

Article

Anti-Inflammatory Effects of Sesamin-Loaded Nanoparticles in LPS-Stimulated RAW 264.7 Macrophages

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Abstract

Background/Objectives: Sesamin is a bioactive lignan with well-documented anti-inflammatory activity but limited therapeutic application due to poor aqueous solubility and low bioavailability. This study developed phosphatidylcholine-based sesamin-loaded nanoparticles (NSM) to enhance sesamin dispersibility, stability, and anti-inflammatory efficacy. **Methods:** NSM were prepared by solvent displacement. In vitro release was evaluated. Cytotoxicity testing in RAW 264.7 macrophages identified non-toxic concentration ranges for subsequent assays. Anti-inflammatory activity was assessed in lipopolysaccharide (LPS)-stimulated macrophages. **Results:** NSM exhibited a hydrodynamic diameter of 113.6 ± 3.6 nm with an acceptable PDI, remaining physically and chemically stable for 90 days at 4 °C. In vitro release revealed rapid and complete sesamin liberation from NSM within 2 h, whereas pure sesamin showed negligible release due to poor solubility. In LPS-stimulated macrophages, NSM significantly enhanced nitric oxide (NO) inhibition with an IC₅₀ of 4.92 ± 0.40 µg/mL, markedly lower than sesamin (21.11 ± 3.42 µg/mL) and blank nanoparticles. NSM also strongly suppressed LPS-induced secretion of PGE₂, TNF-α, IL-1β, and IL-6 in a dose-dependent manner, demonstrating superior inhibitory effects compared with pure sesamin. **Conclusions:** These findings indicate that phosphatidylcholine-based nanoparticles substantially enhance the anti-inflammatory potency of sesamin by increasing its solubility, cellular uptake, and biological activity. NSM represents a promising delivery platform for natural anti-inflammatory agents and warrants further investigation for therapeutic applications.

Keywords: sesamin; lipid nanoparticles; inflammation management; health-promoting natural compounds

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1. Introduction

Sesamin is a lignan compound abundantly in sesame seeds (*Sesamum indicum* L.), approximately 50% of the total lignans in sesame. The structure of sesamin consists of a central furofuran core with methylenedioxy-substituted benzene rings, as shown in

Figure 1 [1,2]. Sesamin is widely used in both food and medical applications across various traditional systems. Sesamin has been reported to exert multiple pharmacological effects, including antioxidant, anticancer, antihypertensive, hepatoprotective, and especially anti-inflammatory activities [2,3]. Many studies have reported the anti-inflammatory effects of sesamin [4], such as inhibiting the enzyme delta-5-desaturase (Δ -5D), which leads to the reduced production of prostaglandin E2 (PGE₂) [5], reducing the production of pro-inflammatory cytokines, which are interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), as well as inhibiting p38 mitogen-activated protein kinase (p38 MAPK) and nuclear factor kappa β (NF- κ β) pathway [6,7]. Sesamin and its metabolites also decrease nitric oxide (NO) by downregulating inducible nitric oxide synthase (iNOS) in LPS-stimulated J774.1 macrophages [8]. Although sesamin has anti-inflammatory activity, its administration is limited by poor water solubility (only 2.5 μ g/mL) and low bioavailability, classifying it as a BCS class II [9].

To overcome these limitations, nanotechnology-based drug delivery systems have been explored as promising measures for enhancing the solubility, stability, and therapeutic efficacy of hydrophobic natural products [10]. Wang et al. developed a self-nanoemulsifying drug delivery system (SNEDDS) for sesamin to obtain a nanoemulsion and markedly improved intestinal permeability and systemic exposure. The SNEDDS increased relative and absolute bioavailability approximately 12.9-fold and from 0.3% to 4.4%, respectively, compared with crystalline sesamin [9]. Liu et al. subsequently reported sesamin-loaded sodium caseinate nanoparticles prepared by simple coacervation and markedly enhanced micellization efficiency in simulated gastric and intestinal fluids (approximately 3–5-fold), indicating improved solubilization and protection against gastrointestinal degradation [11]. In another approach, Sato et al. designed a solid dispersion system using α -glycosylated stevia as a carrier, which converted sesamin into an amorphous state, increased its dissolution ~190-fold, and elevated oral bioavailability ~30-fold in rats. The formulation also enhanced the nutraceutical function of sesamin by protecting against drug-induced photodermatitis in vivo [12]. These studies demonstrate that nano- and solid dispersion-based delivery systems can substantially enhance the solubility, stability, and functional bioactivity of sesamin, supporting the rationale for further development of sesamin-loaded nanocarriers, such as phosphatidylcholine-based nanoparticles, in the present work.

Lipid-based nanoparticles are most often used in pharmaceutical and medical research due to their multiple advantages, including protection of drugs from degradation, enhanced solubility, improved bioavailability, increased therapeutic efficiency, and targeted drug delivery [13,14]. Among these, nanoparticles formulated with phosphatidylcholine (PC) are particularly attractive. PC is a phospholipid consisting of a hydrophilic head group and two hydrophobic fatty acid chains. It exhibits biocompatibility and biodegradability, a high capacity to encapsulate lipophilic drugs, and the ability to enhance drug delivery, particularly by improving penetration through biological barriers such as the skin [14–16]. In inflammation, macrophages play a central role in producing pro-inflammatory mediators, including NO, PGE₂, TNF- α , IL-1 β , and IL-6 [17–19]. Lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls, is commonly used to stimulate RAW 264.7 cells, a macrophage-like cell line, thereby inducing an inflammatory response via the Toll-like receptor 4 (TLR4)/NF- κ B signaling pathway and iNOS [20,21]. This model is well-established for evaluating the anti-inflammatory activity of compounds and formulations. However, data on the anti-inflammatory efficacy of sesamin in nanoparticle formulations, particularly in LPS-induced macrophage models, remain limited. Therefore, this study aimed to develop a phosphatidylcholine-based sesamin-loaded nanoparticle (NSM) to enhance its solubility and bioavailability as well as evaluate its physical and chemical stability. Anti-inflammatory activity was evaluated using LPS-

stimulated RAW 264.7 macrophages, measuring NO production by the Griess assay and the concentrations of PGE₂, TNF- α , IL-1 β , and IL-6 were quantified using enzyme-linked immunosorbent assay (ELISA). To facilitate understanding of the formulation design, a schematic illustration of the proposed NSM architecture is provided in Figure 2.

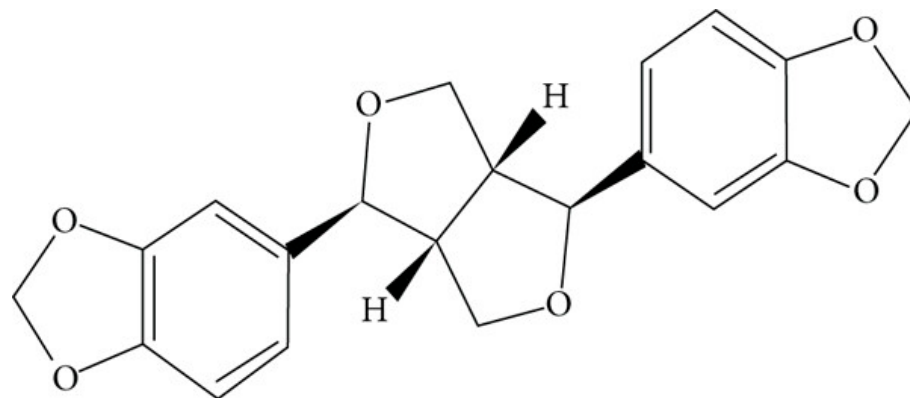


Figure 1. Chemical structure of sesamin [1].

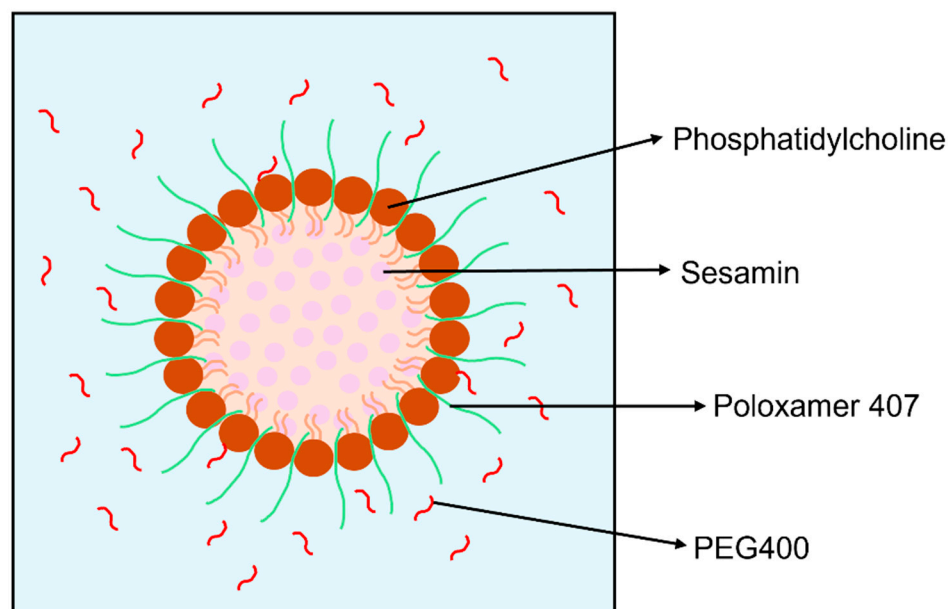


Figure 2. Schematic illustration of NSM, showing a lipid matrix from phosphatidylcholine stabilized by poloxamer 407, with PEG 400 present in the aqueous phase.

2. Materials and Methods

2.1. Materials

Sesamin was kindly provided by Dr. Pratchaya Kongtaweelert (Chiang Mai, Thailand) [22]. Culture reagents including Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS), phosphate-buffered saline (PBS), and penicillin/streptomycin were obtained from Gibco (Thermo Fisher Scientific, Waltham, MA, USA). L-NG-nitroarginine methyl ester (L-NAME) and lipopolysaccharide (LPS) derived from *Escherichia coli* O111:B4 were sourced from Sigma-Aldrich (St. Louis, MO, USA). BAY 11-7083, phosphatidylcholine, and polyethylene glycol 400 (PEG400) were purchased from MySkinRecipes (Bangkok, Thailand). Sulfanilamide, N-(1-naphthyl)ethylenediamine (NED), and phosphoric acid were also purchased from Sigma-Aldrich (St. Louis, MO, USA). Transwell® inserts were obtained from Corning Inc. (Corning, NY, USA). Methanol (HPLC grade),

dimethyl sulfoxide (DMSO), and acetone (analytical grade) were purchased from RCL Labscan Limited (Bangkok, Thailand). MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] was sourced from Amresco Inc. (Solon, OH, USA). ELISA kits for PGE₂, IL-1 β , TNF- α , and IL-6 were obtained from R&D Systems (Minneapolis, MN, USA).

2.2. Methods

2.2.1. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR was performed to identify the characteristic functional groups of sesamin. The FTIR spectrum of sesamin was recorded using an INVENIO® S FTIR spectrometer (Bruker, Billerica, MA, USA.) equipped with an attenuated total reflectance (ATR) accessory. The spectrum was collected over the wavenumber range of 4000–400 cm⁻¹ at room temperature and presented in transmittance mode. The obtained ATR-FTIR spectrum was used to confirm the chemical identity of sesamin based on its characteristic absorption bands.

2.2.2. Preparation of Sesamin-Loaded Nanoparticles

Sesamin-loaded nanoparticles were prepared using the solvent displacement method. Sesamin (4.25 mg) was dissolved in 3 mL of acetone containing phosphatidylcholine (15 mg) to form the organic phase. The aqueous phase was prepared using 1% (*w/v*) Poloxamer 407 in 15 mL of ultrapure water (Milli-Q). Once both phases were prepared, the organic phase was loaded into a syringe fitted with an 18-gauge needle. The organic phase was then added dropwise to the aqueous phase at 3 mL/h under magnetic stirring at 750 rpm. The addition continued until the entire organic phase had been transferred. The resulting dispersion was left to stand to allow acetone evaporation, thereby inducing the spontaneous formation of sesamin-loaded nanoparticles (NSM).

2.2.3. Determination of Particle Size, Size Distribution, and Physical Stability of Sesamin-Loaded Nanoparticles

The particle size and polydispersity index (PDI) of NSM and NPs were determined using dynamic light scattering (DLS) with a Zetasizer Nano ZS (Malvern Instruments, Worcestershire, UK). For measurement, the samples were diluted by mixing 100 μ L of the nanoparticle suspension with 900 μ L of deionized water (10-fold dilution). The measurements were performed in triplicate from three independent experiments, and results are expressed as mean $\pm$ SD. To evaluate long-term physical stability, the NSM and NPs were stored in sealed containers at 4 $^{\circ}$ C, 30 $^{\circ}$ C, and 45 $^{\circ}$ C. Particle size and PDI were monitored at 0, 30, 60, and 90 days. Changes in size distribution and PDI over time were used as indicators of nanoparticle stability.

2.2.4. Morphological Characterization by Transmission Electron Microscopy (TEM)

The morphology of the NSM formulations was examined using TEM (JEM-2100 Plus, JEOL, Tokyo, Japan) at 100 kV. NSM samples were diluted fivefold. One drop of the diluted dispersion was applied onto a carbon-coated copper grid using a dropper and allowed to air-dry at room temperature. Then, one drop of 0.5% phosphotungstic acid solution was added for negative staining and the grid was left to dry again before observation.

2.2.5. Determination of Sesamin Concentration in Nanoparticles and Chemical Stability of Sesamin-Loaded Nanoparticles

The concentration of sesamin in NSM was quantified using reversed-phase HPLC (Agilent Technologies, Inc. Santa Clara, CA, USA) equipped with a C18 reverse-phase column (250 mm $\times$ 4.6 mm, 5 μ m; Thermo Scientific, Waltham, MA, USA). The mobile phase

consisted of methanol and water (80:20, *v/v*). The flow rate was maintained at 1.0 mL/min, and the injection volume was 10 µL. Sesamin was detected at a wavelength of 280 nm. A standard curve was prepared by dissolving sesamin in methanol at concentrations ranging from 5 to 500 µg/mL. To determine the total sesamin content in the nanoparticles, the samples were completely dissolved in methanol before HPLC analysis. For the stability study, NSM was stored at 4 °C, 30 °C, and 45 °C for 90 days. Samples were collected on days 0, 30, 60, and 90. At each time point, the samples were prepared by completely dissolving the nanoparticles in methanol prior to HPLC analysis. The encapsulation efficiency (%EE) of NSM and the remaining sesamin were quantified using the standard curve and expressed as a percentage of the freshly prepared sample.

Encapsulation efficiency (%) was calculated using the following equation:

$$\%EE = \frac{\text{amount of sesamin in NPs}}{\text{amount of sesamin added in formulation}} \times 100$$

Sesamin remaining (%) was calculated using the following equation:

$$\%Sesamin\ remaining = \frac{\text{amount of sesamin in NPs}}{\text{amount of sesamin in freshly prepared NPs}} \times 100$$

2.2.6. In Vitro Drug Release Study

The in vitro drug release profile of sesamin from NSM was evaluated using a modified Transwell® insert method adapted from a previously reported study [23]. A 24-well Transwell® plate with polycarbonate membrane inserts (0.4 µm pore size; Corning Inc., Corning, NY, USA) was used to simulate the diffusion barrier. Two samples were tested: pure sesamin (1 mg/mL in phosphate-buffered saline (PBS; pH 6.5) and NSM (283.33 µg/mL) prepared as described above. For the pure sesamin, the compound was dispersed by vortexing and sonication, with visible precipitate due to its poor aqueous solubility. DLS analysis of a 10-fold dilution showed an average particle size of 6300 ± 800 nm. For each sample, 200 µL was added to the donor compartment (upper chamber), while the receptor compartment (lower chamber) was filled with 1.0 mL of preheated PBS (pH 6.5) and maintained at 37 ± 0.5 °C. At predetermined time points (15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h), 50 µL of the release medium was withdrawn from the receptor compartment and immediately replaced with 50 µL of new preheated PBS to maintain sink conditions. HPLC as described previously. All measurements were performed in triplicate, and the cumulative percentage of drug released was calculated.

2.2.7. Cell Culture

DMEM supplemented with 10% FBS and 1% penicillin–streptomycin was used to culture RAW 264.7 cells at 37 °C in a humidified atmosphere with 5% CO₂.

2.2.8. Cell Viability of Raw 264.7 Cells Using MTT Assay

The MTT assay was used to assess cell viability. RAW 264.7 cells (2 × 10⁵ cells/mL) were seeded into 96-well culture plates with 100 µL of medium and incubated for 24 h. After incubation, the medium was removed from each well. The cells were then treated with test samples in serum-free medium for 24 h. The samples included sesamin (1000 µg/mL) with 2-fold serial dilutions for 10 concentrations, NSM (283.33 µg/mL) with 2-fold serial dilutions for 10 concentrations, and NPs (1000 µg/mL) with 2-fold serial dilutions for 10 concentrations. Untreated cells served as the control. After treatment, the medium was removed, and 100 µL of MTT solution (0.5 mg/mL) was added to each well, followed by incubation for 3 h. The MTT solution was then removed, and 100 µL of DMSO was

added to each well to dissolve the formazan crystals. SpectraMax M3 microplate reader (Molecular Devices, San Jose, CA, USA) was used to measure the absorbance at 550 nm.

Cell viability (%) was calculated using the following equation:

$$\% \text{Cell Viability} = \frac{\text{OD of Sample}}{\text{OD of Untreated Control}} \times 100$$

2.2.9. Determination of Nitric Oxide Production Stimulated by Lipopolysaccharide on Raw 264.7 Macrophages

The nitric oxide production was measured using the Griess assay. For RAW 264.7 cells (2×10^5 cells/mL), 100 μ L were seeded into 96-well culture plates and incubated for 24 h. The cells were pretreated with test samples or L-NAME (26.9 μ g/mL; equivalent 100 μ M) in serum-free medium for 3 h, followed by stimulation with LPS (5 μ g/mL) for 24 h. L-name used as the positive control. After treatment, the supernatants were aspirated into a new microplate; 100 μ L. 1% Sulfanilamide (50 μ L) and 0.1% N-(1-naphthyl) ethylenediamine (NED) (50 μ L) solutions were added to each well, and the plate was incubated in the dark for 10 min. Absorbance was measured at 540 nm using a microplate reader as described previously. Nitric oxide release (%) was calculated using Equation (1), while nitric oxide inhibition (%) was calculated using Equation (2):

Nitric oxide release (%) was calculated using the following equation:

$$\% \text{Nitric oxide release} = \frac{\text{OD}_{\text{sample}}}{\text{OD}_{\text{LPS}}} \times 100 \quad (1)$$

Nitric oxide inhibition (%) was calculated using the following equation:

$$\% \text{Nitric oxide inhibition} = \frac{\text{OD}_{\text{LPS}} - \text{OD}_{\text{sample}}}{\text{OD}_{\text{LPS}}} \times 100 \quad (2)$$

2.2.10. Measurement of Inflammatory Cytokines (PGE₂, TNF- α , IL1- β , IL-6) Secretion Stimulated by Lipopolysaccharide on RAW 264.7 Macrophages

The levels of inflammatory cytokines, including PGE₂, TNF- α , IL-1 β , and IL-6, were quantified using ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocols. RAW 264.7 cells were seeded at a density of 2×10^5 cells/mL in 96-well plates (100 μ L/well) and incubated at 37 °C in a 5% CO₂ for 24 h. Cells were pretreated with test samples, indomethacin (IDM, 3.58 μ g/mL; equivalent to 10 μ M), or BAY 11-7083 (BAY, 2.07 μ g/mL; equivalent to 10 μ M) in serum-free medium for 3 h. Subsequently, inflammation was induced by LPS stimulation at 5 μ g/mL for 24 h. IDM was used as a positive control for PGE₂ inhibition, while BAY was used as a positive control for the inhibition of TNF- α , IL-1 β , and IL-6. After treatment, the cell culture supernatants were collected and used for cytokine quantification by ELISA.

2.2.11. Statistical Analysis

Statistical analysis of data was completed using an analysis of variance (one-way ANOVA), (GraphPad Prism 8, La Jolla, CA, USA). $p < 0.05$, $p < 0.01$, $p < 0.001$, and $p < 0.0001$ were considered statistically significant.

3. Results

3.1. FTIR Characterization of Sesamin

FTIR analysis was performed to confirm the chemical identity of sesamin. The FTIR spectrum of sesamin exhibited characteristic absorption bands, as shown in Figure 3,

consistent with previously reported FTIR data [24]. Absorption bands at approximately 1606, 1498, and 1441 cm^{-1} were assigned to aromatic ring stretching, confirming the presence of benzene rings. A distinct absorption band observed at 1248 cm^{-1} is associated with the methylenedioxy ($-\text{O}-\text{CH}_2-\text{O}-$) groups linked to the aromatic rings, which represent a characteristic structural feature of sesamin. Additional absorption bands in the range of 1093–1034 cm^{-1} were attributed to C–O–C stretching of ether linkages within the furofuran structure. Furthermore, absorption bands at 749 and 718 cm^{-1} correspond to out-of-plane C–H bending of substituted aromatic rings. These characteristic FTIR bands confirm the chemical identity of sesamin used in this study.

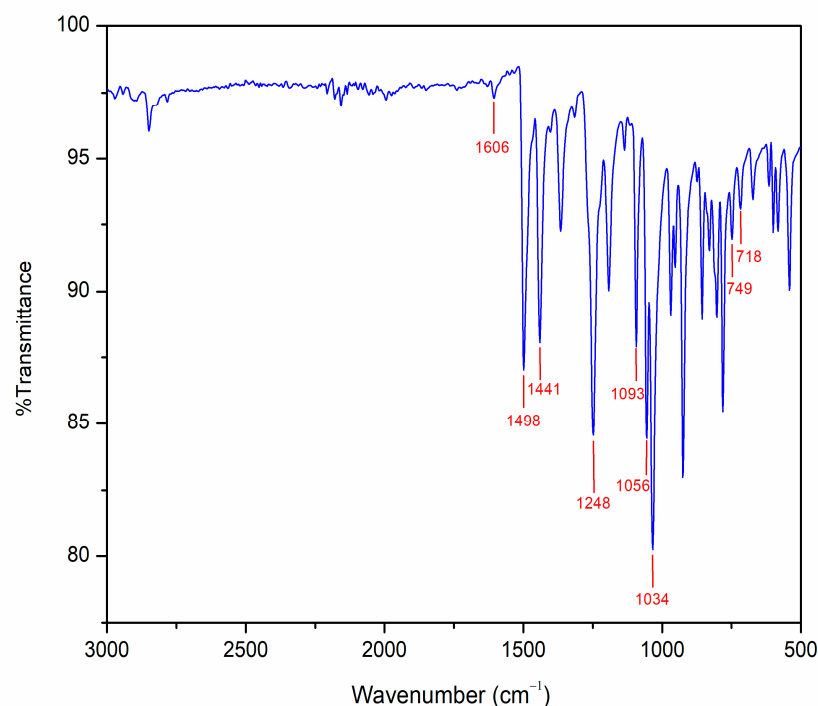


Figure 3. FTIR transmittance spectrum of sesamin.

3.2. Physical Stability of Sesamin-Loaded Nanoparticles

The physical stability of NSM and NPs was evaluated by measuring particle size and the polydispersity index (PDI) using DLS technique during storage at 4 °C, 30 °C, and 45 °C for 90 days. As shown in Figure 4, the initial particle sizes of NSM and NPs on day 0 were approximately 113.6 ± 3.6 nm and 117.6 ± 1.2 nm, respectively, and the corresponding initial PDI values were 0.354 ± 0.043 and 0.219 ± 0.008 , respectively. For NSM, no significant change in particle size was observed at 4 °C throughout the storage period. In contrast, a marked increase in particle size was detected at 30 °C and 45 °C, particularly on days 30 and 90, indicating temperature-dependent instability. The PDI of NSM remained almost unchanged at 4 °C. However, a significant increase in PDI was observed at 30 °C and especially at 45 °C on day 30. The PDI values partially returned toward baseline at later time points. For NPs, similar trends were observed. The initial particle size was comparable to that of NSM. Significant size increases were detected at 30 °C and 45 °C starting from day 30, whereas particles stored at 4 °C remained stable. Only small changes in PDI were observed at 4 °C, whereas significant increases were observed at 30 °C and 45 °C, indicating reduced stability at elevated temperatures.

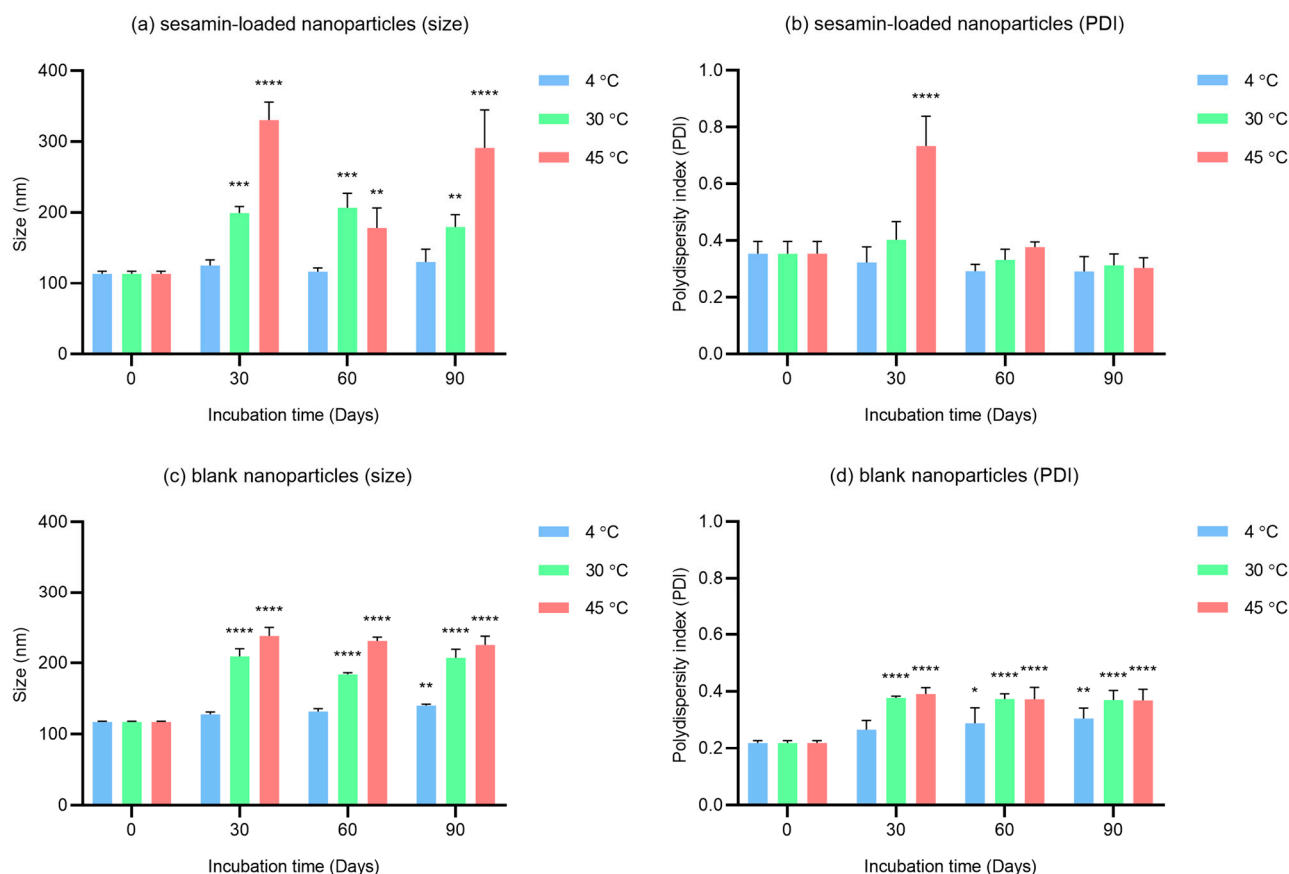


Figure 4. Particle size and polydispersity index (PDI) of (a,b) NSM and (c,d) NPs after storage at 4 °C, 30 °C, and 45 °C for 90 days, compared with day 0. Data are presented as mean $\pm$ SD from three independent experiments. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to Day 0.

3.3. Morphology of Sesamin-Loaded Nanoparticles Under Transmission Electron Microscopy

TEM was used to examine the morphology of NSM. TEM images showed discrete, nanosized particles with nearly spherical morphology, as shown in Figure 5. The particles were observed in the nanometer size range of approximately 110 nm, which is consistent with the hydrodynamic diameter measured by DLS.

3.4. Encapsulation Efficiency and Stability of Sesamin Content in Nanoparticles

Quantification was performed using reversed-phase HPLC equipped with a C18 column and a methanol:water (80:20, *v/v*) mobile phase. To ensure accurate measurement of total drug content, the nanoparticles were completely dissolved in methanol prior to analysis, rather than being analyzed as intact colloids. The representative HPLC chromatograms, presented as a zoomed-in view in Figure 6 and in full-scale (0–30 min) in the Supplementary Information (Figure S1), confirm the specific detection of sesamin without interference from formulation components. The sesamin content in freshly prepared NSM was 250.05 ± 3.42 $\mu\text{g/mL}$, with an encapsulation efficiency of $88.25 \pm 1.20\%$, indicating effective incorporation of sesamin within the phosphatidylcholine-based lipid matrix. The chemical stability of sesamin in NSM during storage at 4 °C, 30 °C, and 45 °C for 90 days is presented in Figure 7. At 4 °C and 30 °C, the remaining sesamin content remained stable throughout the study period, indicating good chemical stability. In contrast, samples stored at 45 °C exhibited a significant decrease in sesamin content at day 90, with the remaining percentage reduced to $90.5 \pm 6.3\%$ ($p < 0.001$), indicating temperature-dependent reduction in measured sesamin content under accelerated storage conditions.

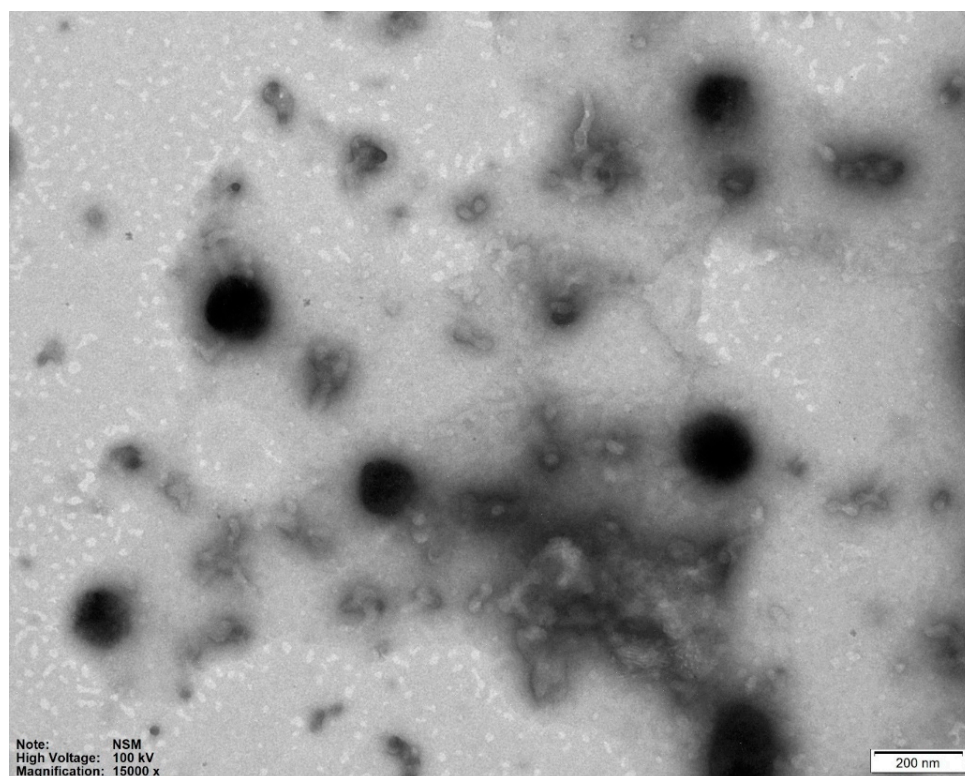


Figure 5. TEM image of NSM.

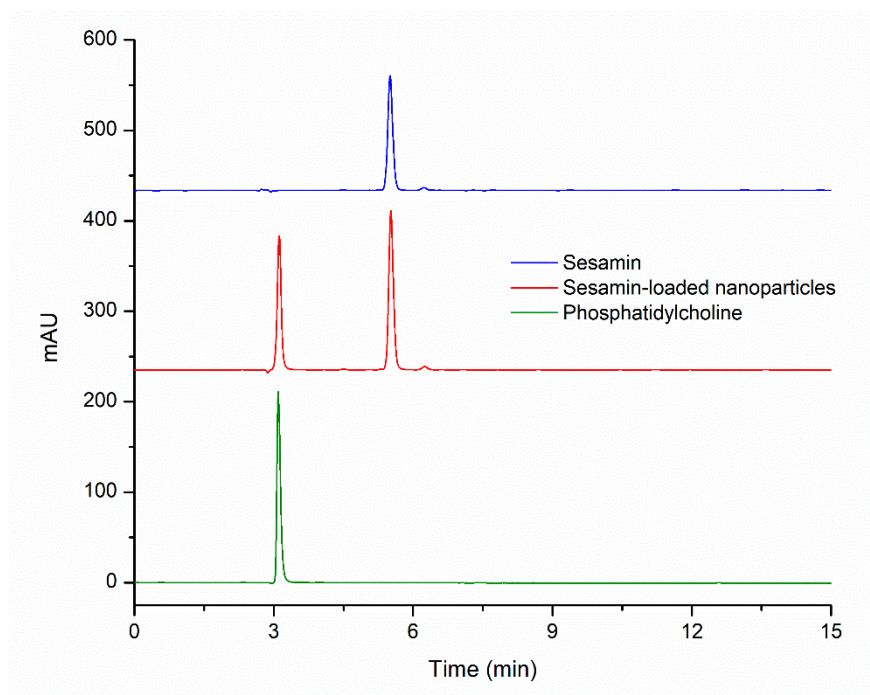


Figure 6. HPLC chromatogram of sesamin, NSM, and phosphatidylcholine.

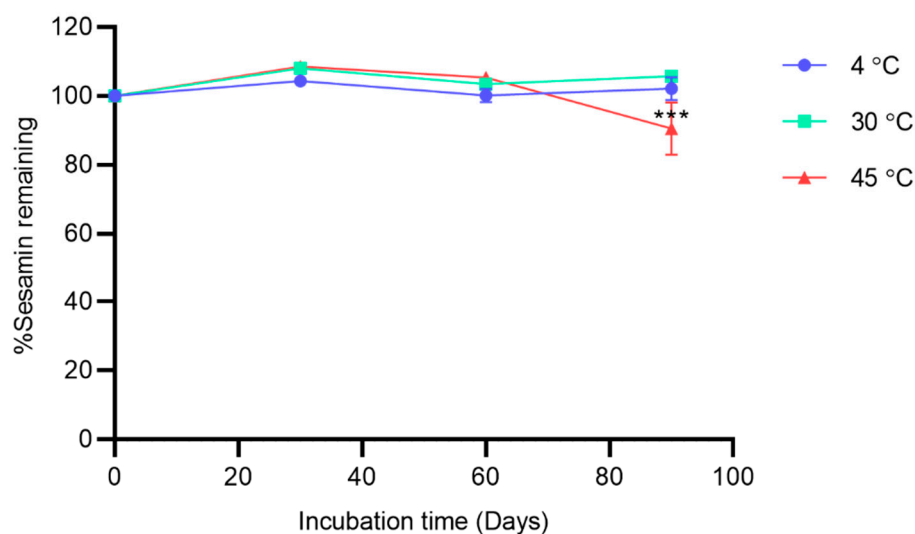


Figure 7. Percent sesamin remaining in NSM during storage at 4 °C, 30 °C, and 45 °C over 90 days, compared with freshly prepared samples (Day 0). Data are presented as mean $\pm$ SD ($n = 3$). *** $p < 0.001$ compared to Day 0.

3.5. In Vitro Release of Sesamin from the Sesamin-Loaded Nanoparticles

As illustrated in Figure 8, NSM showed a rapid release profile, with around 80% of the drug released within the first 30 min and nearly 100% within 2 h. Subsequently, the release plateaued and remained stable for up to 24 h. In contrast, the pure sesamin sample exhibited minimal release over 24 h. The cumulative release remained close to 0%, highlighting its poor solubility and limited diffusion in aqueous conditions without encapsulation or prior dissolution in a suitable solvent.

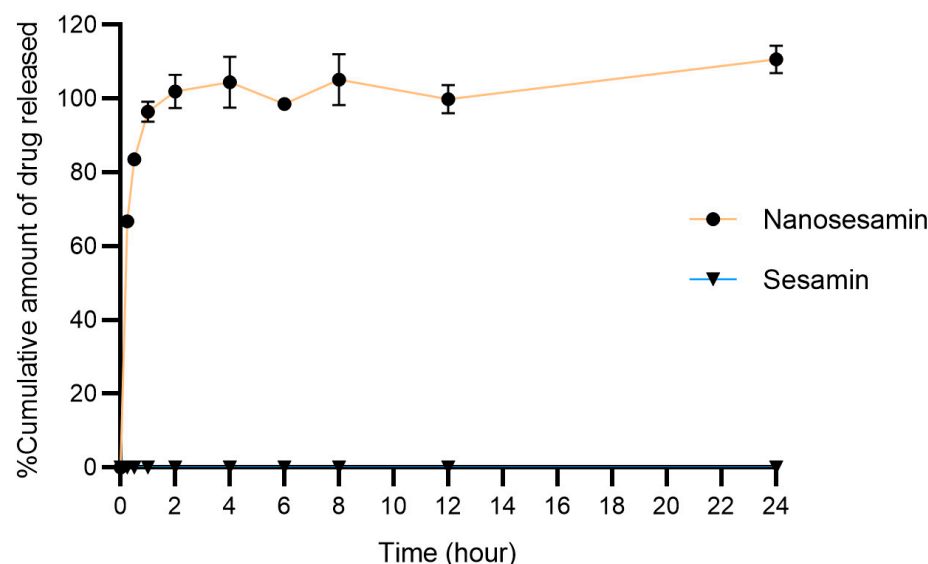


Figure 8. In vitro release profile of sesamin from pure sesamin and NSM in PBS at 37 °C. Samples were collected at 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 12 h, and 24 h. The amount of sesamin released at each time point was analyzed using HPLC. Data are presented as mean $\pm$ SD ($n = 3$).

3.6. Cytotoxicity of Sesamin and Sesamin-Loaded Nanoparticles on Cell Viability Using MTT Assay

The MTT assay was performed to assess the cytotoxicity of sesamin, NSM, and NPs on RAW 264.7 macrophages, to determine safe concentrations for subsequent anti-inflammatory activity via nitric oxide (NO) inhibition. Cells were treated with various concentrations of each sample for 24 h. Cell viability was calculated as a percentage compared to untreated control cells. As shown in Figure 9, sesamin and NPs were non-cytotoxic at concentrations ranging from 1.95 to 31.25 $\mu\text{g/mL}$, whereas higher concentrations (≥ 62.5 $\mu\text{g/mL}$) reduced cell viability to below 80%. For NSM, concentrations between 0.55 and 17.71 $\mu\text{g/mL}$ were considered non-cytotoxic, whereas concentrations of 35.42 $\mu\text{g/mL}$ and above reduced cell viability to below 80%. The half-maximal inhibitory concentration (IC_{50}) values for sesamin, NSM, and NPs were 202.97 ± 12.39 $\mu\text{g/mL}$, 57.13 ± 1.45 $\mu\text{g/mL}$, and 149.67 ± 14.1 $\mu\text{g/mL}$, respectively. To avoid cytotoxic effects, concentrations that maintained cell viability above 80% were selected for further nitric oxide inhibition assays to evaluate anti-inflammatory effects.

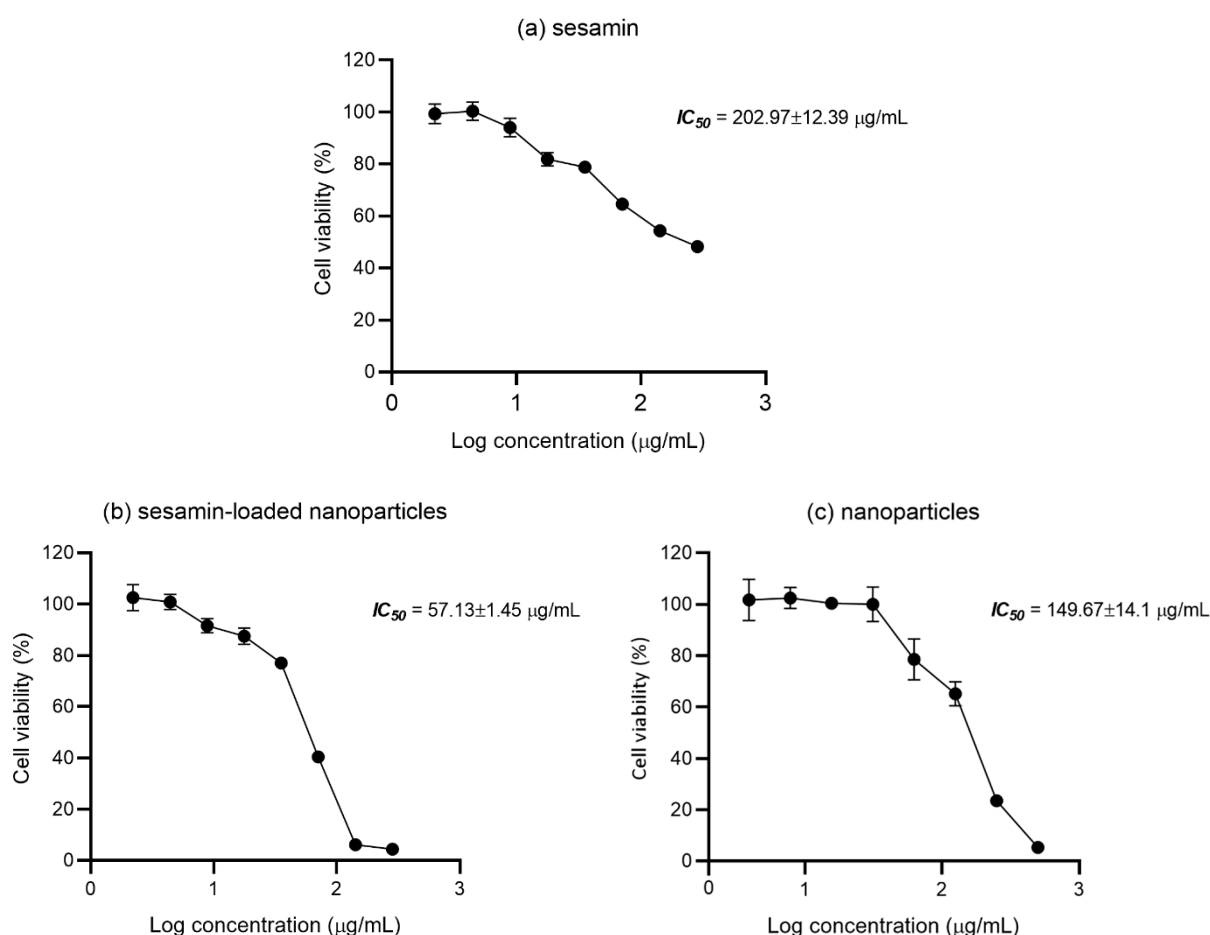


Figure 9. Cell viability of RAW 264.7 cells treated with different concentrations of (a) sesamin, (b) NSM, and (c) NPs for 24 h, assessed by the MTT assay. Data are presented as mean $\pm$ SD of three independent experiments.

3.7. Effects of Sesamin and Sesamin-Loaded Nanoparticles on Lipopolysaccharide-Induced Nitric Oxide Production in Raw 264.7 Macrophages

Following cytotoxicity evaluation by the MTT assay, only non-toxic concentrations (cell viability > 80%) of sesamin, NSM, and NPs were selected to evaluate their anti-inflammatory activity by determining the percentage of NO production in LPS-stimulated RAW 264.7 macrophages using the Griess assay. As shown in Figure 10, LPS stimulation significantly increased NO production compared to the untreated control group. Sesamin treatment inhibited NO production in a dose–response manner. A significant reduction first occurred at 3.91 $\mu\text{g/mL}$ ($p < 0.05$), and inhibition was stronger at 7.81 $\mu\text{g/mL}$ and higher concentrations ($p < 0.0001$), showing an effect that was as effective as the positive control, (L-NAME, 26.9 $\mu\text{g/mL}$; equivalent 100 μM). NSM significantly suppressed NO production starting at 2.21 $\mu\text{g/mL}$ ($p < 0.01$), with strong inhibition occurring at concentrations of 4.43 $\mu\text{g/mL}$ and above ($p < 0.0001$). NPs had a significant inhibition of NO release at $\geq 7.81 \mu\text{g/mL}$ ($p < 0.0001$); however, the magnitude of inhibition was less remarkable compared to both sesamin and NSM. These results suggest that sesamin and NSM can significantly inhibit the LPS-induced NO production in RAW 264.7 cells, and NSM has increased potency at lower concentrations, which may be due to the higher efficiency of cellular delivery with nanoparticle formulation. Consistent with the dose–response observed in Figure 10, the IC_{50} values of NO inhibition (Table 1) further confirmed the superior inhibitory potency of NSM. The IC_{50} value of sesamin was $21.11 \pm 3.42 \mu\text{g/mL}$, while NPs exhibited a comparable IC_{50} value of $21.26 \pm 1.69 \mu\text{g/mL}$, indicating similar inhibitory strength between pure sesamin and the carrier alone. In contrast, NSM exhibited a significantly lower IC_{50} of $4.92 \pm 0.40 \mu\text{g/mL}$ ($p < 0.001$), indicating a marked enhancement in NO inhibitory efficiency upon nanoparticle loading. Overall, these results show that NSM enhances the anti-inflammatory effect of sesamin by producing higher NO inhibition at much lower concentrations than pure sesamin.

Table 1. The IC_{50} of nitric oxide inhibition induced by LPS in RAW 264.7 cells.

Sample	Nitric Oxide Inhibition (IC_{50} ; $\mu\text{g/mL}$)
Sesamin-loaded nanoparticles	4.92 ± 0.40 ***
Sesamin	21.11 ± 3.42
Blank Nanoparticles	21.26 ± 1.69
L-NAME	ND

Data are presented as mean $\pm$ SD of three independent experiments. *** $p < 0.001$ compared to each group.

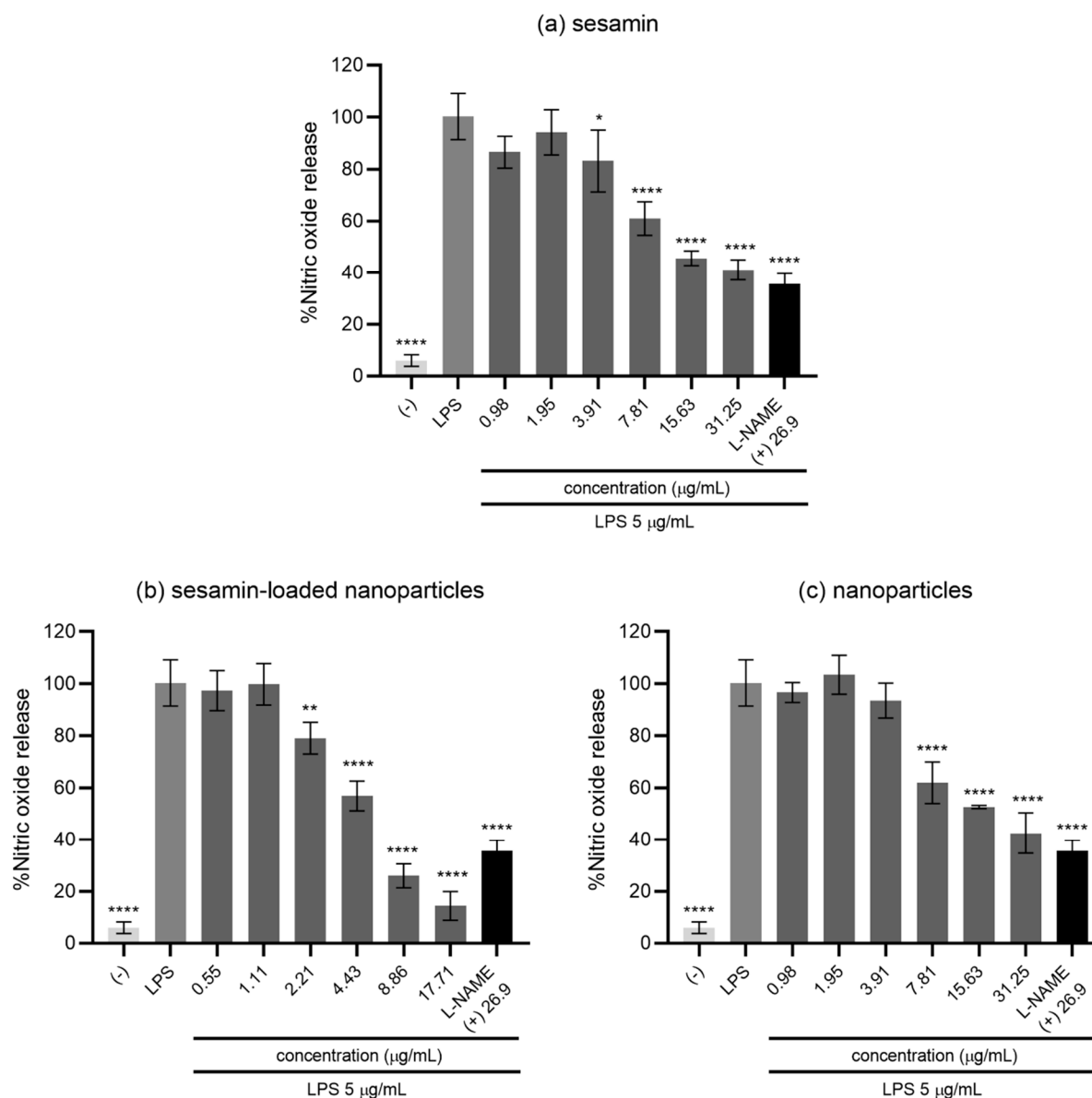


Figure 10. Effects of (a) sesamin, (b) NSM, and (c) NPs on LPS-induced NO production in Raw 264.7 macrophages. Cells were treated with LPS (5 μg/mL) and varying concentrations of the samples for 24 h. Nitrite levels were measured using the Griess assay. L-NAME (26.9 μg/mL; equivalent to 100 μM) was used as a positive control. Data are presented as mean ± SD of three independent experiments. * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$ compared to the LPS group.

3.8. Effect of Sesamin and Sesamin-Loaded Nanoparticles on Lipopolysaccharide-Induced Pro-Inflammatory Cytokines Production in Raw 264.7 Macrophages

The anti-inflammatory effects of sesamin, NSM, and NPs on LPS-induced Raw 264.7 macrophages were evaluated by measuring the levels of four key pro-inflammatory mediators: PGE₂, TNF-α, IL-1β, and IL-6. For PGE₂ (Figure 11a), untreated cells showed low basal secretion (4.6 ± 2.4 pg/mL), whereas LPS stimulation increased PGE₂ levels to 857 ± 39 pg/mL. NSM treatment reduced PGE₂ to 75 ± 51 and 109 ± 36 pg/mL at 17.71 and 8.86 μg/mL, respectively. Sesamin at 31.25 and 15.63 μg/mL showed minimal effects (740 ± 22 and 813 ± 44 pg/mL), while NPs at 31.25 μg/mL reduced PGE₂ to 495 ± 76 pg/mL. Indomethacin (3.58 μg/mL; 10 μM) reduced PGE₂ to 33 ± 17 pg/mL.

For TNF- α (Figure 11b), untreated cells showed low basal secretion (2.1 ± 0.1 pg/mL), whereas LPS stimulation increased TNF- α levels to 414 ± 53 pg/mL. NSM reduced TNF- α to 248 ± 6 and 312 ± 4 pg/mL at 17.71 and 8.86 μ g/mL, respectively. Sesamin at 15.63 μ g/mL showed no significant effect. Sesamin and NPs at 31.25 showed only minor effects. BAY 11-7083 (2.07 μ g/mL; 10 μ M) reduced TNF- α to 12.6 ± 0.8 pg/mL.

For IL-1 β (Figure 11c), untreated cells showed low basal secretion (12.0 ± 2.8 pg/mL), whereas LPS stimulation increased IL-1 β to 73 ± 4 pg/mL. NSM reduced IL-1 β to 17.7 ± 2.7 and 19 ± 1 pg/mL at 17.71 and 8.86 μ g/mL, respectively. Sesamin at 31.25 μ g/mL and 15.63 μ g/mL reduced IL-1 β to 42 ± 2 pg/mL and 69 ± 9 pg/mL, respectively. While NPs at 31.25 μ g/mL reduced IL-1 β levels to 33 ± 9 pg/mL, BAY 11-7083 reduced IL-1 β to 10.1 ± 5.8 pg/mL.

For IL-6 (Figure 11d), untreated cells showed low basal secretion (1.1 ± 0.4 pg/mL), whereas LPS stimulation increased IL-6 levels to 1860 ± 44 pg/mL. NSM reduced IL-6 to 594 ± 17 and 808 ± 15 pg/mL at 17.71 and 8.86 μ g/mL, respectively. Sesamin at 31.25 and 15.63 μ g/mL showed no significant effect, while NPs at 31.25 μ g/mL reduced IL-6 to 713 ± 8 pg/mL. BAY 11-7083 reduced IL-6 to 5.5 ± 0.5 pg/mL. These findings demonstrate that NSM exerts consistent and potent inhibitory effects on LPS-induced pro-inflammatory cytokine secretion in macrophages and outperforms both sesamin and NPs.

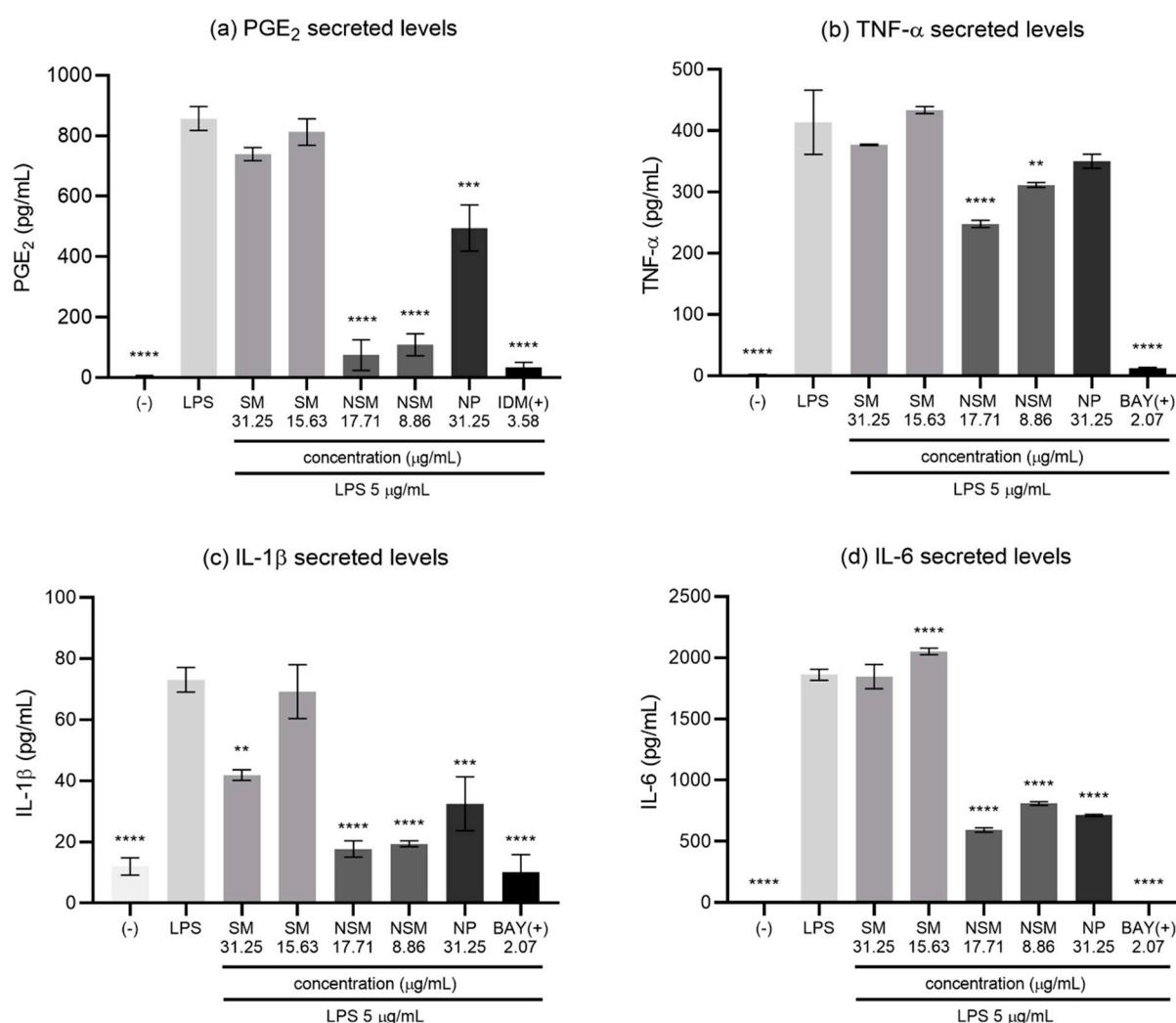


Figure 11. Effects of sesamin, NSM, and NPs on LPS-induced secretion of pro-inflammatory mediators in RAW 264.7 macrophages: (a) PGE₂; IDM (3.58 μ g/mL; equivalent to 10 μ M) was used as positive control. (b) TNF- α , (c) IL-1 β , and (d) IL-6; BAY (2.07 μ g/mL; equivalent to 10 μ M) was used

as positive control. Data are shown as mean $\pm$ SD of three independent experiments, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to the LPS group.

4. Discussion

In this study, NSM was formulated using phosphatidylcholine as the phospholipid component of soy lecithin origin. The NSM had an average hydrodynamic diameter of 113.6 ± 3.6 nm with a PDI of 0.354 ± 0.043 , indicating a moderately polydisperse but acceptable size distribution for lipid-based nanoparticles [25], and remained stable at 4 °C for more than 90 days. TEM analysis further supported the physical characteristics of the NSM formulation. The predominantly spherical morphology observed is consistent with nanoscale lipid vesicles formed through phosphatidylcholine self-assembly during the solvent displacement process. The dispersion stability is achieved by using poloxamer 407 as a stabilizer and polyethylene glycol 400. Both polymers are nonionic and hydrophilic surfactants. Poloxamer 407 adsorbs onto the nanoparticle surface, forming a hydrated polymer layer that provides steric stabilization. In contrast, PEG400, due to its low molecular weight, is expected to remain primarily in the aqueous phase or transiently associate with the lipid–water interface, where it acts as a cosolvent that facilitates nanoparticle formation and improves dispersion [26]. Together, these effects generate steric repulsion, preventing particle contact and aggregation, which is the major contributor to colloidal stability, being recognized as an effective stabilization mechanism for the lipid-based nanoparticles in pharmaceutical formulations [27,28]. However, temperature-dependent instability at 30 °C and 45 °C may be due to dynamic instability arising from aggregation, as evidenced by increased size and PDI values. Progressive growth of particles with time and at higher temperatures is partly because of partial softening and fusion of the phospholipid membrane. Chemical stability studies of NSM indicate that sesamin content did not change significantly during storage at 4 °C and 30 °C, indicating that under these conditions the nanoparticle matrix effectively protects sesamin. At 45 °C, sesamin content declined gradually, with a pronounced reduction by the 90th day. Although this could suggest chemical degradation, it is also possible that the physical destabilization of the nanoparticles at this temperature led to sesamin leakage. This may be linked to a destabilizing effect on the phospholipid matrix, which increases the exposure of sesamin to the aqueous environment. Considering its low aqueous solubility, the released sesamin may have precipitated and was consequently excluded during analysis [9]. In the absence of observed degradation products in the HPLC profiles, this reduction is attributed to the overall instability of the formulation under high-temperature stress. This is consistent with the physical instability observed at 45 °C, where increasing lipid softening, fusion, and partial structural disruption allow sesamin to diffuse out of the nanoparticles, making it more susceptible to concentration loss.

The in vitro release study showed that NSM released sesamin rapidly, achieving nearly complete release within 2 h, whereas pure sesamin showed no detectable release due to its large particle size and poor aqueous solubility, which limited its diffusion across the membrane. These findings indicate that the PEG400 and poloxamer help improve NSM dispersion and apparent solubilization of sesamin in aqueous conditions.

Inflammation is a response to tissue injury or infection; however, if left unresolved, it can contribute to the development of severe condition or chronic disease [19]. To model inflammation in vitro, lipopolysaccharide (LPS), is commonly used due to its ability to stimulate immune cells. Upon contact with Toll-like receptor 4 (TLR4) on macrophage surfaces, LPS activates the nuclear factor-kappa B (NF- κ B) signaling cascade, leading to the induction of inflammatory mediators such as pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), which produce nitric oxide (NO) and prostaglandin E₂ (PGE₂), respectively [20,21,29]. Although sesamin has

previously been reported to suppress pro-inflammatory mediators via this pathway [4], the present study primarily aimed to determine whether its encapsulation in a phosphatidylcholine-based nanoformulation could further enhance this effect. The results of this study clearly show that sesamin encapsulated in phosphatidylcholine significantly inhibits nitric oxide production at substantially lower concentrations than pure sesamin and NPs, as evidenced by a markedly lower IC_{50} value. This inhibition aligns with earlier studies indicating that sesamin reduces iNOS expression and nitric oxide generation in LPS-activated BV2 microglial cells [30]. This enhanced biological potency may be due to greater aqueous dispersibility and improved cellular uptake upon nanoparticle delivery. In this study, NSM also significantly suppressed the tested pro-inflammatory cytokines. NSM significantly reduced PGE_2 secretion in a dose-dependent manner, whereas sesamin exhibited minimal effect. NPs also reduced PGE_2 levels. The stronger suppression observed with NSM suggests a combined effect of the nanoparticle carrier and sesamin delivery. Since COX-2 primarily regulates PGE_2 production in LPS-stimulated macrophages [31], the reduction observed with NSM suggests a potential influence on the COX-2/ PGE_2 pathway, consistent with the known PGE_2 -suppressive action of indomethacin. However, direct modulation of COX-2 by NSM warrants further investigation. Moreover, NSM clearly inhibited the secretion of $TNF-\alpha$ and $IL-1\beta$, whereas its effect on $IL-6$ was comparable to that of NPs. In contrast, sesamin did not reduce $IL-6$ levels and exhibited only weak or partial inhibition for the other cytokines. While previous studies have demonstrated the anti-inflammatory potential of sesamin, differences in experimental conditions may account for the observed discrepancy. For example, Ye et al. (2020) showed that sesamin decreased $TNF-\alpha$, $IL-1\beta$, and $IL-8$ levels in rat plasma and attenuated NF- κ B signaling by upregulating A20 and TAX1BP1 [6]. Li Ma et al. (2015) demonstrated that sesamin inhibited $TNF-\alpha$ production and NF- κ B activity, suppressed TLR4 expression in RAW 264.7 cells, and reduced p-p38 and p-I κ B in vivo, as evidenced by Western blot analysis [32]. Likewise, Jeng et al. (2005) reported that sesamin suppressed LPS-induced $IL-6$ and $TNF-\alpha$ production in BV-2 microglial cells by inhibiting the p38 MAPK and NF- κ B signaling pathways [7]. In contrast to these reports, the present study did not observe a pronounced sesamin-dependent suppression of $IL-6$. Instead, blank nanoparticles alone produced a substantial reduction in $IL-6$ levels, comparable to that observed for NSM. This finding indicates that $IL-6$ suppression under the present experimental conditions is largely carrier-driven, attributable to the phosphatidylcholine-based lipid system rather than to sesamin itself. Although sesamin loading may contribute marginally, this effect was not sufficient to confer a clear additional benefit beyond the blank nanoparticle. Therefore, these findings support the present results, in which NSM effectively reduced multiple pro-inflammatory cytokines, suggesting that nanoparticle-based delivery enhances the functional anti-inflammatory activity of sesamin.

Interestingly, NPs also exhibited moderate NO inhibition and pro-inflammatory cytokines at higher concentrations. This may be related to the intrinsic anti-inflammatory properties of phosphatidylcholine. Indeed, Treede et al. (2007) demonstrated that exogenous phosphatidylcholine directly suppresses $TNF-\alpha$ -induced NF- κ B activation, p38/ERK MAPK signaling, and downstream pro-inflammatory gene expression in both epithelial cells and macrophages [33]. Consistently, Mizuno et al. (2025) reported that phosphatidylcholine suppresses LPS-induced inflammation by inhibiting NF- κ B and JNK/p38 MAPK signaling, resulting in reduced $TNF-\alpha$, $IL-1\beta$, and $IL-6$ production in MG6 microglial cells [34]. These findings suggest that the observed $IL-6$ reduction may primarily result from the phosphatidylcholine carrier, with sesamin contributing little additional effect. This evidence supports that the overall anti-inflammatory activity of NSM results from the combined effects of sesamin and the phosphatidylcholine-based carrier.

From the available data, the present NSM formulation differs from previously reported sesamin delivery systems, such as SNEDDS and solid dispersions, primarily in study emphasis rather than in fundamental formulation strategy. SNEDDS formulations have been reported to produce smaller nanoemulsion droplets and to enhance sesamin solubility and oral bioavailability [9], while the NSM particles developed in this study remained within a comparable nanoscale range. Solid dispersion systems have also demonstrated improved sesamin dissolution and biological effects [12]. Direct quantitative comparison with these systems is not feasible, as prior studies focused mainly on solubility, oral bioavailability, or pharmacokinetic endpoints rather than cellular anti-inflammatory activity. In contrast, the present study focused on *in vitro* anti-inflammatory responses in an LPS-stimulated macrophage model, providing preliminary insight into biological effects at the cellular level.

Moreover, this study has certain limitations that should be acknowledged. The evaluation focused primarily on the suppression of pro-inflammatory mediators following treatment with sesamin-based formulations, without direct investigation of upstream NF- κ B regulatory signaling, and the current work was limited to *in vitro* experiments. These mechanistic aspects, including the assessment of key signaling proteins such as p-p38 and p-I κ B α , will be addressed in future studies. In addition, macrophage polarization was not directly assessed in the present study, the observed suppression of NO, TNF- α , and IL-6 in LPS-stimulated RAW 264.7 macrophages is consistent with attenuation of a pro-inflammatory M1-like activation state [35]. Previous studies have reported that sesamin can modulate macrophage polarization by suppressing M1-associated signaling pathways, including NF- κ B and MAPK, while promoting anti-inflammatory responses [36]. These findings suggest that the anti-inflammatory effects observed for NSM may, at least in part, be associated with the modulation of macrophage activation status. Nevertheless, direct evaluation of M1/M2 surface markers, such as CD86 and CD206, will be required to confirm macrophage phenotype switching and will be addressed in future studies. Lastly, further *in vivo* and preclinical investigations will be necessary to confirm the translational relevance of the NSM formulation.

5. Conclusions

This study demonstrates the anti-inflammatory potential of NSM in an LPS-stimulated RAW 264.7 macrophage model. NSM exhibited good physicochemical properties (~ 114 nm; PDI ~ 0.35) and storage stability. Within non-cytotoxic ranges, NSM significantly suppressed nitric oxide and key pro-inflammatory mediators (PGE₂, TNF- α , IL-1 β , IL-6), outperforming sesamin and NPs at comparable concentrations. In contrast to previously reported sesamin delivery systems that mainly focus on enhancing solubility and oral bioavailability, the present NSM formulation provides direct pharmacological evidence of anti-inflammatory activity at the cellular level, likely arising from the combined effects of sesamin and the phosphatidylcholine-based carrier. These findings support NSM as a promising lipid-based delivery system for further mechanistic and translational investigation.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pharmaceutics18020226/s1>, Figure S1: HPLC chromatogram of sesamin, NSM and phosphatidylcholine (full scale 0–30 min).

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T.C., S.O., and C.C.; supervision, K.K., S.M., T.C., and C.C.; project administration, C.C.; funding acquisition, S.O. All authors have read and agreed to the published version of the manuscript.

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