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Formulation and characterization of *Curcuma mangga* Val. extract-loaded transferosome and its antibacterial, antioxidant, and anti-inflammatory activities

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ABSTRACT

Introduction: Currently, *Curcuma mangga* has been found to display immunomodulatory activities on phagocytosis, antibody production, and cytokine release. The current study was conducted to formulate and characterize a *C. mangga* extract-loaded transferosome (CMT) and evaluate its effects against bacteria, oxidative stress, and protein denaturation by *in vitro* studies.
Methods: A thin-layer hydration method was used to develop transferosomes using phosphatidylcholine and Tween 80. Several characteristics, including particle size, zeta potential, pH, morphological structure, entrapment efficiency, and *in vitro* drug release, were assessed. Its antioxidant activity was determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) methods. Meanwhile, antibacterial and anti-inflammatory effects were investigated using broth microdilution and protein denaturation methods, respectively.
Results: The transferosome entrapped 95.80% *C. mangga* extract (CME) with a particle size of 216.9 ± 0.74 nm, and a zeta potential of -40.2 ± 0.28 mV. CMT indicated a spherical form with good size distribution. The transferosome inhibited protein denaturation and exhibited strong antibacterial effects against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acnes*. Additionally, it showed strong antioxidant effects, with IC_{50} values of 70.31 ± 0.28 and 27.59 ± 0.01 µg/mL using the DPPH and ABTS methods, respectively.
Conclusion: The results indicate that CMTs have the potential to be used in treating infections and inflammation induced by a dysregulated immune system.

Implication for health policy/practice/research/medical education:
The results of this study showed the scientific evidence of antibacterial, antioxidant, and anti-inflammatory effects of *Curcuma mangga* extract-loaded transferosome. The transferosome formulation enhances the delivery and efficacy of *C. mangga,* highlighting its potential as an alternative agent for treating infections and inflammation induced by a dysregulated immune system.

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Introduction

Skin infections resulting from microbial invasion of the skin layers and underlying soft tissues are a significant clinical concern in global health issues. These infections can range in severity from minor to fatal, and their prevalence can vary from one to another (1). Skin microbial invasion triggers a rapid innate immune response, followed by an acquired immune response. This response involves inflammation, in which the blood flow increases, allowing immune cells to reach the site of infection. Inflammatory processes can induce the production of reactive oxygen species (ROS), which may lead to protein denaturation (2). When appropriately controlled, this natural and beneficial inflammation drives a localized gathering of the cells and molecules required to eliminate infections and restore damaged tissue. The inflammation typically resolves naturally over time after the threat has been removed. However, if the inflammation persists and develops into a chronic condition, it can become pathological. The inflammatory activity can be suppressed by inhibiting protein denaturation (3). Therefore, agents that can prevent protein denaturation would be beneficial for the development of anti-inflammatory drugs.

In the skin, there is a stratum corneum that serves as a mechanical barrier. Therefore, the development of a drug delivery system to overcome this barrier is necessary (4). Nanoencapsulation using a lipid-based vesicular system, such as transferosome, which is composed of phospholipids and edge activator, has been used to overcome this challenge. Transferosomes can alter the flexibility of their membranes and penetrate the skin pores spontaneously (5). Therefore, this carrier system may enhance the penetration of drugs, including plant active compounds.

Recently, the investigation of medicinal plants has gained momentum. The pharmacological activities of the *Curcuma* species have been well studied. One of the medicinal plants utilized as alternative medicine is *Curcuma mangga* rhizome, which has been used to treat cancer, fever, and gastrointestinal disorders (6). Numerous active secondary metabolites, including curcumin, bis-demethoxycurcumin, (E)-15,15-diethoxylabda-8(17),12-dien-16-al, demethoxycurcumin, and 15,16-bisnorlabda-8(17),11-dien-13-one have been discovered to be present (7). Our previous studies have shown that *C. mangga* has immunomodulatory effects on cellular and humoral-mediated immunity (8,9). Moreover, toxicological evaluation of *C. mangga* rhizome extract displayed that it was nontoxic (LD_{50} value > 5000 mg/kg) (10). Additionally, it was demonstrated that pregnant mice given *C. mangga* orally at certain doses were safe without uterine or fetal toxicities (11). However, its active compounds have poor bioavailability. Therefore, the drug delivery development is necessary to overcome this problem. This current study was conducted to develop and characterize *C. mangga* extract-loaded transferosomes (CMT) and evaluate their antibacterial, antioxidant, and anti-inflammatory activities through *in vitro* studies.

Materials and Methods

Chemicals and reagents

Chloroform, methanol, and sodium chloride were purchased from Merck, Germany. Tween 80, phosphatidylcholine, phosphate-buffered saline (PBS), bovine serum albumin (BSA), and dimethyl sulfoxide (DMSO) were obtained from Sigma-Aldrich, St. Louis, MO, USA. Broth heart infusion (BHI) and McFarland standard No. 0.5 were obtained from Himedia (Mumbai, India). Propylene glycol, triethanolamine, carboxypolymethylene 940, and phenoxyethanol from Merck (Germany), sodium diclofenac (Dexa Medica), and tetracycline (Sigma-Aldrich, St. Louis, MO, USA) were also used in this study.

Bacterial strains

Propionibacterium acnes (ATCC 6919), *Staphylococcus aureus* (ATCC 25923), and *Staphylococcus epidermidis* (ATCC 12228) were obtained from the National Agency of Drug and Food Control Indonesia.

Plant material and extraction

The rhizomes of *C. mangga* were collected from North Sumatra, Indonesia, and identified by a biologist from the Herbarium Medanense, Universitas Sumatera Utara, Indonesia, with voucher number 5669/MEDA/2021. Then, the dried rhizomes (541 grams) were macerated using 99% ethanol (1:10) as the solvent. Then, the macerate was collected and evaporated using a rotary evaporator (Buchi Heating Bath B-100) at a temperature of 50±5 °C to yield 9.54% *C. mangga* ethanol extract.

Formulation of *C. mangga*-loaded transferosome

The preparation of transferosomes was performed using the thin-layer hydration method (5). Phosphatidylcholine: Tween 80 (95:5) was used. Briefly, phosphatidylcholine was dissolved in chloroform, then Tween 80 and *C. mangga* were dissolved in methanol. The concentrations of CME loaded to transferosome were 100, 200 and 400 µg/mL The mixture was evaporated from a thin layer. Thereafter, the thin layer was hydrated using PBS, and its particle size was reduced using an ultra-turrax at 12,000 rpm for the first 7 minutes, followed by a speed of 15,000 rpm for the next 3 minutes. Finally, the transferosomes were sonicated in a bath sonicator for 30 minutes.

FTIR analysis

The FTIR spectrum of the components constituting the transferosome was measured using a Bruker Tensor II FTIR spectrometer over a wavelength range of 4000-500 cm^{-1}. Then, the data were analyzed using the software OriginPro 2022 for data analysis and graphing.

Characterization of *C. mangga*-loaded transferosome

Particle size, polydispersion index, pH, and zeta potential

The particle size and polydispersity index of the transfersome sample were measured using Dynamic Light Scattering (DLS) (Horiba SZ-100) with three replications. Meanwhile, a pH meter (pH-009(I)A) was used to measure the pH of the *C. mangga*-loaded transferosome (CMT) after calibration using a buffer solution. Zeta potential was evaluated using a Laser Doppler electrophoresis (Horiba SZ-100).

Entrapment efficiency

The entrapment efficiency was determined using curcumin as a standard at concentrations ranging from 2 to 10 µg/mL. The transferosome was lysed using methanol and sonicated for 10 minutes; then, the absorbance of curcumin from the transferosome was measured using a UV-Vis spectrophotometer (Agilent) at 420 nm and calculated as the total *C. mangga* drug in the transferosome. The amount of free drug was determined by centrifugation of *C. mangga*-loaded transferrin at 10,000 rpm for 1.5 hours, after which the supernatant was measured at 420 nm. The percentage of entrapment efficiency was calculated according to the following formula:

$$\text{Entrapment efficiency percentage} = \frac{\text{Total drug - Free drug}}{\text{Total drug}} \times 100\%$$

Morphology of structure

Transmission electron microscopy (HRTEM, Talos F200C G2) at scales of 500 and 200 nm was used to identify the morphology of the transferosome structure.

Stability evaluation

The stability of CMT was evaluated using the cycling test method. After five cycles, the transferosomes were physically analyzed to evaluate particle size, polydispersity index, zeta potential, and entrapment efficiency

The antibacterial activity study was conducted using a modified broth microdilution assay method (12). Briefly, the media, samples (CME or CMT at 4.88; 9.76; 19.53; 39.06; 78.12; 156.25; 312.5; 625; 1250 µg/mL or tetracycline as a positive control at 0.97; 1.95; 3.90; 7.81; 15.62; 31.25; 62.5; 1215 µg/mL), and bacterial suspension (1×10^6 CFU/mL) were placed into a 96-well plate and then incubated at 37 °C for 24 hours. The lowest concentration with a clear solution was designated as the minimum inhibitory concentration (MIC). The lowest concentration that could kill the bacteria, indicated by the absence of bacterial growth, was designated as the minimum bactericidal concentration (MBC). DMSO and tetracycline were used as negative and positive controls, respectively.

Anti-inflammatory activity

The anti-inflammatory activity of *C. mangga* extract (CME) and CMT was conducted following a modified protein denaturation method (13). Briefly, 0.2% BSA was dissolved in Tris Buffer Saline (TBS), pH 6.2-6.5. Then, 2.85 mL of 0.2% BSA solution was incubated with 150 µL of the sample for 15 minutes at room temperature. Furthermore, the mixture was heated to 70 °C for 15 minutes in a water bath and then cooled to room temperature over a period of 20 minutes. A UV-Vis spectrophotometer at 660 nm (Agilent Technologies Cary 60 UV-Vis) was used the measure the absorbance, and the percentage inhibition was calculated using the following formula:

$$\text{Inhibitaion percentage} = \frac{\text{Blank absorbance - sample absorbance}}{\text{Blank absorbance}} \times 100\%$$

Methanol and sodium diclofenac were used as negative and positive controls, respectively.

Antioxidant activity

ABTS assay

The ABTS (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)) free radical capture assay was performed according to a previous study (14). Briefly, 750 µL of the samples was added to 2.25 mL of the ABTS solution, then incubated at room temperature for 6 minutes in the dark. Furthermore, the mixture was centrifuged at 10,000 rpm for 5 min. The IC_{50} values were calculated based on the absorbance value of the supernatant, which was measured at 745 nm using a UV-Vis spectrophotometer (Agilent Technologies Cary 60 UV-Vis).

DPPH assay

The DPPH (2,2-Diphenyl-1-picrylhydrazyl) free radical capture assay was conducted using a modified method of Sebaaly et al (15). An aliquot of 500 µL of the sample was mixed with 500 µL of a 0.1 mM DPPH solution. Methanol (MeOH) was then added to adjust the final volume to 3000 µL. The resulting mixture was thoroughly mixed, incubated in the dark at room temperature for 30 minutes, and subsequently analyzed using a UV-Vis spectrophotometer (Agilent Technologies Cary 60 UV-Vis) at a wavelength of 515 nm. The percentage of radical capture was calculated using the following formula:

$$\text{Scavenging percentage} = \frac{\text{Blank absorbance - sample absorbance}}{\text{Blank absorbance}}$$

Statistical analysis

Data were analyzed using SPSS version 21. Data were analyzed using a one-way ANOVA or Kruskal-Wallis for multiple comparisons. $P < 0.05$ was considered statistically significant.

Results

Characterization and stability evaluation of C. mangga-loaded transferosome

Table 1 shows the characterization of CMT, including particle size, polydispersity index, zeta potential, and

entrapment efficiency. TF-0, as the base formula, was also characterized. Among the formulas, CMT 0.1 displayed the highest entrapment efficiency (95.80 ± 0.00).

Furthermore, stability evaluation was conducted to ensure the stability of the formula. As shown in Table 2, TF-0 and CMT 0.1 exhibited notable stability throughout the observed period, maintaining consistent particle size ranges. However, CMT 0.2 and CMT 0.4 became unstable, demonstrated by a drastic increase in particle size post-treatment, indicating aggregation or agglomeration. The particle size of TF-0 was the smallest among all the formulas. This small size could be one of the factors that make TF-0 stable. CMT 0.1 showed a slight increase in particle size; however, this still indicated that the formula remained stable.

According to the Polydispersity Index (PDI), all formulations exhibited PDI values below 0.7, indicating a relatively uniform particle size distribution. However, an increase in PDI post-treatment, particularly in TFTM 0.1, indicated a broadening of the particle size distribution. The PDI values of CMT 0.2 and 0.4 after treatment could not be measured because the formula was not stable.

All formulations exhibited negative zeta potential values, indicative of electrostatic stability. Moreover, a shift towards more negative values post-treatment suggested an enhancement of electrostatic repulsion, potentially contributing to increased stability in TF-0 and CMT 0.1. The zeta potential values of CMT 0.2 and 0.4 after treatment could not be measured because the formula was not stable.

CMT formulations demonstrated high entrapment efficiency, exceeding 80% in all cases. However, a slight

Table 1. Characterization of *Curcuma mangga* extract-loaded transferosome

Treatment	Particle size (nm)	Polydispersity index	Zeta potential (mV)	Entrapment Efficiency (%)
TF-0	145.7 ± 2.28	0.410 ± 0.02	-4.06 ± 0.28	-
CMT 0.1	216.9 ± 0.74	0.373 ± 0.01	-40.2 ± 0.28	95.80 ± 0.00
CMT 0.2	187.9 ± 0.65	0.412 ± 0.01	-42.7 ± 0.12	89.86 ± 0.01
CMT 0.4	115.2 ± 0.14	0.544 ± 0.01	-42.7 ± 0.05	84.16 ± 0.02

TF-0: Blank transferosome; CMT 0.1, CMT 0.2, and CMT 0.4: *Curcuma mangga* ethanol extract 100, 200, and 400 µg/mL loaded transferosome, respectively (n=3).

Table 2. Stability evaluation of *Curcuma mangga* extract-loaded transferosome

Formula	Parameters	Before	After	*P*
TF-0	Physical		Stable	
	Particle size (nm)	145.7 ± 2.28	244.4 ± 0.38	0.109
	Polydispersity index	0.41 ± 0.02	0.432 ± 0.00	0.109
	Zeta potential (mV)	-40.57 ± 0.26	-54.3 ± 0.4	0.109
	Entrapment efficiency (%)	-	-	-
CMT 0.1	Physical		Stable	
	Particle size (nm)	216.9 ± 0.74	231.7 ± 0.05	0.109
	Polydispersity index	0.373 ± 0.01	0.640 ± 0.02	0.180
	Zeta potential (mV)	-40.2 ± 0.28	-55.17 ± 0.17	0.109
	Entrapment efficiency (%)	95.80 ± 0.00	94.40 ± 0.01	0.285
CMT 0.2	Physical		Unstable	
	Particle size (nm)	187.9 ± 0.65	2,282.32 ± 0.83	0.109
	Polydispersity index	0.412 ± 0.01	-	
	Zeta potential (mV)	-42.7 ± 0.12	-59.7 ± 0.28	0.109
	Entrapment efficiency (%)	89.86 ± 0.01	87.36 ± 0.01	0.109
CMT 0.4	Physical		Unstable	
	Particle size (nm)	115.2 ± 0.14	15,044.57 ± 0.65	0.109
	Polydispersity index	0.544 ± 0.01	-	
	Zeta potential (mV)	-42.7 ± 0.05	-60.3 ± 0.42	0.109
	Entrapment efficiency (%)	84.16 ± 0.02	89.86 ± 0.01	0.109

TF-0: Blank transferosome; CMT 0.1, CMT 0.2, and CMT 0.4: *Curcuma mangga* ethanol extract 100, 200, and 400 µg/mL loaded transferosome, respectively (n=3).
Note: $P < 0.05$ significant difference between before and after five cycles of stability evaluation.

decrease in entrapment efficiency was observed post-treatment, particularly in CMT 0.4, which correlated with its instability.

FTIR analysis of *C. mangga*-loaded transferosome

The FTIR spectra of the individual components, *Curcuma mangga* ethanol extract (CMEE), blank transferosome (TF-0), and CMEE-loaded transferosomes (TFM 1, 2, and 3), are shown in Figure 1, demonstrating the assessment results of potential chemical interactions between the extract and the vesicular matrix. CMEE exhibited characteristic bands at 2929 cm^{-1} and 2841 cm^{-1} (C–H stretching), 1682 cm^{-1} (C=O stretching), and 1055 cm^{-1} (C–N or C–O stretching), indicating the presence of phenolic and flavonoid compounds. Tween 80 (TW) and phosphatidylcholine (FD) both displayed peaks at 2921, 2858/2851, 1736, and 1096 cm^{-1}, typical of C–H stretching, ester C=O, and ether C–O–C vibrations, confirming their lipidic and structural roles in vesicle formation.

The blank transferosome (TF-0) exhibited characteristic peaks at 3306 cm^{-1} (O–H stretching) and 1635 cm^{-1} (N–H bending), typical of phosphatidylcholine vesicles. Similarly, the CMEE-loaded transferosomes (TFM 1, 2, and 3) showed identical spectra with no new or shifted peaks, indicating the absence of chemical interaction and confirming that the extract was encapsulated without altering the vesicle structure.

The morphology of C. mangga-loaded transferosome

Figure 2 shows the morphology of a vesicle. Transferosome vesicles of CME were spherical vesicles and had a monodisperse size distribution based on TEM morphology data.

Anti-inflammatory activity

Table 3 presents the results of an anti-inflammatory study. CMT demonstrated low inhibition on protein denaturation. The protein denaturation inhibitory activity of CME and its transferosome formulation was much lower than that of ibuprofen, the positive control. However, the anti-inflammatory activity of CMT was higher than that of CME only, especially at the concentration of 200 µg/mL ($P < 0.05$).

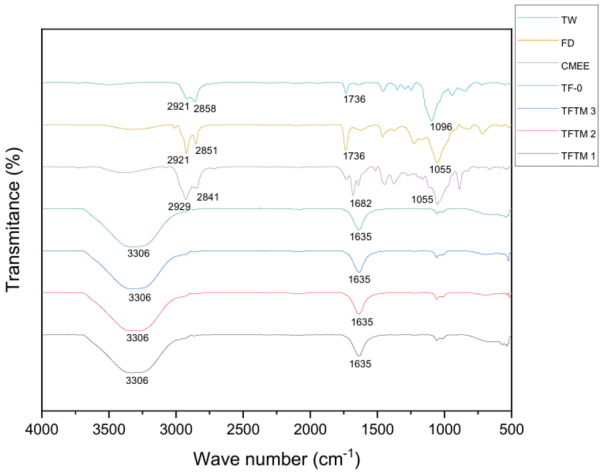

Figure 1. FTIR spectrum of *Curcuma mangga extract* (CME), phosphatidylcholine (FD), polysorbate 80 (TW), blank transferosome (TF-0), and *C. mangga*-loaded transferosomes (TFTM 1,2,3).

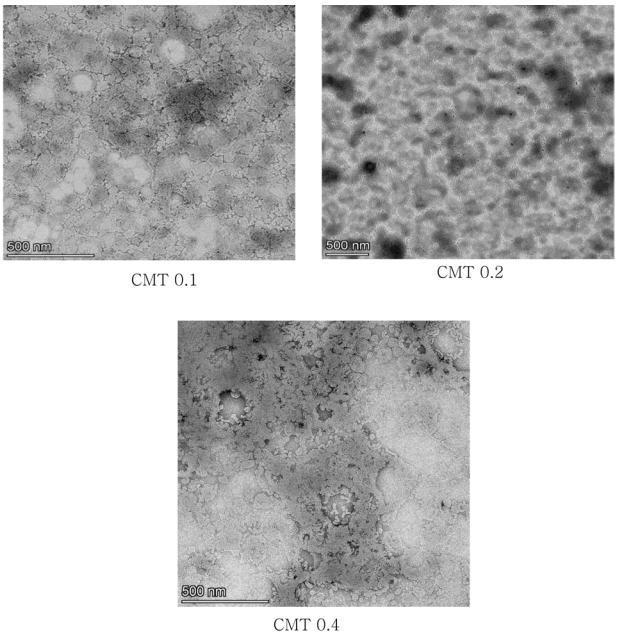

Figure 2. The morphology of transferosome vesicles. TF-0: blank transferosome; CMT 0.1, 0.2, and 0.4: *Curcuma mangga* ethanol extract 100, 200, and 400 µg/mL loaded transferosomes.

Antibacterial activity

Table 4 presents the MIC values of various substances evaluated using the microdilution method against three bacterial strains: *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acnes*. These bacteria are commonly associated with skin infections, particularly acne.

The crude extract of *C. mangga* showed relatively high MIC values (31.25-250 µg/mL) against all three bacterial strains, indicating weak antibacterial activity. Encapsulating CM extract in transferosome (CMT)

Table 3. Anti-inflammatory activity of *Curcuma mangga*-loaded transferosome

Treatment	Percentage of inhibition (%)	
	CME	CMT
100 µg/mL	42.45 ± 0.04	18.55 ± 0.04
200 µg/mL	58.02 ± 0.03*	33.04 ± 0.02 *
400 µg/mL	72.95 ± 0.00	40.54 ± 0.01
Ibuprofen 150 µg/mL	99.90 ± 0.01	

CME: *Curcuma mangga* ethanol extract.
CMT: *Curcuma mangga* ethanol extract-loaded transferosome.
* Significant difference between CME and CMT ($P < 0.05$).

Table 4. Antibacterial activity of *Curcuma mangga*-loaded transferosome

Formula	MIC (µg/mL)			MBC (µg/mL)		
	SA	SE	PA	SA	SE	PA
CME	31.25	500	7.81	32.25	500	31.25
CMT 0.1	1.95	1.95	1.95	3.9	3.9	3.9
CMT 0.2	3.9	7.81	3.9	500	31.25	7.81
CMT 0.4	7.81	7.81	7.81	15.62	7.81	1000
Tetracycline	0.97	7.81	0.97	7.81	15.62	7.81

CME: *C. mangga* ethanol extract; CMT 0.1, CMT 0.2, and CMT 0.4: *C. mangga* ethanol extract of 100, 200, and 400 µg/mL-loaded transferosome. SA: *Staphylococcus aureus*; SE: *Staphylococcus epidermidis*; PA: *Propionibacterium acne.*

dramatically enhanced its antibacterial activity. CMT exhibited significantly lower MIC values (1.95-3.90 µg/mL) compared to the crude extract.

Antioxidant activity

Table 5 presents the antioxidant activity of CME and its transferosome formulation. The antioxidant activity was evaluated using two different assays: DPPH and ABTS. CMT 0.1 exhibited significantly higher antioxidant activity than CME, as evidenced by a lower IC_{50} value (122.78 µg/mL for CME and 70.31 µg/mL for CMT 0.1).

Discussion

The current study formulated CME into CMT and evaluated its antibacterial, antioxidant, and anti-inflammatory effects. The formulation was characterized in terms of its particle size, polydispersity index, zeta potential, and entrapment efficiency. CMT 0.1 demonstrated the highest entrapment efficiency among the CMT formulas (95.80%). Increased loading can be attributed to the drug's lipophilicity and its ability to integrate into lipid bilayers. Phospholipids provide structural integrity to the vesicle, whereas cholesterol improves stability and prevents drug leakage, hence increasing entrapment efficiency (16).

A clear correlation was observed between the stability of the formulas and the particle size and zeta potential values. Formulas categorized as stable showed a small change in particle size and zeta potential. Formulas categorized as unstable showed a significant change in particle size, and the zeta potential value could not be measured. This data set provides valuable insights into the physicochemical properties and adsorption behavior of transferosome formulations. Moreover, the stable formula (CMT 0.1) was continued to be evaluated for its pharmacological effects. The findings underscore the importance of optimizing formulation stability to ensure consistent performance and efficacy (17).

Table 5. IC_{50} values of antioxidant activity of *Curcuma mangga* extract-loaded transferosome.

Treatment	Transferosome		Category
	DPPH (µg/mL)	ABTS (µg/mL)	
CME	112.78 ± 0.04	71.49 ± 0.48	
CMT 0.1	70.31 ± 0.28	27.59 ± 0.01	
CMT 0.2	75.07 ± 0.10	28.45 ± 0.02	Very strong
CMT 0.4	85.83 ± 0.08	39.15 ± 0.01	
Quercetin	2.25 ± 0.00	1.67 ± 0.01	

CME: *C. mangga* ethanol extract; CMT 0.1, CMT 0.2, and CMT 0.4: *C. mangga* ethanol extract of 100, 200, and 400 µg/mL-loaded transferosome. DPPH: 2,2-diphenyl-1-picrylhydrazyl; ABTS:2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid).

Cellular intake or internalization is a critical physicochemical criterion to consider before in vivo applications. The absorption of tiny molecules and particles by any cell primarily relies on endocytosis, among other mechanisms. Endocytosis is the active transport mechanism by which cells internalize materials by enveloping them with their phospholipid bilayer, utilizing energy in the form of ATP. The primary mechanisms of endocytosis are identified as pinocytosis and phagocytosis. Phagocytic cells, including macrophages, neutrophils, and dendritic cells, primarily internalize cellular material by swallowing particles exceeding 1 µm in size. The dimensions of drug delivery systems significantly affect pharmacokinetics, tissue distribution, and clearance. Various physiological processes, including hepatic absorption and accumulation, tissue diffusion, tissue extravasation, and renal excretion, are greatly influenced by particle size (17). Lipidic nanocarriers may be retained within tissue due to the diameters of capillary pores or the interstitial space. The size of vesicles is a crucial factor in lipid nanocarriers, influencing stability, entrapment efficiency, drug release, distribution, bioavailability, mucoadhesion, and cellular uptake. It is well-established that nanoparticulate formulations, such as TFS, can achieve significant enhancement in tissue penetration by minimizing particle size (17-19).

The FTIR results indicate that no covalent interactions occurred between CME phytoconstituents and the lipid components of the transferosome, suggesting that the extract was physically entrapped without altering the structural integrity of the vesicles. This is supported by the absence of new or shifted peaks in the spectra. Similar findings have been reported in ginger and *Solanum xanthocarpum* extract-loaded transferosomes, confirming

encapsulation through non-covalent interactions (20).

Furthermore, the CMT was investigated for its anti-inflammatory effects. The anti-inflammatory activity of CMT was higher than that of CME only. This suggests that the transferosome formulation enhances the delivery and efficacy of *C. mangga*. These findings support the potential use of *C. mangga*, particularly in a transferosome delivery system, as a natural anti-inflammatory agent. The impact of transfersomes on pharmacological activity aligns with the study of a curcumin-loaded transfersomal gel, which effectively transports curcumin to arthritic dermal tissue via topical application, exhibiting notable therapeutic efficacy. The curcumin-encapsulated transferosome gel demonstrated superior in vitro skin penetration compared to unmodified curcumin (21). A similar observation was made by Tawfeek et al, who found that the anti-inflammatory efficacy of Lornoxicam-loaded transferosomes significantly reduces the percentage of swelling in produced edema compared to the plain formulation (22).

Curcuma mangga is recognized for its anti-inflammatory properties, which have been attributed to compounds such as curcuminoids. The data suggest that incorporating this extract into a transferosome system might enhance its delivery and efficacy. This research opens up promising avenues for developing novel therapeutic strategies for inflammatory conditions using natural products. In a prior study, *C. xanthorrhiza* essential oil was synthesized using thin-film hydration for the preparation of the transferosome system. *C. xanthorrhiza* essential oil-loaded transferosome exhibited a sevenfold greater inhibition percentage in anti-inflammatory activity compared to free *C. xanthorrhiza* essential oil (23). The increase in such activity has implications for vesicles, which are colloidal particles consisting of an aqueous compartment enclosed by a concentric bilayer composed of amphiphilic molecules (24). Vesicular drug delivery systems are effective in transporting hydrophilic drugs encapsulated in the inner aqueous compartment, whereas hydrophobic drugs are contained within the lipid bilayer (15,24). Transferosomes are highly deformable and self-optimizing drug carrier vesicles. Their ability to traverse the skin is primarily linked to the membrane flexibility, hydrophilicity, and integrity of the vesicles (15,18).

Transferosomes are flexible, ultra-deformable vesicles composed of phospholipids and edge activators. They enhance permeation, penetrate smaller pores, facilitate the solubilisation of hydrophobic drugs, and improve the efficiency of drug absorption and lipid flow in skin permeation (23,25,26). Encapsulating CM extract in transferosomes (CMT) dramatically enhances its antibacterial activity. CMT exhibits significantly lower MIC values compared to the crude extract, demonstrating a substantial improvement in its ability to inhibit bacterial growth. This suggests that the transferosome delivery system improves the efficacy of CME. The enhanced activity of CMT 0.1 compared to CME could be attributed to improved penetration and delivery of the active compounds into the bacterial cells, facilitated by the transferosome carrier system. The strong antibacterial activity of CMT against *P. acnes*, a key contributor to acne development, suggests its potential as a natural therapeutic agent for acne treatment. Tetracycline, a known antibiotic, shows potent antibacterial activity with MIC values ranging from 0.97 to 15.62 µg/mL. It is particularly effective against *S. aureus* and *P. acnes*. The data highlight the potential of natural products, such as *C. mangga*, particularly in a more effective delivery system like transferosomes, as alternative therapeutic options to combat antibiotic resistance. This study demonstrates a significant enhancement in the antibacterial activity of CME when encapsulated in transferosomes. The findings suggest that CMT holds promise as a potential natural therapy for acne and other skin infections. Similar to the previous study, the transferosome containing *C. xanthorrhiza* essential oils showed considerable antibacterial effectiveness against *P. acnes* and *S. epidermidis.* Transferosome could enhance the antibacterial efficacy of free *C. xanthorrhiza* essential oils against *P. acnes* by a factor of 32. The lipid vesicle further enhanced the effectiveness of *C. xanthorrhiza* essential oils against *S. epidermidis*. This discovery suggests that the partition coefficient of membrane lipids increased the antibacterial efficacy of essential oil when supplemented with lipid-based vesicles (23).

The encapsulation of *C. mangga* resulted in an enhanced antioxidant effect. CMT exhibited significantly higher antioxidant activity than CME. This suggests that the encapsulation of *C. mangga* in a transferosome system enhances its ability to scavenge DPPH free radicals. However, quercetin demonstrated the strongest antioxidant activity among all the samples, highlighting its potent capacity to scavenge free radicals. Similar to the DPPH assay, CMT 0.1 exhibits superior antioxidant activity compared to CME in the ABTS assay, with an IC_{50} value of 71.48 and 27.59 µg/mL for CME and CMT 0.1, respectively. This further supports the notion that the transferosome system improves the antioxidant potential of *C. mangga*. Again, quercetin exhibits the most potent antioxidant activity, with an IC50 value of 2.25 µg/mL, thereby reinforcing its superior free radical scavenging ability.

The enhanced antioxidant activity of CMT 0.1 compared to CME can be attributed to its improved solubility, bioavailability, and cellular uptake of CME, resulting from encapsulation in the transferosome system. The strong antioxidant activity of CMT 0.1 suggests its potential use in various applications, such as food preservation, cosmetics, and pharmaceuticals, where protection against oxidative stress is desired. This data provides evidence that the encapsulation of *C. mangga* in a transferosome system (CMT 0.1) significantly enhances its antioxidant activity

compared to the unencapsulated form (CME). A previous study also reported the enhancement in the antioxidant activity of the formula containing transferosome. The antioxidant effectiveness of transferosome cream with glutathione was improved by 23.63% compared to glutathione cream without transferosomes (18). The prior study yielded comparable findings. Transferosomes loaded with *C. xanthorrhiza* essential oil showed 18–19 times more antioxidant activity compared to free *Curcuma xanthorrhiza* essential oils (23).

Conclusion

This research provides compelling evidence for the therapeutic potential of *Curcuma mangga* extract, particularly when formulated into a transferosome delivery system. The enhanced stability, delivery, and efficacy observed with CMT highlight its potential as a natural alternative for various applications, including anti-inflammatory, antibacterial, and antioxidant therapies. Furthermore, preclinical and clinical studies are required to evaluate its pharmacodynamic and pharmacokinetic properties

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Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical considerations

The authors declare that the current study is original and that all sources used have been properly cited and acknowledged.

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