

Development of Pickering emulsion stabilized by *Peperomia pellucida* L. extract and beta-glucan: an *in vitro* study for wound healing applications

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Received 10 August 2025 ♦ Accepted 23 October 2025 ♦ Published 6 November 2025

Citation: Lidia, Insanu M, Kurniati NF, Viviani RN, Suciati T (2025) Development of Pickering emulsion stabilized by *Peperomia pellucida* L. extract and beta-glucan: an *in vitro* study for wound healing applications. Pharmacia 72: 1–16. <https://doi.org/10.3897/pharmacia.72.e168283>

Abstract

Excessive reactive oxygen species (ROS) impair wound healing by inducing oxidative stress and compromising fibroblast function. To address this, we developed a novel Pickering emulsion (PESUBG) incorporating *Peperomia pellucida* extract, rich in flavonoids, and beta-glucan, a bioactive polysaccharide. The formulation exhibited small droplet size, low interfacial tension, and robust stability under thermal stress, freeze-thaw cycles, and prolonged storage. Amphiphilic flavonoids contributed to interfacial stabilization and antioxidant activity, with PESUBG demonstrating the highest radical-scavenging capacity among all tested formulations. In *in vitro* assays, PESUBG (50 µg/mL) significantly enhanced fibroblast viability compared to the base emulsion control ($100.32 \pm 11.47\%$) and improved cell survival under H₂O₂-induced oxidative stress ($22.00 \pm 2.66\%$ increase), while also promoting collagen synthesis. These findings suggest that PESUBG is a promising bioactive and biocompatible formulation with the potential to mitigate oxidative stress and support tissue regeneration. Further studies are warranted to optimize formulation parameters and validate its wound-healing efficacy *in vivo*.

Keywords

antioxidant, beta-glucan, *Peperomia pellucida* extract, Pickering emulsion, wound healing

Introduction

Wound healing is a dynamic biological process involving four overlapping stages: hemostasis, inflammation, proliferation, and remodeling. These phases collectively restore tissue integrity, with extracellular matrix (ECM) regeneration,

particularly collagen synthesis, being essential for tensile strength and tissue remodeling (Rodrigues et al. 2019; Mathew-Steiner et al. 2021). During the early inflammatory phase, reactive oxygen species (ROS) contribute to pathogen clearance and cellular signaling. However, excessive ROS production induces oxidative stress, leading to cellular

damage, fibrosis, and delayed healing (Golebiewska and Poole 2015; Dunnill et al. 2017; Sanchez et al. 2018).

Antioxidants play a key role in neutralizing ROS, restoring redox balance, and regulating inflammation (Moseley et al. 2004; Piera-Velazquez and Jimenez 2021). Among natural antioxidants, flavonoid plant-derived polyphenols are notable for their potent antioxidant, anti-inflammatory, and antimicrobial properties. Their bioactivity is influenced by hydroxylation at positions 5, 7, 3, and 4, which enhances radical-scavenging capacity (Carvalho et al. 2021). *Peperomia pellucida* (SU), a medicinal plant rich in flavonoids such as apigenin, casticin, and acacetin, has demonstrated strong antioxidant potential. These compounds reduce ROS levels, increase antioxidant enzyme activity—including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH)—and promote re-epithelialization (Lopez-Jornet et al. 2014; Shukla et al. 2016; Ho et al. 2022a).

Complementary to SU, beta-glucan (BG), a natural polysaccharide, has been shown to support fibroblast proliferation, collagen synthesis, and neovascularization, thereby contributing to granulation tissue formation and epithelial regeneration (Davis and Perez 2009; Fusté et al. 2019). Despite their therapeutic potential, both SU and BG face challenges related to solubility, bioavailability, and targeted delivery to wound sites. To overcome these limitations, Pickering emulsions stabilized by solid particles rather than conventional surfactants offer notable advantages, including enhanced stability, biocompatibility, and targeted delivery of bioactive agents (Asfour et al. 2017; Nimaming et al. 2024). BG can interact with flavonoids through hydrogen bonding and hydrophobic interactions, forming hybrid colloidal particles that stabilize emulsion interfaces, prevent droplet coalescence, and enhance antioxidant protection (Deng et al. 2022). Although Pickering emulsions stabilized by natural polysaccharides and flavonoids have been reported, their application in wound healing is still scarce. While both *Peperomia pellucida* extract and beta-glucan have individually demonstrated relevance in wound healing, their combined incorporation into a Pickering emulsion as a dual-active, naturally stabilized system remains unexplored. To date, no study has systematically evaluated flavonoid-polysaccharide Pickering emulsions for wound healing, highlighting the research gap addressed in this work.

Considering the role of interfacial structure in emulsion stability, this study utilized Tween 80, a nonionic emulsifier, as a co-stabilizer (Cui et al. 2024), in combination with two primary stabilizers used at fixed concentrations (1% each): SU extract and BG. The formulation aimed to investigate how individual and combined stabilizers contribute to emulsion characteristics, physical stability, and wound-healing activity. During emulsification, controlled heating was applied to disrupt hydrogen bonding between phenolic compounds and citric acid in SU, enabling their migration to the oil-water interface (Rosdianto et al. 2023). BG was also expected to form polyphenol complexes that contribute to droplet stabilization

(Deng et al. 2022). Tween 80 served to reduce interfacial tension, while humectants such as glycerol and propylene glycol enhanced molecular mobility. Arginine was included to prevent particle aggregation by forming hydrogen bonds (Li et al. 2014; Albano et al. 2018).

This study provides an initial evaluation of the formulation and functional performance of Pickering emulsions containing SU and BG, focusing on their physical properties and *in vitro* wound-healing potential. The findings are expected to contribute to the development of stable, biocompatible emulsion systems incorporating natural agents for topical wound treatment.

Materials and methods

Plant collection

SU herbs were harvested from Bukit Besar, Palembang City, and their identification was carried out at the School of Life Sciences and Technology, Bandung Institute of Technology, Indonesia, with voucher specimen number 3276/IT1.C11.2/TA.00/2023.

Preparation of the SU herb extract

The SU herb was extracted using the previously reported method with slight modification (Kumar et al. 2023; Zhang et al. 2024). In brief, the dried SU herb was macerated in a solution of 70% ethanol and 1% citric acid over three 24-hour cycles. Afterward, the mixture was filtered to collect the filtrate, which was then concentrated using a rotary evaporator. The concentrated extract was subsequently freeze-dried using a lyophilizer (Buchi L-300, Switzerland) to yield a dry extract. The final product was stored at 2–8 °C in a refrigerator for future use.

$$\text{Yield (\%)} = \frac{\text{Weight of extract (g)}}{\text{Weight of the plant (g)}} \times 100\%$$

Characterization of SU extract

Phytochemical screening

The SU extract was analyzed for secondary metabolites, including phenolic compounds, flavonoids, saponins, tannins, steroids, and triterpenoids.

Phenolic identification: One hundred mg of the extract was dissolved in 2 mL of water, filtered, and treated with FeCl₃. The green color indicated phenolics (Rahimah et al. 2019).

Flavonoid: To identify flavonoids, saponins, and tannins, the extract was dissolved in hot water, filtered, and labeled as Filtrate A. Flavonoids were detected by mixing Filtrate A with magnesium powder and concentrated HCl. A red, yellow, or orange color in the amyl alcohol layer indicates flavonoids (Farnsworth 1966; Harahap et al. 2023).

Saponins: Filtrate A was shaken for 10 seconds, allowed to stand for 10 minutes, and then treated with HCl. The presence of stable foam indicates saponins (Farnsworth 1966; Harahap et al. 2023).

Tannins: Filtrate A was divided into two test tubes. A gelatin solution added in the first tube formed a white precipitate, while 5% FeCl₃ in the second tube produced a blue or green color (Farnsworth 1966; Harahap et al. 2023).

Quinones: 1 N NaOH was added to Filtrate A, resulting in a red-blue coloration (Rahimah et al. 2019).

Steroid and triterpenoid: The extract was dissolved in chloroform, filtered, and evaporated. The residue was treated with the Liebermann-Burchard reagent (a mixture of acetic anhydride and concentrated sulfuric acid), with blue or green indicating steroids, while red, pink, or purple suggested triterpenoids (Rahimah et al. 2019).

Determination of total flavonoids in extracts

Aluminum chloride and quercetin were used as references for measuring the flavonoid concentration (Shraim et al. 2021). Solutions of quercetin were prepared at concentrations ranging from 50 to 100 µg/mL. To each 100 µL of these dilutions, 300 µL of methanol, 20 µL of aluminum chloride, 20 µL of sodium acetate, and 560 µL of water were added; the mixtures were then incubated for 30 minutes. The SU extract sample at 1000 µg/mL in methanol was prepared with a blank and treated similarly to the quercetin standard. Absorbance was measured at 415 nm. All measurements were performed in triplicate and confirmed in independent experiments. A quercetin standard curve was generated to calculate the extract's total flavonoid content (TFC), expressed as mg QE/g.

Determination of total phenols in the extract

The Folin-Ciocalteu method was used to determine the total phenolic content (TPC). Solutions of gallic acid ranging from 60 to 100 µg/mL were prepared in methanol. To each 50 µL of solution, 400 µL of sodium carbonate and 500 µL of Folin-Ciocalteu reagent were added, followed by a 15-minute incubation. The absorbance at 765 nm was measured in triplicate and confirmed in independent experiments. A calibration curve was plotted, and a linear regression equation was established. The total phenols were expressed as milligrams of gallic acid equivalent (GAE) per gram (mg GAE/g). The test sample was an SU extract in analytical-grade methanol at 1000 µg/mL (Sukardi et al. 2020).

Phytochemical analysis of SU extract using LC-MS/MS analysis

Characterization of the SU extract was performed using liquid chromatography-tandem mass spectrometry (Thermo HPLC-Dionex Ultimate-TSQ Quantum Access

MAX Triple Quadrupole Mass Spectrometer) with a Thermo Scientific Hypersil GOLD C18 Selectivity HPLC stationary phase. The mobile phase (water:acetonitrile, 0.1% formic acid) was subjected to a flow rate of 0.3 mL/min. Gradient elution was applied as follows: 95:5 from 0 to 1 min, 5:95 from 7 to 10 min, and 95:5 from 11 to 13 min. Before analysis, the SU extract was prepared by dissolving 5 mg of the sample in 5 mL of HPLC-grade methanol (final concentration 1 mg/mL), and then filtered using a nylon syringe filter (0.22 µm). For analysis, 5 µL of this solution was injected (Vaiano et al. 2016).

Preparation of Pickering emulsions

The Pickering emulsion was prepared using the previous method with slight modifications (Rosdianto et al. 2023). The formulas for each of the preparations studied are shown in Table 1. The concentration of each stabilizer was maintained at 1% (w/v) to compare their individual and combined effects on emulsion properties directly. This approach also facilitates the identification of additive or enhancing effects when multiple stabilizers are present in the system. The emulsions are named based on their stabilizers: PESU contains only the SU extract as an emulsifier and does not include BG; PEBG consists solely of BG as the stabilizer; and PESUBG incorporates both the SU extract and BG as stabilizers.

The different emulsions were prepared as described (Fig. 1). For PESUBG, mixtures A, B, and E were heated to 80°C in their respective containers, then mixed and homogenized using an Ultra-Turrax at 9,000 rpm for 3 minutes.

Table 1. Pickering emulsions as natural wound-healing agents: emulsion formula.

Components	Concentration (%)			
	PESU	PEBG	PESUBG	BS
Mixture A				
VCO	2	2	2	2
Tween 80	1	1	1	1
Propylene glycol	1.5	3	1.5	3
Mixture B				
SU extract	1	–	1	–
Propylene glycol	1.5	–	1.5	–
Water	2	–	2	–
Mixture C				
BG	–	1	1	–
Water	–	2	2	–
Mixture D				
Arginine	0.5	0.5	0.5	0.5
Water	2	2	2	2
Mixture E				
Glycerol	2	2	2	2
Water			Ad 100	

Note: Tween 80 was incorporated into the oil phase, while propylene glycol was evenly divided between the oil and aqueous phases. The oil phase (VCO + Tween 80 + 50% PG) accounted for 4.5%, yielding an oil-to-water ratio of 4.5:95.5 (≈1:21.2). All other components were dissolved or dispersed in the aqueous phase.

The SU extract concentration of 1% (w/w) corresponds to approximately 10 mg/mL in the emulsion, assuming an emulsion density of 1 g/mL.

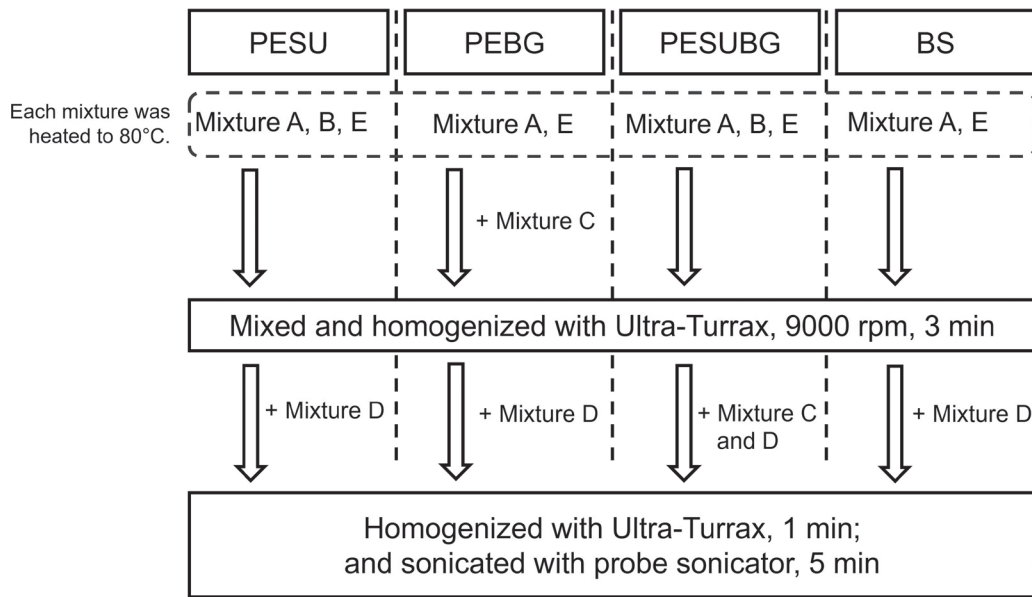


Figure 1. The preparation of emulsions: PESU, PEBG, PESUBG, and BS. Mixture A: VCO, Tween 80, and propylene glycol; mixture B: SU extract, propylene glycol, and water; mixture C: BG solution; mixture D: arginine solution; and mixture E: a mixture of glycerol and remaining water.

Next, mixture C was added, followed by mixture D. The entire mixture was homogenized again at the same speed for 1 minute. Finally, the emulsion was sonicated with a probe sonicator (Ultrasonic Homogenizer CY-500, JP Selecta, Part No. 5059600) equipped with a titanium probe (5.6 mm diameter, 60 mm length). Sonication was performed at 20 kHz for 5 minutes at 70% amplitude, using a 45:15-second pulse setting. For PESU, mixtures A, B, and E were heated and homogenized as described above. Mixture D was then added, followed by homogenization and sonication under the same conditions. For PEBG, mixtures A and E were heated, combined with mixture C, and then mixture D was added. This was followed by homogenization and sonication, as previously described. For BS (a conventional emulsion stabilized only with surfactants), mixtures A and E were heated and homogenized with the Ultra-Turrax, with subsequent steps performed under the same conditions. The overall process for preparing each emulsion is summarized in Fig. 1, showing the order of addition, homogenization, and sonication for all formulations. The BS formulation served as the non-bioactive base control, containing the same excipients as the active emulsions (VCO, Tween 80, propylene glycol, glycerol, arginine, and water) but excluding SU extract and beta-glucan. This design enabled the evaluation of the base formulation's intrinsic effects, independent of bioactive components.

Measurement of the surface properties of the formulation components

The liquid surface properties, including surface and interfacial tension, were measured to evaluate the hydrophobic and hydrophilic characteristics of the formula components, following a modified version of a previously

reported method (Cui et al. 2024). Interfacial tension plays a crucial role in determining the size of globules, which in turn affects the total interfacial area (Ho et al. 2022b). Surface and interfacial tension measurements were conducted at room temperature using a digital tensiometer (TD1 Lauda Scientific, Germany). The surface tension values obtained from the instrument were adjusted by applying a correction factor according to the following equation.

$$f = 0.8759 + \frac{0.000918 \times O_{Sruk}}{p}$$

The r represents the sample's specific gravity (g/cm^3), while O_{Sruk} denotes the uncorrected surface tension (mN/m). The absolute surface tension value, measured in mN/m , is obtained by multiplying the uncorrected surface tension (obtained from the instrument) by the calculated correction factor (f). All measurements were performed in triplicate to ensure reproducibility.

Characterizations of Pickering emulsion formula

The emulsions were characterized in terms of globule size, polydispersity index (PDI), zeta potential, and surface morphology. Size, PDI, and zeta potential measurements were performed after threefold dilution with water at room temperature ($\sim 25^\circ\text{C}$) using a Delsa Nano C Particle Size Analyzer (Beckman Coulter, USA) equipped with a He-Ne laser ($\lambda = 658\text{ nm}$) at scattering angles of 165° for size and PDI and 30° for zeta potential. All measurements were carried out in triplicate to ensure reproducibility, following previously reported procedures for Pickering emulsions (Asfour et al. 2017). Surface morphology was examined using transmission electron microscopy (TEM) (Le et al. 2020). A $15\text{ }\mu\text{L}$ aliquot of the diluted emulsion

was applied onto a TEM grid, air-dried at room temperature, and stained with 15 μL of 2% uranyl acetate. The grid was left to dry for 1 hour before observation. TEM imaging was performed using a Hitachi HT7700 operating at 120 kV in bright-field mode, with magnifications ranging from 2000 $\times$ to 200,000 $\times$ depending on sample quality.

Physical stability test

The physical stability of the studied emulsions was assessed through freeze-thaw cycles, thermal cycling, and storage at temperatures of $25 \pm 2^\circ\text{C}$ and $40 \pm 2^\circ\text{C}$. The appearance and globule size were measured at the beginning and end of the storage period. All measurements were performed in triplicate to ensure reproducibility.

Freeze-thaw: A 5 mL emulsion sample was stored at -20°C until frozen, then returned to room temperature for 3 hours to complete one cycle. This process was repeated for three cycles (Chen et al. 2019).

Thermal cycling test: Samples were alternately stored at $4 \pm 2^\circ\text{C}$ and $40 \pm 2^\circ\text{C}$, each for 24 hours, resulting in a total of six cycles (Wulansari et al. 2017).

Storage temperature study: Samples were stored at $40 \pm 2^\circ\text{C}$ for 14 days and at $25 \pm 2^\circ\text{C}$ for 28 days (Wulansari et al. 2017; Somala et al. 2022).

Antioxidant activity test with 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH)

The DPPH assay was utilized to evaluate the antioxidant activity of the extract, following the methods described by Ayele et al. (2022) and Huo et al. (2022). A standard curve was generated using ascorbic acid concentrations ranging from 4 to 10 $\mu\text{g/mL}$. A 1:1 mixture of DPPH solution (65 $\mu\text{g/mL}$ in methanol) and each ascorbic acid concentration was incubated in the dark for 30 minutes. The absorbance was subsequently measured at λ 517 nm using a UV-Vis spectrophotometer. The control consisted of a 1:1 methanol-DPPH mixture, with methanol alone serving as the blank. The percentage of inhibition was calculated and plotted against ascorbic acid concentration to generate a linear regression equation. The percentage of inhibition was calculated using the following equation.

$$\% \text{ Inhibition} = \frac{[(\text{Abs DPPH} - \text{Abs Sample}) / \text{Abs DPPH}] \times 100}{1}$$

This calibration curve was used to determine the antioxidant activity of the extract and emulsions, tested at a concentration of 70 $\mu\text{g/mL}$ under the same conditions. For single-component emulsions (PESU or PEBG), the concentration was based on the respective active compound. For the mixed emulsion (PESUBG), the concentration of 70 $\mu\text{g/mL}$ refers to the SU fraction, while BG was present at the same ratio. The base emulsion (BS) without SU or BG was tested in parallel as a negative control. All measurements were performed in triplicate to ensure reproducibility and

are expressed as milligrams of ascorbic acid equivalent per gram of sample (mg AAE/g) (Djiazet et al. 2021).

Viability test on 3T3 fibroblast cells

The viability of 3T3 fibroblast cells was evaluated under normal and oxidative stress conditions (stimulated with hydrogen peroxide [H_2O_2]) to assess the cytocompatibility and protective effects of the formulations (Zhang et al. 2020b; Zenin et al. 2022). Cells ($1 \times 10^4/\text{well}$) were seeded in 96-well plates and incubated in Dulbecco's Modified Eagle's Medium (DMEM) with 10% fetal bovine serum (FBS) for 24 hours. The medium was then replaced with serum-free DMEM containing BS (base emulsion), SU, BG, PESU, PEBG, or PESUBG at concentrations of 25, 50, 75, or 100 $\mu\text{g/mL}$ for 24 hours. The stated concentrations refer specifically to the equivalent content of the active stabilizers within the emulsions, while BS contained no active stabilizers and served as a negative control to account for the effects of the base emulsion components. For the mixed emulsion (PESUBG), the concentration was standardized to the SU fraction, while BG was present at the same ratio. This concentration range was selected based on previous *in vitro* studies. (Vaid et al. 2020; Ebadi and Fazeli 2021; Liu et al. 2022). For oxidative stress assays, cells were pre-exposed to 250 μM H_2O_2 in serum-free DMEM for 24 hours, followed by treatment with the same formulations and concentrations for an additional 24 hours. After treatment, 10% PrestoBlue was added, and cells were incubated for a further 3 hours. Fluorescence (560/590 nm) was measured to determine cell viability, expressed as a percentage relative to untreated controls. The cell viability for each formulation and concentration was then compared to that of BS, allowing assessment of the enhancement in cell survival provided by the active stabilizers in the emulsions.

$$\text{Cell viability}(\%) = \frac{(\text{o}\lambda_2 A \lambda_1) - (\text{o}\lambda_1 A \lambda_2)}{(\text{o}\lambda_2 a \lambda_1) - (\text{o}\lambda_1 a \lambda_2)} \times 100\%$$

Description: $\text{O}\lambda_1$ and $\text{O}\lambda_2$ are the molar extinction coefficients of the PrestoBlue oxidized form at 570 nm (80,586) and 600 nm (117,216). A is the absorbance of the sample, a is the absorbance of the medium control, and λ_1 and λ_2 are the wavelengths at 570 and 600 nm, respectively. All quantitative experiments were performed in triplicate to ensure reproducibility. The *in vitro* study utilized the 3T3 mouse fibroblast cell line, obtained from the cell culture collections of the School of Pharmacy, Institut Teknologi Bandung (ITB, Indonesia). As no human or live animal subjects were involved in this experiment, ethical approval was not required.

In vitro collagen assay

Collagen deposition by 3T3 fibroblast cells was assessed using the Sirius Red staining method (Szász et al. 2023). Cells ($1.2 \times 10^4/\text{well}$) were seeded in 48-well plates and incubated for 24 hours at 37°C with 5% CO_2 .

The medium was then replaced with BS, SU, BG, PESU, PEBG, or PESUBG at concentrations of 25, 50, 75, and 100 µg/mL in DMEM supplemented with 2% FBS for an additional 24 hours. After treatment, cells were washed with phosphate-buffered saline (PBS) and stained with 200 µL of 0.1% Sirius Red in saturated picric acid for 60 minutes. Excess dye was removed with PBS three times. For qualitative observation, collagen deposition was examined under a light microscope. Quantification was performed by solubilizing the bound dye with 150 µL of 0.5 N NaOH, gently stirring for 30 minutes, and measuring absorbance at 540 nm using a microplate reader (Szász et al. 2023). All quantitative experiments were performed in triplicate to ensure reproducibility.

Statistical analysis

All experiments were performed in triplicate, and results are expressed as mean $\pm$ standard deviation (SD). Statistical analyses were performed using Minitab 21.3.1 software (Minitab LLC, USA). When significant differences were observed ($p < 0.05$), data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test (Carriço et al. 2019), except for stability studies, which were evaluated using a paired *t*-test.

Results

Characterization of SU extract

SU herbs were extracted using maceration with 70% ethanol and 1% citric acid, adapted from Rente et al. (2021), yielding $15.95 \pm 0.10\%$. The method was selected for its simplicity and ability to preserve thermolabile compounds such as flavonoids and phenolics (Jovanović et al. 2017). Citric acid enhanced polyphenol solubility via hydrogen bonding, improving extraction efficiency (Kumar et al. 2012; Rente et al. 2021).

Phytochemical screening confirmed the presence of dominant bioactive constituents (Pant et al. 2017), with flavonoids noted for their dual role as antioxidants and natural solid stabilizers in Pickering emulsions (Dufton 2018). Their activity supports cell proliferation, angiogenesis,

and collagen synthesis—key processes in wound healing (Aalbaayit et al. 2015; Działo et al. 2016). The extract's high total phenolic and flavonoid contents (Table 2) further affirm its therapeutic potential in reducing oxidative stress and promoting tissue repair (Yener et al. 2020).

LC-MS/MS analysis identified key flavonoids in the SU extract: apigenin, acacetin, isovitexin, casticin, and velutin (Table 3, Fig. 2). These compounds exhibit varying lipophilicity and hydrogen bonding potential, which influence their ability to adsorb at the oil–water interface and stabilize Pickering emulsions (Gao et al. 2017). Flavonoids with moderate log *P* values (1–3), such as apigenin, acacetin, velutin, and casticin, display amphiphilic behavior conducive to interfacial adsorption and droplet stabilization (Luo et al. 2012). Isovitexin, though more hydrophilic, possesses high HBA and HBD values, enabling strong hydrogen bonding with co-stabilizers such as BG (Deng et al. 2022). These interactions, including those with arginine and polysaccharides, contribute to the formation of a robust interfacial layer (Ribeiro et al. 2021; Ren et al. 2024).

Table 2. Qualitative and quantitative analysis of phytochemicals of the SU extract.

Qualitative	
Flavonoids	+
Saponins	+
Tannins	+
Quinones	+
Steroids	+
Triterpenoids	+
Quantitative	
a. Total phenolic content (mg GAE/g)	53.87 ± 0.05
b. Total flavonoid content (mg QE/g)	39.99 ± 0.08
c. DPPH scavenging activity (mg AAE/g)	115.70 ± 0.24

Table 3. Tentative identifications of flavonoid compounds of the SU extract, LC-MS/MS results.

No	Flavonoids	RT (Retention time)	Molecular mass	HBA	HBD	Log P*
1	Apigenin	3,28	270	3	5	1.7
2	Acacetin	3,62	284	2	5	2.1
3	Isovitexin	3,90	432	10	7	0.2
4	Casticin	4,70	374	8	2	3.1
5	Velutin	5,76	314	6	2	2.0

* Data were obtained from PubChem (computed by XLogP3 3.0).

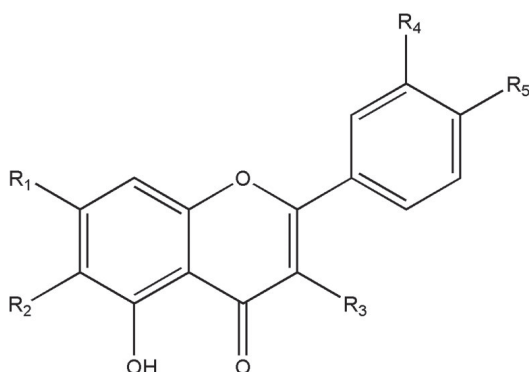


Figure 2. Tentative structures of identified flavonoids of the SU extract.

Flavonoid	R1	R2	R3	R4	R5
Apigenin	OH	H	H	H	OH
Acacetin	OH	H	H	H	OCH ₃
Isovitexin	OH	Glu	H	H	OH
Casticin	OCH ₃	OCH ₃	OCH ₃	OH	OCH ₃
Velutin	OCH ₃	H	H	OCH ₃	OH

Characterization of surface activity

Surface tension measurements (Fig. 3A) revealed that the SU extract exhibited low surface tension, which decreased further upon combination with propylene glycol (PG), indicating enhanced surface activity and good interfacial compatibility with VCO. This behavior aligns with previous findings on basil extract, where amphiphilic phenolics contributed to interfacial stabilization (Rosdianto et al. 2023). Flavonoids in SU—apigenin, acacetin, casticin, isovitexin, and velutin—likely exhibit similar amphiphilic behavior due to their intermediate log P values (Zembyla et al. 2018; Velderrain-Rodríguez et al. 2021). In contrast, BG showed higher surface tension, reflecting its hydrophilic nature and limited interfacial affinity. Its stabilizing effect is attributed to irreversible adsorption and formation of a hydrated colloidal network (Veverka et al. 2018; Cui et al. 2021). PG, with lower polarity than glycerol, appeared more effective at reducing SU surface tension, possibly by disrupting hydrogen bonds and increasing amphiphile exposure.

Interfacial tension (IFT) measurements (Fig. 3B) supported these findings. The VCO–SU system exhibited lower IFT than VCO–BG, while PG and glycerol combinations yielded moderate values. The addition of Tween 80 significantly reduced IFT in all systems, consistent with its role as a nonionic surfactant that enhances interfacial adsorption (Li X et al. 2014). Overall, SU and BG functioned as primary stabilizers, with Tween 80 and humectants contributing to interfacial energy reduction and molecular mobility, promoting droplet formation and emulsion stability (Ho et al. 2022a; Berton-Carabin and Villeneuve 2023).

Analysis of the emulsification process

Pickering emulsions were formulated using VCO as the oil phase, with SU extract (rich in flavonoids and phenolics), beta-glucan, Tween 80, propylene glycol, glycerol, and arginine. Tween 80, a nonionic surfactant, effectively reduced interfacial tension and enhanced emulsion stability

(Leticia et al. 2020; Cui et al. 2024), outperforming ionic surfactants in surface activity (Jiang et al. 2018).

SU extract and beta-glucan served as both bioactive agents and natural stabilizers. Amphiphilic flavonoids from SU adsorbed at the oil–water interface, while heating with propylene glycol promoted *in situ* solidification and increased hydrophobic interactions (Rosdianto et al. 2023). Glycerol further reduced interfacial tension, aiding particle adsorption (Rente et al. 2021).

Beta-glucan stabilized droplets via hydrophobic adsorption and steric hindrance from its hydrophilic chains (Cui et al. 2021; Gong et al. 2024). It also formed cohesive interfacial layers through hydrogen bonding with SU polyphenols (Deng et al. 2022). Post-emulsification, arginine acted as a hydrogen bond donor, minimizing particle aggregation and reinforcing colloidal stability via guanidinium-mediated interactions with flavonoids and beta-glucan (Albano et al. 2018).

Characterization of Pickering emulsions

Pickering emulsions (PESU, PEBG, PESUBG) showed mean droplet sizes below 200 nm (Table 4), indicating effective particle adsorption and potential for enhanced bioavailability (Chen et al. 2020; Santos et al. 2022; Ding et al. 2023). PESUBG had the smallest droplet size, suggesting superior stabilization from SU extract and BG synergy.

PDI values ranged from 0.2 to 0.3, indicating uniform droplet dispersion across formulations (Hoseini et al. 2023). Zeta potential values ranged from -16 to -18.5 mV, with PESUBG exhibiting the most negative charge, indicating stronger electrostatic repulsion and improved colloidal stability (Kumar et al. 2017).

TEM imaging (Fig. 4) revealed microstructures of PESU, PEBG, PESUBG, and BS emulsions at the 100 nm scale. All Pickering emulsions exhibited compact particulate layers surrounding oil droplets, confirming particle adsorption at the oil–water interface and formation of colloidal networks—hallmarks of Pickering stabilization (Falsafi et al. 2020; Rosdianto et al. 2023).

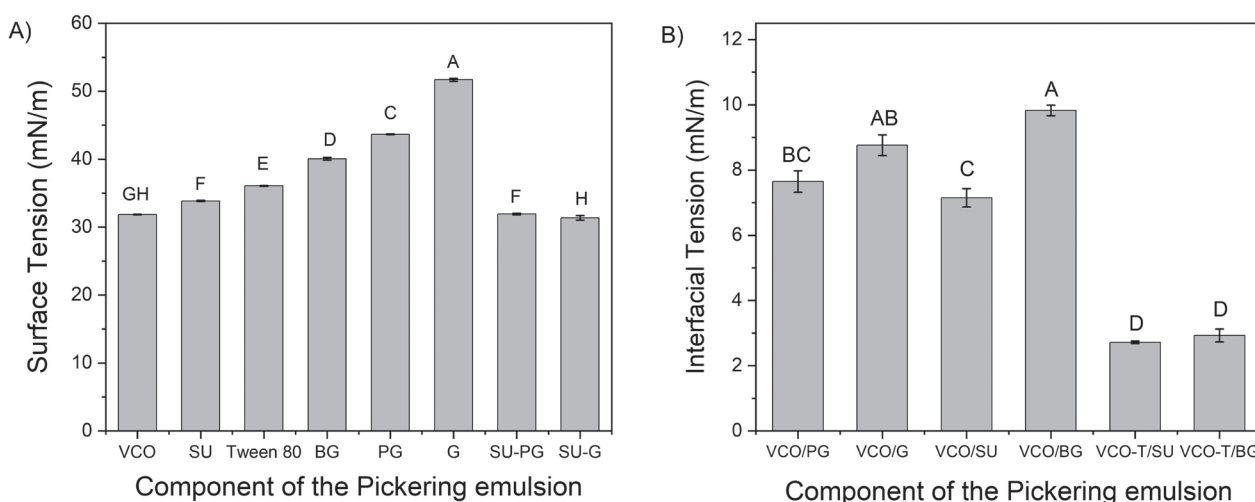


Figure 3. Surface (A) and interfacial (B) tension of Pickering emulsion components. Data are presented as mean $\pm$ SD ($n = 3$). Different letters denote statistically significant differences ($p < 0.05$) between individual components and their combinations.

Table 4. Characteristics of studied emulsions.

Formulation	Globule size (nm) ± SD	PDI ± SD	Zeta potential ± SD
BS	217.03 ± 1.10 ^A	0.295 ± 0.04	-9.72 ± 0.42 ^A
PESU	190.82 ± 1.27 ^C	0.227 ± 0.02	-16.10 ± 0.88 ^B
PEBG	196.77 ± 0.95 ^B	0.265 ± 0.05	-15.55 ± 0.68 ^B
PESUBG	186.76 ± 2.38 ^D	0.284 ± 0.02	-18.47 ± 0.59 ^C

Different letters in the same column indicate significant differences ($p < 0.05$). N = 3.

Stability study

Emulsion stability was evaluated under room temperature (25 ± 2 °C, 28 days), in a climate chamber (40 ± 2 °C, 14 days), under freeze-thaw (3 cycles), and under thermal cycling (6 cycles) (Fig. 5). All emulsions remained visually stable without phase separation at room temperature, under freeze-thaw conditions, and during thermal cycling, indicating good kinetic stability. Sedimentation occurred at elevated temperatures in BS, PESU, and PEBG, while PESUBG remained stable.

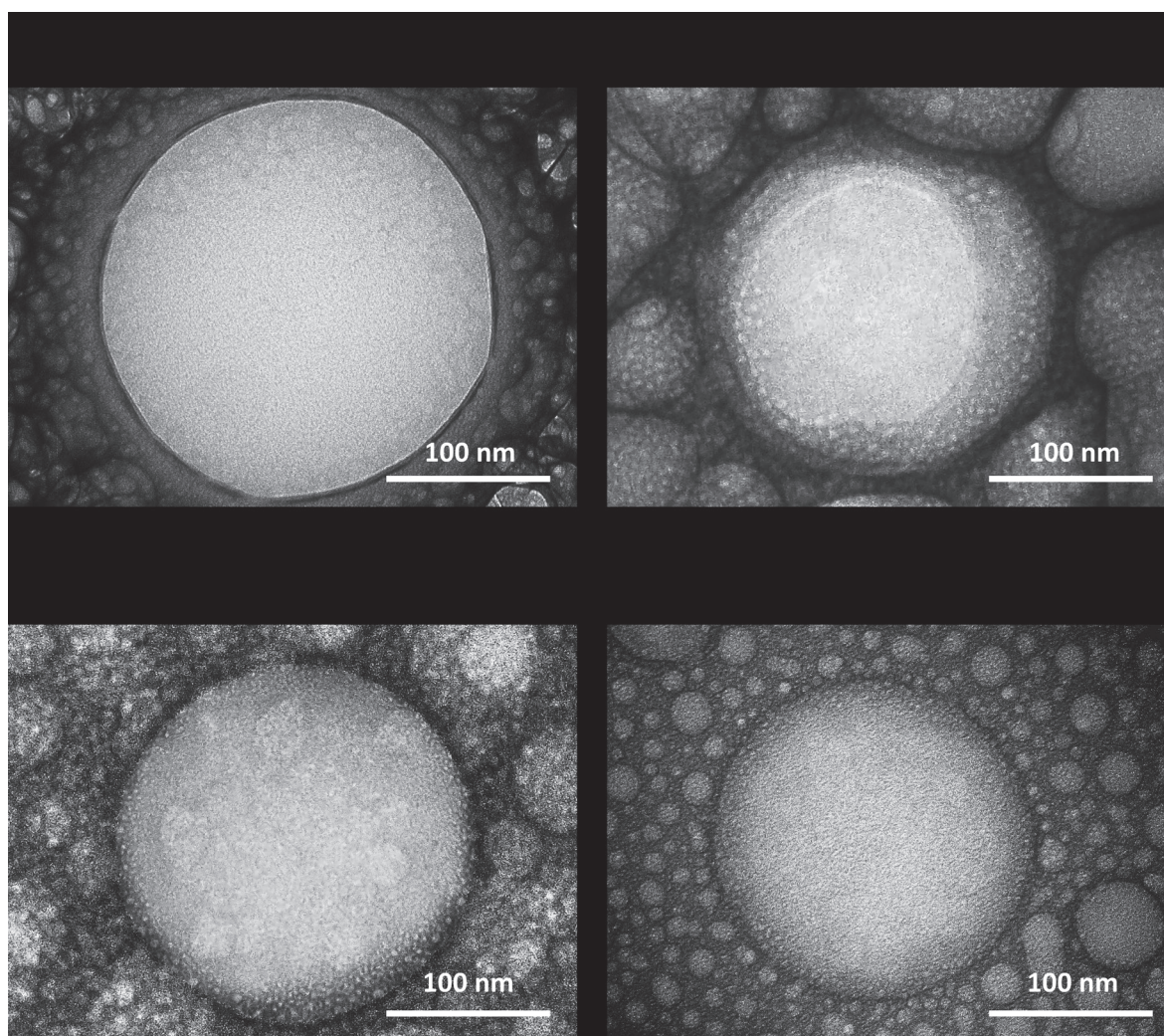
PESUBG maintained a consistent droplet size across all stress conditions, unlike other formulations that showed

droplet growth, likely due to interfacial layer disruption. This superior stability is attributed to the synergistic roles of SU extract and beta-glucan, amphiphilic flavonoids, and phenolics, enabling interfacial adsorption, steric stabilization by beta-glucan, and interfacial tension reduction by Tween 80 (Li X et al. 2014; Cui et al. 2021; Deng et al. 2022).

Analysis of antioxidant activity

Antioxidant activity was evaluated using the DPPH assay and expressed as mg AAE/g (Rahman et al. 2015). The SU extract, rich in flavonoids such as apigenin, acacetin, and isovitexin, exhibited strong antioxidant mechanisms, including free radical scavenging, metal ion chelation, and enhancement of endogenous enzymes (Lv et al. 2016; Alghamdi et al. 2022).

Fig. 6 shows that Pickering emulsions (PESU, PEBG, PESUBG) significantly enhanced antioxidant activity compared to individual components. PESUBG demonstrated the highest activity, attributed to polyphenol-polysaccharide complex formation between SU extract and beta-glucan, which increases hydroxyl group availability for proton donation (Aytekin et al. 2011; Rui et al. 2017; Liu et al. 2023).

**Figure 4.** TEM images of BS, PESU, PEBG, and PESUBG samples. Scale bar: 100 nm.

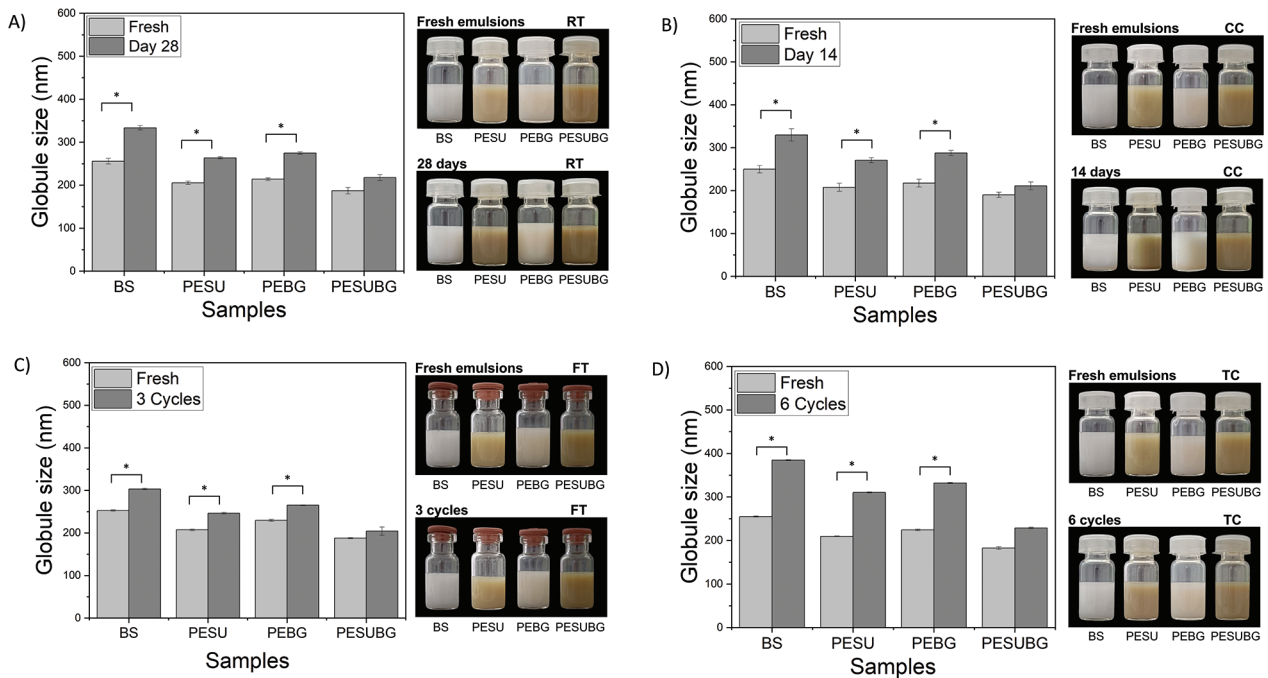


Figure 5. Visual appearance and droplet size variation of emulsions under stability tests. A. Room temperature; B. Climatic chamber; C. Freeze-thaw, and D. Thermal cycling. Data are mean $\pm$ SD ($n = 3$); * indicates significant difference from time zero ($p < 0.05$).

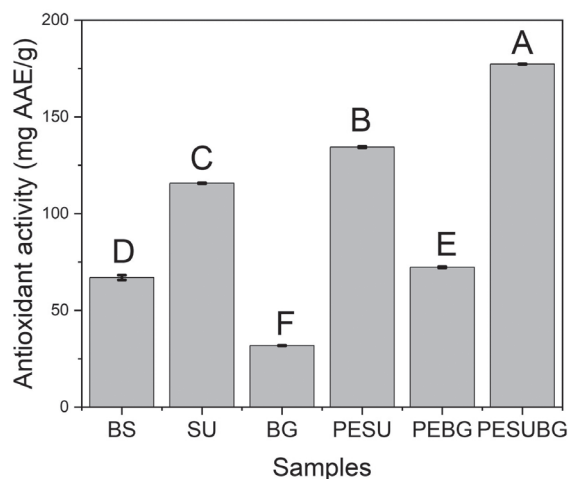


Figure 6. *In vitro* antioxidant activity determined by DPPH assay. Data are presented as mean $\pm$ SD ($n = 3$). Different letters denote significant differences ($p < 0.05$) between all formulations.

Analysis of the viability of 3T3 fibroblast cells

In vitro assays were conducted using 3T3 fibroblast cells under both normal and H_2O_2 -induced oxidative stress conditions to evaluate the protective effects of the Pickering emulsions. Each formulation was tested at concentrations of 25, 50, 75, and 100 $\mu\text{g/mL}$. Under non-stimulated conditions, PESUBG at 50 $\mu\text{g/mL}$ (without FBS) showed the highest cell viability ($237.81 \pm 13.61\%$), even surpassing the 10% FBS control (Fig. 7), indicating strong proliferative potential (Ebadi and Fazeli 2021; Iosageanu et al. 2024).

Relative to the base emulsion (BS), PESUBG exhibited the greatest enhancement in cell viability

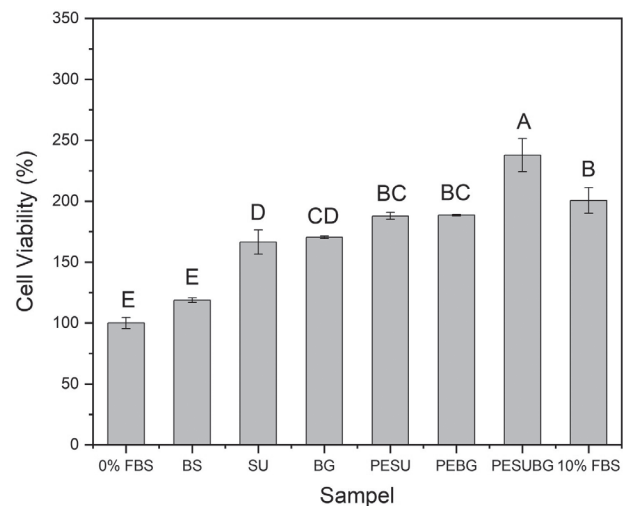


Figure 7. Cell viability of 3T3 fibroblast cells treated with BS, SU, BG, PESU, PEBG, and PESUBG (50 $\mu\text{g/mL}$) without H_2O_2 , with 0% FBS, and 10% FBS as controls. Data are presented as mean $\pm$ SD ($n = 3$). Different letters denote statistically significant differences ($p < 0.05$) between all groups.

($100.32 \pm 11.47\%$), with statistically significant differences compared to all other formulations. Since 50 $\mu\text{g/mL}$ consistently produced the most pronounced effects, the viability data at this concentration are highlighted. Complete dose-response data, including comparative analysis against BS across all concentrations, are provided in Suppl. material 1.

Hydrogen peroxide (H_2O_2) was used to induce oxidative stress in 3T3 fibroblast cells, simulating wound-related oxidative damage (Vaid et al. 2020). Cell viability was assessed across concentrations of 25–100 $\mu\text{g/mL}$ for each formulation.

At 50 $\mu\text{g/mL}$ (without FBS), PESUBG restored cell viability to $123.17 \pm 2.68\%$, comparable to the 10% FBS control and significantly higher than all other formulations ($p < 0.05$), as shown in Fig. 8. This suggests a strong cytoprotective effect, likely due to the combined antioxidant activity of SU extract and beta-glucan. BG may further contribute through indirect defense mechanisms, supporting cellular repair.

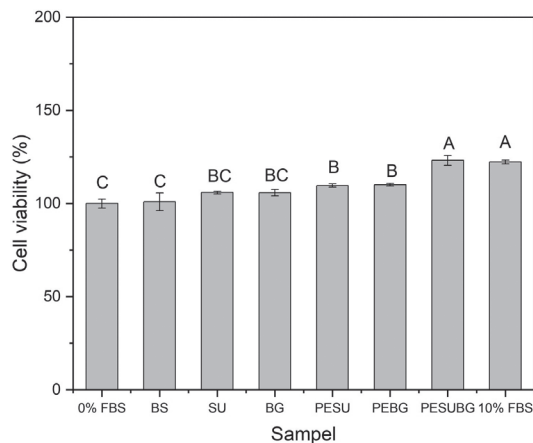


Figure 8. Cell viability of 3T3 fibroblast cells treated with BS, SU, BG, PESU, PEBG, and PESUBG (50 $\mu\text{g/mL}$) under oxidative stress induced by H_2O_2 , with 0% FBS and 10% FBS as controls. Data are presented as mean $\pm$ SD ($n = 3$). Different letters denote statistically significant differences ($p < 0.05$) between all groups.

To evaluate the role of individual stabilizers, relative increases in viability were calculated against the base emulsion (BS). PESUBG showed the most pronounced enhancement under oxidative stress, with a $22.00 \pm 2.66\%$ increase at 50 $\mu\text{g/mL}$ ($p < 0.05$). Detailed comparative data across all concentrations, including values relative to BS, are provided in Suppl. material 1.

Analysis of collagen expression

Collagen expression in 3T3 fibroblasts was evaluated as a key indicator of tissue repair. Fig. 9A shows collagen deposition visualized by Sirius Red staining, while Fig. 9B presents the corresponding quantitative analysis. At 50 $\mu\text{g/mL}$, PESUBG exhibited the highest collagen

expression ($136.85 \pm 0.88\%$), comparable to the 10% FBS control and significantly higher than all other formulation groups ($p < 0.05$). This suggests that the combination of flavonoids and beta-glucan in the Pickering emulsion effectively promotes collagen synthesis through modulation of TGF- β 1 signaling and fibroblast activation (Pang et al. 2017; Grip et al. 2018).

To further assess the contribution of individual stabilizers, the percentage increase in collagen expression relative to the base emulsion (BS) was calculated across all concentrations. At 50 $\mu\text{g/mL}$, PESUBG showed the most significant enhancement ($34.95 \pm 0.87\%$), which was statistically significant compared to all other formulations ($p < 0.05$). Detailed quantitative data and comparative analysis against BS are provided in Suppl. material 1.

Discussion

Wound healing is a tightly regulated process involving inflammation, cell proliferation, angiogenesis, and extracellular matrix (ECM) remodeling (Dong and Wang 2023). While reactive oxygen species (ROS) play essential roles in host defense and signaling, their excessive accumulation disrupts redox homeostasis, leading to lipid peroxidation, mitochondrial dysfunction, and impaired fibroblast proliferation (Hunt et al. 2024). Chronic oxidative stress delays granulation and collagen synthesis and induces fibroblast senescence, characterized by growth arrest and secretion of pro-inflammatory mediators (Wilkinson and Hardman 2020; Mccarty and Kearney 2025). The accumulation of senescent fibroblasts is increasingly recognized as a hallmark of chronic, non-healing wounds (Chen et al. 2024), highlighting the importance of antioxidant-based therapeutic strategies.

SU extract, rich in flavonoids such as apigenin, exhibits potent antioxidant and anti-inflammatory activities by scavenging ROS, modulating TGF- β 1 signaling, and suppressing cytokine production (Pang et al. 2017; Li et al. 2024). BG complements these effects by stimulating fibroblast proliferation and engaging TGF- β 1-mediated pathways (Grip et al. 2018). Together, these compounds regulate integrin-FAK signaling and promote balanced collagen remodeling, thereby

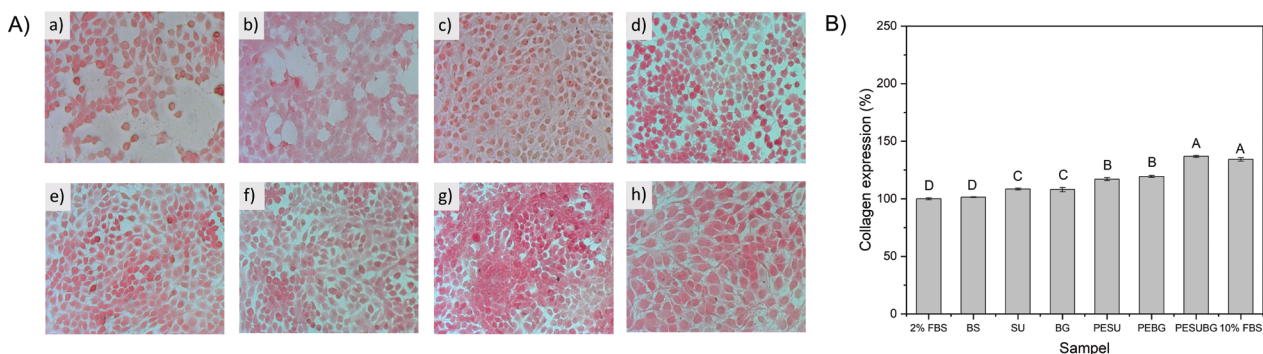


Figure 9. Collagen expression in 3T3 fibroblasts. **A.** Sirius Red staining of different treatments: (a) 2% FBS, (b) BS, (c) SU, (d) BG, (e) PESU, (f) PEBG, (g) PESUBG, (h) 10% FBS. **B.** Quantification at 50 $\mu\text{g/mL}$. Data are presented as mean $\pm$ SD ($n = 3$). Different letters denote statistically significant differences ($p < 0.05$) between all groups.

reducing hypertrophic scarring and inflammation (Shan et al. 2017; Ayadi et al. 2020; Zhang et al. 2022).

In this study, we developed PESUBG, a Pickering emulsion combining SU extract and BG, and evaluated its protective and regenerative effects under oxidative stress. Under H_2O_2 -induced oxidative stress, PESUBG restored fibroblast viability to levels comparable with the 10% FBS positive control (growth medium) and significantly outperformed other formulations. This suggests its ability to counteract oxidative stress-induced cellular senescence by reducing damage and preserving proliferative capacity. Under normal conditions, PESUBG further enhanced fibroblast viability ($237.81 \pm 13.61\%$) and collagen expression ($136.85 \pm 0.88\%$), exceeding the effects of the 10% FBS control. These findings suggest that the enhanced biological performance of PESUBG results from an additive interaction between SU-derived flavonoids and BG polysaccharides, each contributing complementary antioxidant and proliferative effects that collectively promote fibroblast function and wound-healing potential. Consequently, PESUBG not only supports fibroblast proliferation and collagen synthesis but also promotes balanced collagen remodeling, reduces the risk of excessive scarring, and contributes to enhanced wound-healing outcomes (Shan et al. 2017; Ayadi et al. 2020).

The unique architecture of Pickering emulsions, characterized by a solid particle shell at the oil-water interface, protects bioactive compounds from oxidative degradation and provides sustained release (Jafari et al. 2020; Berton-Carabin and Villeneuve 2023). Similar curcumin-based Pickering emulsions stabilized by protein isolates have demonstrated increased fibroblast proliferation, neovascularization, and collagen deposition in diabetic wound models (Hosseini B et al. 2024). In PESUBG, flavonoids and BG are enriched at the emulsion interface, enhancing antioxidant activity, scavenging ROS, and preventing lipid peroxidation.

The amphiphilic nature of plant flavonoids from SU (*Peperomia pellucida*), characterized by hydrophobic aromatic rings and hydrophilic hydroxyl groups, underlies their ability to stabilize Pickering emulsions (Rente et al. 2021; Rosdianto et al. 2023). The hydrophobic rings preferentially orient toward the oil phase, facilitating adsorption at the oil-water interface, while the hydroxyl groups form hydrogen bonds with surrounding water molecules, resulting in a compact interfacial layer. This configuration reduces interfacial tension, prevents droplet coalescence, and preserves droplet integrity. Beta-glucan, a highly hydrophilic polysaccharide, interacts with flavonoid polyphenols through additional hydrogen bonding and hydrophobic interactions, thereby reinforcing the interfacial layer and providing steric stabilization. Its polymer chains in the aqueous phase also form a hydrated network that impedes droplet aggregation, further enhancing emulsion stability (Cui et al. 2021; Deng et al. 2022). Collectively, these polarity-driven and hydrogen-bonding interactions establish a clear structure-function relationship, linking the molecular features of flavonoids and beta-glucan to the stability of Pickering emulsions.

PESUBG Pickering emulsions demonstrate clear advantages over other natural stabilizers. Chitosan and alginate stabilize emulsions primarily through electrostatic interactions or ionic gelation, forming relatively rigid interfacial layers that may limit droplet flexibility (Rescignano et al. 2015). CNCs, while effective for particle adsorption-based Pickering stabilization, generally lack intrinsic antioxidant and wound-healing activities (Wardhono et al. 2019). In contrast, beta-glucan in PESUBG not only provides steric stabilization and viscoelastic reinforcement at the droplet interface but also complements SU flavonoids to enhance localized antioxidant activity. This combination ensures both mechanical droplet stability and improved biological performance, including fibroblast proliferation and collagen deposition, within a single emulsion formulation. Thus, PESUBG represents a multifunctional and novel approach that integrates physical stabilization with bioactive delivery.

The SU-BG Pickering emulsion platform exhibits strong translational potential for topical wound care. It can be incorporated into oil-in-water (O/W) cream bases with liquid-crystalline structures and moderate viscosity, maintaining droplet stability while providing smooth spreading and favorable skin sensory properties (Terescenzo et al. 2024). Integration into hydrogel systems with low to medium viscosity enhances sustained release, bioadhesion, and moisture retention—critical factors for accelerated tissue regeneration (Qiu et al. 2025). By adjusting particle concentration and rheological properties, PESUBG can be formulated into sprayable systems for convenient application on large or irregular wound surfaces or incorporated into hydrogel-based patches for localized and controlled delivery (Wang et al. 2025). This versatility enables adaptation to various wound types and clinical scenarios, demonstrating both physicochemical stability and biofunctional performance.

Compared to hydrogel-based systems, Pickering emulsions offer a distinct delivery strategy in which bioactive compounds are concentrated at the emulsion interface, improving both stability and skin penetration. This complements natural polymer-based wound-healing platforms such as chitosan hydrogels, alginate films, and gellan gum-chitosan hydrogels (GGCH-HGs), which have also been shown to enhance fibroblast proliferation, collagen deposition, and inflammation reduction. For example, GGCH-HGs loaded with apigenin improved fibroblast viability, increased collagen deposition, and downregulated TNF- α in diabetic wound models (Shukla et al. 2016). Thus, Pickering emulsions can be viewed as an alternative yet complementary delivery system to existing polymer-based strategies.

Although this study provides promising evidence of the cytoprotective and regenerative effects of PESUBG, it remains limited to a two-dimensional *in vitro* fibroblast model. Such models cannot fully represent the real wound-healing process, including tissue repair and new blood vessel formation. Therefore, future studies should adopt three-dimensional approaches, such as 3D printing, polymer embedding, or incorporation into hydrogel matrices, to better mimic tissue structure and improve bioactive

delivery. In addition, *in vivo* experiments using animal wound models are needed to confirm whether PESUBG can regulate fibroblast senescence and accelerate wound healing under more realistic physiological conditions.

Conclusion

This study demonstrates that the SU-BG Pickering emulsion (PESUBG) provides a stable and bioactive delivery system for wound healing. PESUBG enhanced antioxidant activity, protected fibroblasts under oxidative stress, and promoted collagen synthesis, reflecting the simultaneous contributions of SU flavonoids and beta-glucan to tissue repair and ECM remodeling. Its superior physicochemical stability compared with single-stabilizer emulsions supports its potential as a natural-based therapeutic platform. Further *in vivo* studies are warranted to validate efficacy and clarify the distinct biological roles of each component.

Acknowledgements

The authors would like to express their heartfelt gratitude to the School of Pharmacy, Bandung Institute of Technology, and Bhakti Pertiwi College of Pharmaceutical Sciences for their unwavering support and encouragement throughout this research.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

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The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

Use of commercially available immortalised human and animal cell lines.

Use of AI

No use of AI was reported.

Funding

This research was funded by the Center for Higher Education Funding and Assessment, Ministry of Higher Education, Science, and Technology of the Republic of Indonesia, through the Indonesian Education Scholarship Program (BPI) under the Indonesia Endowment Fund for Education (LPDP), Grant No. 202209090693

Author contributions

Lidia contributed to conceptualization, methodology, writing the original draft, and data curation. Muhamad Insanu and Rafiqah Nur Viviani contributed to methodology and data analysis. Muhamad Insanu and Neng Fisher Kurniati contributed to editing and supervision. Tri Suciati contributed to conceptualization, methodology, data analysis, review, editing, and supervision

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Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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Supplementary material 1

Additional information

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