu assay provides a measure of total reducing capacity rather than specific phenolics released into the digestion medium. Therefore, similar TPC values in the gastric and intestinal phases may reflect comparable phenolic content between encapsulated and free extract. Further investigations using liposome-incorporated food matrices and quantification techniques such as HPLC are required to confirm these results and to better elucidate the behaviour of liposomal MHPE under realistic food digestion conditions.

4. Conclusions

New Zealand-grown macadamia green husk, an underutilized by-product of nut processing, represents a valuable source of phenolic compounds with strong antioxidant activity and negligible cytotoxicity at concentrations relevant for food or nutraceutical applications. Encapsulation of the extract in liposomes produced stable nanoscale vesicles with high encapsulation efficiency, narrow size distribution, and long-term structural stability at 4 °C. In vitro digestion studies demonstrated that liposomes effectively protected phenolic compounds during the oral and gastric phases while enabling controlled release under intestinal conditions. Cytotoxicity assays further confirmed the biocompatibility of both the free extract and extract-loaded liposomes at relevant concentrations. Collectively, these findings indicate that liposomal delivery is a promising strategy to enhance stability, bioaccessibility, and controlled release of macadamia husk-derived phenolic antioxidants. While laboratory-scale production demonstrates the feasibility of this approach, translating it into industrial-scale applications will require further optimization of processing methods, phospholipid content, and formulation parameters to ensure stable, high-quality products. Future studies should investigate functional performance in real food matrices, in vivo bioavailability, and sensory compatibility to fully realize the potential of these liposomal formulations for functional food and nutraceutical applications.

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References

1. Gonçalves, B.; Pinto, T.; Aires, A.; Morais, M.C.; Bacelar, E.; Anjos, R.; Ferreira-Cardoso, J.; Oliveira, I.; Vilela, A.; Cosme, F. Composition of nuts and their potential health benefits—An overview. *Foods* **2023**, *12*, 942. [CrossRef]
2. Chang, S.K.; Alasalvar, C.; Bolling, B.W.; Shahidi, F. Nuts and their co-products: The impact of processing (roasting) on phenolics, bioavailability, and health benefits–A comprehensive review. *J. Funct. Foods* **2016**, *26*, 88–122. [CrossRef]
3. Gültekin-Özgüven, M.; Davarcı, F.; Paslı, A.A.; Demir, N.; Özçelik, B. Determination of phenolic compounds by ultra high liquid chromatography-tandem mass spectrometry: Applications in nuts. *LWT-Food Sci. Technol.* **2015**, *64*, 42–49. [CrossRef]
4. Alasalvar, C.; Salvadó, J.-S.; Ros, E. Bioactives and health benefits of nuts and dried fruits. *Food Chem.* **2020**, *314*, 126192. [CrossRef] [PubMed]
5. Alasalvar, C.; Bolling, B.W. Review of nut phytochemicals, fat-soluble bioactives, antioxidant components and health effects. *Br. J. Nutr.* **2015**, *113*, S68–S78. [CrossRef]
6. Bolling, B.W.; Chen, C.-Y.O.; McKay, D.L.; Blumberg, J.B. Tree nut phytochemicals: Composition, antioxidant capacity, bioactivity, impact factors. A systematic review of almonds, Brazils, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. *Nutr. Res. Rev.* **2011**, *24*, 244–275. [CrossRef]
7. De Souza, R.G.M.; Schincaglia, R.M.; Pimentel, G.D.; Mota, J.F. Nuts and human health outcomes: A systematic review. *Nutrients* **2017**, *9*, 1311. [CrossRef]
8. El-Hawary, S.; Abubaker, M.; Mahrous, E.A. Extracts of Different Organs of Macadamia Nut Tree (*Macadamia integrifolia*) Ameliorate Oxidative Damage in D-Galactose Accelerated Aging Model in Rats. *Biointerface Res. Appl. Chem.* **2021**, *12*, 7125–7135. [CrossRef]
9. Navarro, S.L.; Rodrigues, C.E. Macadamia oil extraction methods and uses for the defatted meal byproduct. *Trends Food Sci. Technol.* **2016**, *54*, 148–154. [CrossRef]
10. Shuai, X.; Dai, T.; Chen, M.; Liang, R.; Du, L.; Chen, J.; Liu, C. Comparative study of chemical compositions and antioxidant capacities of oils obtained from 15 macadamia (*Macadamia integrifolia*) Cultivars in China. *Foods* **2021**, *10*, 1031. [CrossRef]
11. Shuai, X.; Dai, T.; Chen, M.; Liu, C.-m.; Ruan, R.; Liu, Y.; Chen, J. Characterization of lipid compositions, minor components and antioxidant capacities in macadamia (*Macadamia integrifolia*) oil from four major areas in China. *Food Biosci.* **2022**, *50*, 102009. [CrossRef]
12. Rengel, A.; Pérez, E.; Piombo, G.; Ricci, J.; Servent, A.; Tapia, M.S.; Gibert, O.; Montet, D. Lipid profile and antioxidant activity of macadamia nuts (*Macadamia integrifolia*) cultivated in Venezuela. *Nat. Sci.* **2015**, *7*, 535–547.
13. Abubaker, M.; El Hawary, S.S.; Mahrous, E.A.; Abd El-Kader, E.M. Study of Nutritional contents of *Macadamia integrifolia* Maiden & Betche leaves, kernel and pericarp cultivated in Egypt. *Int. J. Pharmacogn. Phytochem. Res.* **2017**, *9*, 1442–1445.
14. Garg, M.L.; Blake, R.J.; Wills, R.B. Macadamia nut consumption lowers plasma total and LDL cholesterol levels in hypercholesterolemic men. *J. Nutr.* **2003**, *133*, 1060–1063. [CrossRef] [PubMed]
15. Wood, L.G.; Garg, M.L. Macadamia Nuts (*Macadamia integrifolia* and *tetraphylla*) and their Use in Hypercholesterolemic Subjects. In *Nuts and Seeds in Health and Disease Prevention*; Elsevier: Amsterdam, The Netherlands, 2011; pp. 717–725.
16. Jones, J.L.; Sabaté, J.; Heskey, C.; Oda, K.; Miles, F.; Rajaram, S. Macadamia nut effects on cardiometabolic risk factors: A randomised trial. *J. Nutr. Sci.* **2023**, *12*, e55. [CrossRef]

17. Alasalvar, C.; Hoffman, A.M.; Shahidi, F. Antioxidant activities and phytochemicals in hazelnut (*Corylus avellana* L.) and hazelnut by-products. In *Tree Nuts Composition, Phytochemicals, and Health Effects*; Alasalvar, C., Shahidi, F., Eds.; CRC Press: Boca Raton, FL, USA, 2009; pp. 215–235.
18. Alasalvar, C.; Huang, G.; Bolling, B.W.; Jantip, P.A.; Pegg, R.B.; Wong, X.K.; Chang, S.K.; Pelvan, E.; de Camargo, A.C.; Mandalari, G. Upcycling commercial nut byproducts for food, nutraceutical, and pharmaceutical applications: A comprehensive review. *Food Chem.* **2025**, *467*, 142222. [CrossRef]
19. Yang, W.-h.; Lu, C.-z. Phenolic composition and antioxidant properties of 2 taxa of macadamia flowers. *Nat. Prod. Commun.* **2022**, *17*, 1934578X221096176. [CrossRef]
20. Wallace, H.M.; Walton, D. Macadamia (*Macadamia integrifolia*, *Macadamia tetraphylla* and hybrids). In *Postharvest Biology and Technology of Tropical and Subtropical Fruits*; Elsevier: Amsterdam, The Netherlands, 2011; pp. 450–474e.
21. Zhang, M.; Li, Y.; Shuai, X.-x.; Qiao, J.; Wei, C.-b.; Ma, F.-y.; Zhang, Y.-h.; Du, L.-q. Ultrasound-assisted extraction of phenolic compounds from macadamia (*Macadamia integrifolia*) green peel: Purification, identification and antioxidant activities. *LWT* **2023**, *189*, 115552. [CrossRef]
22. Shi, R.; Tao, L.; Tu, X.; Zhang, C.; Xiong, Z.; Rami Horowitz, A.; Asher, J.B.; He, J.; Hu, F. Metabolite Profiling and Transcriptome Analyses Provide Insight Into Phenolic and Flavonoid Biosynthesis in the Nutshell of Macadamia Ternifolia. *Front. Genet.* **2022**, *12*, 809986. [CrossRef]
23. Dailey, A.; Vuong, Q.V. Effect of extraction solvents on recovery of bioactive compounds and antioxidant properties from macadamia (*Macadamia tetraphylla*) skin waste. *Cogent Food Agric.* **2015**, *1*, 1115646. [CrossRef]
24. Dailey, A.; Vuong, Q.V. Optimization of aqueous extraction conditions for recovery of phenolic content and antioxidant properties from Macadamia (*Macadamia tetraphylla*) skin waste. *Antioxidants* **2015**, *4*, 699–718. [CrossRef]
25. Dailey, A.; Vuong, Q.V. Optimisation of ultrasonic conditions as an advanced extraction technique for recovery of phenolic compounds and antioxidant activity from Macadamia (*Macadamia tetraphylla*) skin waste. *Technologies* **2015**, *3*, 302–320. [CrossRef]
26. Ahmed, M.F.; Popovich, D.G.; Whitby, C.P.; Rashidinejad, A. Phenolic compounds from macadamia husk: An updated focused review of extraction methodologies and antioxidant activities. *Food Bioprod. Process.* **2024**, *148*, 165–175. [CrossRef]
27. Fernández-Agulló, A.; Pereira, E.; Freire, M.S.; Valentão, P.; Andrade, P.B.; González-Álvarez, J.; Pereira, J. Influence of solvent on the antioxidant and antimicrobial properties of walnut (*Juglans regia* L.) green husk extracts. *Ind. Crops Prod.* **2013**, *42*, 126–132. [CrossRef]
28. Zhu, Y.; Ma, W.; Zhang, T.; Zhang, C.; Sun, A. Green extraction of polyphenol compound from walnut green husk by microwave-assisted choline chloride-based deep eutectic solvents: Identification, kinetic, comparison and bioactivity. *Food Chem.* **2025**, *492*, 145438. [CrossRef]
29. Momen, E.; Satari, B. Green biorefinery of walnut husk: Phenolic extraction and ethanol production. *Appl. Food Res.* **2024**, *4*, 100500. [CrossRef]
30. Gülüm, L.; Güler, E.; Zırhlı, Ç.B.; Çelik, A.B.; Tutar, Y. Phytochemical profiling and anticancer potential of pistachio wastes against MCF-7 breast cancer cells: A metabolic and apoptotic pathway analysis. *BMC Complement. Med. Ther.* **2025**, *25*, 275. [CrossRef]
31. Farrokhi, H.; Eskandari, M.H.; Shakerardekani, A.; Golmakani, M.T.; Niakousari, M. Pistachio hull extract as a natural antioxidant incorporated into pistachio paste: Antioxidant activity and oxidative stability. *Appl. Food Res.* **2025**, *5*, 100907. [CrossRef]
32. Harnafi, M.; Bekkouch, O.; Touiss, I.; Khatib, S.; Mokhtari, I.; Milenkovic, D.; Harnafi, H.; Amrani, S. Phenolic-rich extract from almond (*Prunus dulcis*) hulls improves lipid metabolism in triton WR-1339 and high-fat diet-induced hyperlipidemic mice and prevents lipoprotein oxidation: A comparison with fenofibrate and butylated hydroxyanisole. *Prev. Nutr. Food Sci.* **2020**, *25*, 254. [CrossRef]
33. Zhang, Y.; Cai, P.; Cheng, G.; Zhang, Y. A brief review of phenolic compounds identified from plants: Their extraction, analysis, and biological activity. *Nat. Prod. Commun.* **2022**, *17*, 1934578X211069721. [CrossRef]
34. Martillanes, S.; Rocha-Pimienta, J.; Cabrera-Bañegil, M.; Martín-Vertedor, D.; Delgado-Adámez, J. Application of phenolic compounds for food preservation: Food additive and active packaging. In *Phenolic Compounds-Biological Activity*; IntechOpen: London, UK, 2017.
35. Nardini, M. Phenolic compounds in food: Characterization and health benefits. *Molecules* **2022**, *27*, 783. [CrossRef]
36. Cao, H.; Saroglu, O.; Karadag, A.; Diaconeasa, Z.; Zoccatelli, G.; Conte-Junior, C.A.; Gonzalez-Aguilar, G.A.; Ou, J.; Bai, W.; Zamarioli, C.M. Available technologies on improving the stability of polyphenols in food processing. *Food Front.* **2021**, *2*, 109–139. [CrossRef]
37. Oancea, S. A review of the current knowledge of thermal stability of anthocyanins and approaches to their stabilization to heat. *Antioxidants* **2021**, *10*, 1337. [CrossRef] [PubMed]
38. Wang, M.; Zhang, H.; Yi, L.; Högger, P.; Arroo, R.; Bajpai, V.K.; Prieto, M.-A.; Simal-Gandara, J.; Wang, S.; Cao, H. Stability and antioxidant capacity of epigallocatechin gallate in Dulbecco's modified eagle medium. *Food Chem.* **2022**, *366*, 130521. [CrossRef] [PubMed]

39. Singh, M.; Thrimawithana, T.; Shukla, R.; Adhikari, B. Managing obesity through natural polyphenols: A review. *Future Foods* **2020**, *1*, 100002. [CrossRef]
40. Aatif, M. Current understanding of polyphenols to enhance bioavailability for better therapies. *Biomedicines* **2023**, *11*, 2078. [CrossRef] [PubMed]
41. Thakur, N.; Raigond, P.; Singh, Y.; Mishra, T.; Singh, B.; Lal, M.K.; Dutt, S. Recent updates on bioaccessibility of phytonutrients. *Trends Food Sci. Technol.* **2020**, *97*, 366–380. [CrossRef]
42. Pasquet, P.; Julien-David, D.; Zhao, M.; Villain-Gambier, M.; Trébouet, D. Stability and preservation of phenolic compounds and related antioxidant capacity from agro-food matrix: Effect of pH and atmosphere. *Food Biosci.* **2024**, *57*, 103586. [CrossRef]
43. Ricci, A.; Stefanuto, L.; Gasperi, T.; Bruni, F.; Tofani, D. Lipid nanovesicles for antioxidant delivery in skin: Liposomes, ufasomes, ethosomes, and niosomes. *Antioxidants* **2024**, *13*, 1516. [CrossRef]
44. Xu, Y.; Yan, X.; Zheng, H.; Li, J.; Wu, X.; Xu, J.; Zhen, Z.; Du, C. The application of encapsulation technology in the food Industry: Classifications, recent Advances, and perspectives. *Food Chem. X* **2024**, *21*, 101240. [CrossRef]
45. Taylor, T.M.; Weiss, J.; Davidson, P.M.; Bruce, B.D. Liposomal nanocapsules in food science and agriculture. *Crit. Rev. Food Sci. Nutr.* **2005**, *45*, 587–605. [CrossRef] [PubMed]
46. Emami, S.; Azadmard-Damirchi, S.; Peighambardoust, S.H.; Valizadeh, H.; Hesari, J. Liposomes as carrier vehicles for functional compounds in food sector. *J. Exp. Nanosci.* **2016**, *11*, 737–759. [CrossRef]
47. Xiang, Y.; Xiang, M.; Mao, Y.; Huang, L.; He, Q.; Dong, Y. Insights into structure-antioxidant activity relationships of polyphenol-phospholipid complexes: The effect of hydrogen bonds formed by phenolic hydroxyl groups. *Food Chem.* **2025**, *485*, 144471. [CrossRef]
48. Zhao, L.; Wang, D.; Yu, J.; Wang, X.; Wang, T.; Yu, D.; Elfalleh, W. Complex phospholipid liposomes co-encapsulated of proanthocyanidins and α-tocopherol: Stability, antioxidant activity and in vitro digestion simulation. *Food Biosci.* **2024**, *61*, 104899. [CrossRef]
49. Rashidinejad, A.; Birch, E.J.; Sun-Waterhouse, D.; Everett, D.W. Delivery of green tea catechin and epigallocatechin gallate in liposomes incorporated into low-fat hard cheese. *Food Chem.* **2014**, *156*, 176–183. [CrossRef]
50. Feng, T.; Wei, Y.; Lee, R.J.; Zhao, L. Liposomal curcumin and its application in cancer. *Int. J. Nanomed.* **2017**, *12*, 6027–6044. [CrossRef]
51. Giordani, B.; Basnet, P.; Mishchenko, E.; Luppi, B.; Škalko-Basnet, N. Utilizing liposomal quercetin and gallic acid in localized treatment of vaginal Candida infections. *Pharmaceutics* **2019**, *12*, 9. [CrossRef]
52. Bonechi, C.; Donati, A.; Tamasi, G.; Leone, G.; Consumi, M.; Rossi, C.; Lamponi, S.; Magnani, A. Protective effect of quercetin and rutin encapsulated liposomes on induced oxidative stress. *Biophys. Chem.* **2018**, *233*, 55–63. [CrossRef] [PubMed]
53. Athirojthanakij, W.; Rashidinejad, A. Delivery of catechins from green tea waste in single-and double-layer liposomes via their incorporation into a functional green kiwifruit juice. *Molecules* **2023**, *28*, 575. [CrossRef] [PubMed]
54. Altin, G.; Gültekin-Özgüven, M.; Ozcelik, B. Chitosan coated liposome dispersions loaded with cacao hull waste extract: Effect of spray drying on physico-chemical stability and in vitro bioaccessibility. *J. Food Eng.* **2018**, *223*, 91–98. [CrossRef]
55. Tran, T.H.; Nguyen, N.T.; Dang, P.H. Evaluating phenolic compounds and antioxidant activity of the pericarps and seed coats extracts of *Macadamia integrifolia* and preparing their nanoemulsions. *Int. J. Chem. Biochem. Sci.* **2023**, *24*, 215–223.
56. Vu, M.T.; Le, N.T.T.; Pham, T.L.-B.; Nguyen, N.H.; Nguyen, D.H. Development and characterization of soy lecithin liposome as potential drug carrier systems for codelivery of letrozole and paclitaxel. *J. Nanomater.* **2020**, *2020*, 8896455. [CrossRef]
57. Păvăloiu, R.-D.; Sha'at, F.; Neagu, G.; Deaconu, M.; Bubueanu, C.; Albulescu, A.; Sha'at, M.; Hlevca, C. Encapsulation of polyphenols from Lycium barbarum leaves into liposomes as a strategy to improve their delivery. *Nanomaterials* **2021**, *11*, 1938. [CrossRef]
58. Fan, M.; Xu, S.; Xia, S.; Zhang, X. Effect of different preparation methods on physicochemical properties of salidroside liposomes. *J. Agric. Food Chem.* **2007**, *55*, 3089–3095. [CrossRef]
59. Miere, F.; Vicas, S.I.; Timar, A.V.; Ganea, M.; Zdrinca, M.; Cavalu, S.; Fritea, L.; Vicas, L.; Muresan, M.; Pallag, A. Preparation and characterization of two different liposomal formulations with bioactive natural extract for multiple applications. *Processes* **2021**, *9*, 432. [CrossRef]
60. Bitwell, C.; Indra, S.S.; Luke, C.; Kakoma, M.K. A review of modern and conventional extraction techniques and their applications for extracting phytochemicals from plants. *Sci. Afr.* **2023**, *19*, e01585. [CrossRef]
61. Folin, O.; Ciocalteu, V. On tyrosine and tryptophane determinations in proteins. *J. Biol. Chem.* **1927**, *73*, 627–650. [CrossRef]
62. Rashidinejad, A.; Ahmmed, M.K. The influence of ripening on the nutrient composition and antioxidant properties of New Zealand damson plums. *Food Sci. Nutr.* **2024**, *12*, 4311–4320. [CrossRef] [PubMed]
63. Sembiring, E.N.; Elya, B.; Sauriasari, R. Phytochemical screening, total flavonoid and total phenolic content and antioxidant activity of different parts of *Caesalpinia bonduc* (L.) Roxb. *Pharmacogn. J.* **2018**, *10*, 123–127. [CrossRef]
64. Gibis, M.; Zeeb, B.; Weiss, J. Formation, characterization, and stability of encapsulated hibiscus extract in multilayered liposomes. *Food Hydrocoll.* **2014**, *38*, 28–39. [CrossRef]

65. Gibis, M.; Vogt, E.; Weiss, J. Encapsulation of polyphenolic grape seed extract in polymer-coated liposomes. *Food Funct.* **2012**, *3*, 246–254. [CrossRef]
66. Barekat, S.; Nasirpour, A.; Keramat, J.; Dinari, M.; Claeys, M.; Sedaghat Doost, A.; Van der Meeren, P. Formulation, characterization, and physical stability of encapsulated walnut green husk (*Juglans regia* L.) extract in phosphatidylcholine liposomes. *J. Dispers. Sci. Technol.* **2024**, *45*, 2180–2193. [CrossRef]
67. Everette, J.D.; Bryant, Q.M.; Green, A.M.; Abbey, Y.A.; Wangila, G.W.; Walker, R.B. Thorough study of reactivity of various compound classes toward the Folin–Ciocalteu reagent. *J. Agric. Food Chem.* **2010**, *58*, 8139–8144. [CrossRef]
68. Dailey, A.; Vuong, Q.V. Optimum conditions for microwave assisted extraction for recovery of phenolic compounds and antioxidant capacity from Macadamia (*Macadamia tetraphylla*) skin waste using water. *Processes* **2015**, *4*, 2. [CrossRef]
69. Somwongin, S.; Sirilun, S.; Chantawannakul, P.; Anuchapreeda, S.; Yawootti, A.; Chaiyana, W. Ultrasound-assisted green extraction methods: An approach for cosmeceutical compounds isolation from *Macadamia integrifolia* pericarp. *Ultrason. Sonochem.* **2023**, *92*, 106266. [CrossRef]
70. Müller, R.H.; Radtke, M.; Wissing, S.A. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv. Drug Deliv. Rev.* **2002**, *54*, S131–S155. [CrossRef] [PubMed]
71. Dubey, A.; Prabhu, P.; Kamath, J. Nano Structured lipid carriers: A Novel Topical drug delivery system. *Int. J. PharmTech Res.* **2012**, *4*, 705–714.
72. Salvi, V.R.; Pawar, P. Nanostructured lipid carriers (NLC) system: A novel drug targeting carrier. *J. Drug Deliv. Sci. Technol.* **2019**, *51*, 255–267. [CrossRef]
73. Joshi, S.; Cooke, J.R.; Chan, D.K.; Ellis, J.A.; Hossain, S.S.; Singh-Moon, R.P.; Wang, M.; Bigio, I.J.; Bruce, J.N.; Straubinger, R.M. Liposome size and charge optimization for intraarterial delivery to gliomas. *Drug Deliv. Transl. Res.* **2016**, *6*, 225–233. [CrossRef]
74. Song, F.; Yang, G.; Wang, Y.; Tian, S. Effect of phospholipids on membrane characteristics and storage stability of liposomes. *Innov. Food Sci. Emerg. Technol.* **2022**, *81*, 103155. [CrossRef]
75. Akgün, D.; Gültekin-Özgüven, M.; Yücetepe, A.; Altin, G.; Gibis, M.; Weiss, J.; Özçelik, B. Stirred-type yoghurt incorporated with sour cherry extract in chitosan-coated liposomes. *Food Hydrocoll.* **2020**, *101*, 105532. [CrossRef]
76. Hızır-Kadı, İ.; Gültekin-Özgüven, M.; Altin, G.; Demircan, E.; Özçelik, B. Liposomal nanodelivery systems generated from proliposomes for pollen extract with improved solubility and in vitro bioaccessibility. *Heliyon* **2020**, *6*, e05030. [CrossRef] [PubMed]
77. González-Ortega, R.; Šturm, L.; Skrt, M.; Di Mattia, C.D.; Pittia, P.; Poklar Ulrih, N. Liposomal encapsulation of oleuropein and an olive leaf extract: Molecular interactions, antioxidant effects and applications in model food systems. *Food Biophys.* **2021**, *16*, 84–97. [CrossRef]
78. Baljak, J.; Dekanski, D.; Pirković, A.; Mitić, N.; Rašković, A.; Kladar, N.; Jovanović, A.A. Valorization of Olive Leaf Extract via Tailored Liposomal Carriers: Comparative Analysis of Physicochemical Features, Antioxidant Capacity, and Stability. *Pharmaceuticals* **2025**, *18*, 1639. [CrossRef]
79. Prevete, G.; Carvalho, L.G.; del Carmen Razola-Diaz, M.; Verardo, V.; Mancini, G.; Fiore, A.; Mazzonna, M. Ultrasound assisted extraction and liposome encapsulation of olive leaves and orange peels: How to transform biomass waste into valuable resources with antimicrobial activity. *Ultrason. Sonochem.* **2024**, *102*, 106765. [CrossRef] [PubMed]
80. Trucillo, P.; Campardelli, R.; Aliakbarian, B.; Perego, P.; Reverchon, E. Supercritical assisted process for the encapsulation of olive pomace extract into liposomes. *J. Supercrit. Fluids* **2018**, *135*, 152–159. [CrossRef]
81. Roberts, S.A.; Lee, C.; Singh, S.; Agrawal, N. Versatile encapsulation and synthesis of potent liposomes by thermal equilibration. *Membranes* **2022**, *12*, 319. [CrossRef]
82. Akbarzadeh, A.; Rezaei-Sadabady, R.; Davaran, S.; Joo, S.W.; Zarghami, N.; Hanifehpour, Y.; Samiei, M.; Kouhi, M.; Nejati-Koshki, K. Liposome: Classification, preparation, and applications. *Nanoscale Res. Lett.* **2013**, *8*, 102. [CrossRef] [PubMed]
83. Torchilin, V.P. Recent advances with liposomes as pharmaceutical carriers. *Nat. Rev. Drug Discov.* **2005**, *4*, 145–160. [CrossRef]
84. Dag, D.; Oztop, M.H. Formation and characterization of green tea extract loaded liposomes. *J. Food Sci.* **2017**, *82*, 463–470. [CrossRef]
85. Jovanović, A.A.; Balanč, B.; Volić, M.; Pećinar, I.; Živković, J.; Šavikin, K.P. Rosehip extract-loaded liposomes for potential skin application: Physicochemical properties of non-and UV-irradiated liposomes. *Plants* **2023**, *12*, 3063. [CrossRef]
86. Micheletto, Y.M.S.; Jesus, B.V.d.; Peres, G.L.; Pinto, V.Z. A Systematic Preparation of Liposomes with Yerba Mate (*Ilex paraguariensis*) Extract. *Plants* **2025**, *14*, 1325. [CrossRef]
87. Jovanović, A.A.; Balanč, B.; Petrović, P.M.; Čutović, N.; Marković, S.B.; Djordjević, V.B.; Bugarski, B.M. Liposome-Based Encapsulation of Extract from Wild Thyme (*Thymus serpyllum* L.) Tea Processing Residues for Delivery of Polyphenols. *Foods* **2025**, *14*, 2626. [CrossRef] [PubMed]
88. Lopez-Pinto, J.; González-Rodríguez, M.; Rabasco, A. Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. *Int. J. Pharm.* **2005**, *298*, 1–12. [CrossRef]

89. Fathi-Azarbayjani, A.; Jouyban, A.; Chan, S.Y. Impact of surface tension in pharmaceutical sciences. *J. Pharm. Pharm. Sci.* **2009**, *12*, 218–228. [CrossRef]
90. Bordi, F.; Cametti, C.; Sennato, S.; Viscomi, D. Counterion release in overcharging of polyion-liposome complexes. *Phys. Rev. E—Stat. Nonlinear Soft Matter Phys.* **2006**, *74*, 030402. [CrossRef]
91. Vitorino, C.; Almeida, J.; Gonçalves, L.; Almeida, A.; Sousa, J.; Pais, A. Co-encapsulating nanostructured lipid carriers for transdermal application: From experimental design to the molecular detail. *J. Control. Release* **2013**, *167*, 301–314. [CrossRef] [PubMed]
92. Kumbhar, D.D.; Pokharkar, V.B. Engineering of a nanostructured lipid carrier for the poorly water-soluble drug, bicalutamide: Physicochemical investigations. *Colloids Surf. A Physicochem. Eng. Asp.* **2013**, *416*, 32–42. [CrossRef]
93. Danaei, M.; Dehghankhold, M.; Ataei, S.; Hasanzadeh Davarani, F.; Javanmard, R.; Dokhani, A.; Khorasani, S.; Mozafari, M. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. *Pharmaceutics* **2018**, *10*, 57. [CrossRef] [PubMed]
94. Savaghebi, D.; Barzegar, M.; Mozafari, M.R. Manufacturing of nanoliposomal extract from *Sargassum boveanum* algae and investigating its release behavior and antioxidant activity. *Food Sci. Nutr.* **2020**, *8*, 299–310. [CrossRef]
95. Zhao, L.; Temelli, F.; Curtis, J.M.; Chen, L. Preparation of liposomes using supercritical carbon dioxide technology: Effects of phospholipids and sterols. *Food Res. Int.* **2015**, *77*, 63–72. [CrossRef]
96. Gumustas, M.; Sengel-Turk, C.T.; Gumustas, A.; Ozkan, S.A.; Uslu, B. Effect of polymer-based nanoparticles on the assay of antimicrobial drug delivery systems. In *Multifunctional Systems for Combined Delivery, Biosensing and Diagnostics*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 67–108.
97. Honary, S.; Zahir, F. Effect of zeta potential on the properties of nano-drug delivery systems-a review (Part 1). *Trop. J. Pharm. Res.* **2013**, *12*, 255–264.
98. Gibis, M.; Ruedt, C.; Weiss, J. In vitro release of grape-seed polyphenols encapsulated from uncoated and chitosan-coated liposomes. *Food Res. Int.* **2016**, *88*, 105–113. [CrossRef]
99. Zhang, L.; Pornpattananangkul, D.; Hu, C.-M.; Huang, C.-M. Development of nanoparticles for antimicrobial drug delivery. *Curr. Med. Chem.* **2010**, *17*, 585–594. [CrossRef]
100. Dwiastuti, R.; Noegrohati, S.; Istyastono, E.P.; Hadimartono, M. Formulation and physical properties observations of soy lecithin liposome containing 4-n-butylresorcinol. *AIP Conf. Proc.* **2016**, *1755*, 160005. [CrossRef]
101. Xu, X.; Zhao, W.; Ye, Y.; Cui, W.; Dong, L.; Yao, Y.; Li, K.; Han, J.; Liu, W. Novel nanoliposome codelivered DHA and anthocyanidin: Characterization, in vitro infant digestibility, and improved cell uptake. *J. Agric. Food Chem.* **2021**, *69*, 9395–9406. [CrossRef] [PubMed]
102. Zhang, J.; Huang, Y.; Shen, W.; Zeng, Y.; Miao, Y.; Feng, N.; Ci, T. Effects of Surface Charge of Inhaled Liposomes on Drug Efficacy and Biocompatibility. *Pharmaceutics* **2025**, *17*, 329. [CrossRef] [PubMed]
103. Saroglu, O.; Atalı, B.; Yıldırım, R.M.; Karadag, A. Characterization of nanoliposomes loaded with saffron extract: In vitro digestion and release of crocin. *J. Food Meas. Charact.* **2022**, *16*, 4402–4415. [CrossRef]
104. Birru, W.A.; Warren, D.B.; Ibrahim, A.; Williams, H.D.; Benameur, H.; Porter, C.J.; Chalmers, D.K.; Pouton, C.W. Digestion of phospholipids after secretion of bile into the duodenum changes the phase behavior of bile components. *Mol. Pharm.* **2014**, *11*, 2825–2834. [CrossRef]
105. Martinović, J.; Lukinac, J.; Jukić, M.; Ambrus, R.; Planinić, M.; Šelo, G.; Klarić, A.-M.; Perković, G.; Bucić-Kojić, A. In vitro bioaccessibility assessment of phenolic compounds from encapsulated grape pomace extract by ionic gelation. *Molecules* **2023**, *28*, 5285. [CrossRef]
106. Vulić, J.; Šeregelj, V.; Kalušević, A.; Lević, S.; Nedović, V.; Tumbas Šaponjac, V.; Čanadanović-Brunet, J.; Ćetković, G. Bioavailability and bioactivity of encapsulated phenolics and carotenoids isolated from red pepper waste. *Molecules* **2019**, *24*, 2837. [CrossRef] [PubMed]

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