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Literature Review: Formulation and Characterization of Nanoemulgel for Anticellulite Treatment

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ABSTRACT

Cellulite, a skin condition characterized by a dimpled, orange-peel appearance, commonly affects the thighs, abdomen, hips, and buttocks. Nanoemulgel, a combined system of nanoemulsion and gel, has gained attention as an effective topical drug delivery system, particularly for lipophilic drugs. This review examines the potential of nanoemulgel formulations in treating cellulite, focusing on their physical characteristics, drug delivery efficiency evaluated through skin penetration and anti-cellulite effects, specifically their ability to inhibit adipogenesis and reduce triglycerides. A total of 5 articles were selected for further review as they met the eligibility criteria, including nanoemulgel formulations containing active ingredients with potential anti-cellulite properties and in vitro or in vivo testing for anti-cellulite effectiveness. The results show that nanoemulgel formulations could be a new way to deliver lipophilic drugs to specific areas of the skin for treating cellulite.

INTRODUCTION

Cellulite, a common skin condition that affects 80-95% of post-pubertal women, is characterized by dimpled and uneven skin texture, often described as resembling orange peel, which is why it is also called "orange peel syndrome" (Arora et al., 2022; Sadick, 2019). Although cellulite is not painful, it can significantly affect self-esteem due to its aesthetic impact. It typically occurs in areas of high fat storage, such as the thighs, hips, buttocks, and abdomen (Arora et al., 2022). Estrogen, which weakens blood vessels and leads to their rupture and subsequent accumulation of lipocytes, influences the condition without directly linking it to obesity. This accumulation, along with subcutaneous remodeling, creates pockets of fat surrounded by fibrous tissue, contributing to the visible appearance of cellulite (Christensen, 2014).

Various treatment methods exist for cellulite, including diet, physical exercise, massage, endermology, liposuction, laser treatments, and topical drugs. However, research has not proven the full effectiveness of any of these approaches. Among these, topical treatments offer the advantages of being more affordable and easier to formulate for improved efficacy (Christensen, 2014). For topical anticellulite treatments to be effective, they must penetrate the skin to reach the dermal adipocytes. One promising formulation strategy to enhance skin penetration is the use of nanoemulsions, which have particle sizes below 100 nm. Nanoemulsion-based formulations enhance drug concentration in targeted areas, improve skin penetration, increase drug loading capacity,

and provide sustained drug release. When mixed in a hydrogel system, these nanoemulsions create nanoemulgels, which are easier to apply to the skin and work better (Algahtani et al., 2021).

This literature review aims to provide a comprehensive assessment of the potential and limitations of nanoemulgel formulations for the treatment of cellulite.

METHODS

Article Search Strategy

A literature search was conducted across several databases, including Google Scholar, ResearchGate, ScienceDirect, and PubMed, supplemented by manual searches using Google. Boolean operators (AND, OR) were applied to ensure comprehensive coverage of relevant literature. The search terms included: ("nanoemulgel" OR "nano-emulgel" OR "nanoemulsion gel" OR "nanoemulgels") AND ("cellulite" OR "anti-cellulite" OR "anticellulite" OR "dermopanniculosis deformans" OR "adiposis edematosa" OR "orange peel syndrome"). Keywords were selected based on Medical Subject Headings (MeSH) to enhance search precision and scope.

Selection Criteria

The selected articles were organized based on the impact of emulgel formulation on anticellulite efficacy. The authors independently extracted study characteristics. The extracted data included details on emulgel preparation, physical characterization, penetration studies using Franz diffusion cells, and evaluation of anti-cellulite efficacy (adipogenesis lipolysis assay).

Data Handling, Analysis, and Extraction

The inclusion criteria for this literature review were original research articles, written in either English or Indonesian, published between 2014 and 2024, full text, and not duplicate articles. The exclusion criteria for articles were articles not discussing nanoemulgel formulations related to anti-cellulite effectiveness and articles not containing in vitro/in vivo anti-cellulite activity tests. The selected articles were categorized into three main groups: (1) nanoemulgel formulation and characterization; (2) evaluation of nanoemulgel penetration ability using the Franz diffusion method, along with corresponding results; and (3) anticellulite activity assessment through the adipogenesis and lipolysis test, with reported outcomes.

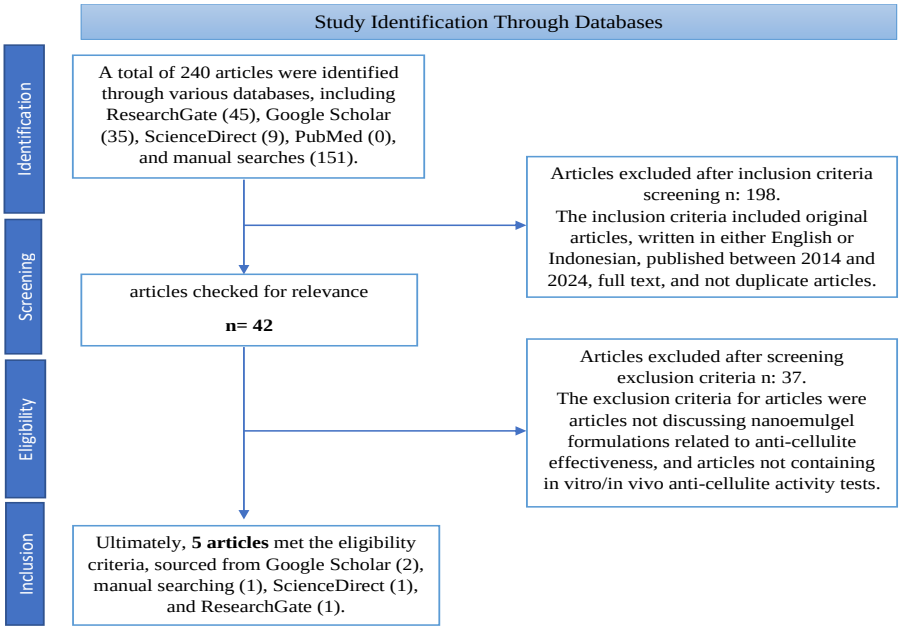

Figure 1. PRISMA flow chart for studies related with formulation and characterization of nanoemulgel for cellulite

RESULT

A total of 42 articles that met the inclusion criteria were further reviewed for eligibility. The selected articles were categorized based on nanoemulgel formulations, nanoemulgel characterization, and anti-cellulite efficacy evaluated through the penetration ability of nanoemulgel preparations using the Franz diffusion cell test or adipogenesis lipolysis test. Of these articles, 4 utilized the Franz diffusion cell test, while 1 employed the adipocyte lipolysis test (notably, the author of the latter study published two articles under different titles as a continuation of the same research). The complete study selection process is outlined in **Figure 1,** following the PRISMA flow diagram.

Active Ingredients for Anticellulite Effectiveness

Based on the findings presented in **Table** 1**,** several active ingredients have been formulated into nanoemulgel dosage forms with demonstrated efficacy as anti-cellulite agents. These include caffeine (Djajadisastra et al., 2014; Priani et al., 2021; Sintov & Greenberg, 2014), nicotinamide (Mehta et al., 2018), and a combination of tea and coffee extracts (Ngamdokmai, Ingkaninan, et al., 2021). The methylxanthine content present in caffeine has been found to alleviate cellulite by inhibiting lipogenesis and phosphodiesterase (preventing fat storage and breaking down fat molecules) (Djajadisastra et al., 2014).

Caffeine, a commonly used anti-cellulite agent, has a Log P value of 0.07, indicating its hydrophilic nature. This property hinders its percutaneous penetration, limiting its effectiveness in topical applications. To overcome this challenge, emulsions can be incorporated into a polymer gel base to create an emulgel formulation. This approach enhances

Table 1. Formulation and characterization of nanoemulgel as an anti-cellulite

Author/ Year	Drug	Optimum Nanoemulsion Formula	Nanoemulgel Formula (Gel Base)	Characterization of Nanoemulgel
(Mehta et al., 2018)	Nicotinamide (1.2%)	Oil: peppermint (30%) Surfactant: Tween 20 (46.15%) Co-Surfactant: - Water (23.07%)	Carbopol 934P (1.1%).	Droplet size: 152 nm Viscosity: 1.4007 ± 0.231 Pa
(Priani et al., 2021)	Caffeine (1%)	Oil: grape seed (5%) Surfactant: Tween 80 (35%) Co-Surfactant: Glycerin (35%) Water (*ad* 100%)	Viscolam Mac 10 (1.5%)	Droplet size: 126 ± 17 nm %Transmittance: 98.2 ± 0.6 % Viscosity: 2482.33 ± 8.49 Cps pH: 6.95 ± 0.09
(Ngamdokmai, Ingkaninan, et al., 2021)	Tea extract (0.05%) and coffee (0.05%)	Oil: mixed oil 5% (herbal oil of ginger, black pepper, long chili, turmeric, cassumunar ginger, lemongrass and kaffir lime) and rice bran oil (8%). Surfactant: PEG-40, hydrogenated castor oil (5%). Co-Surfactant: Propylene glycol (2%) Water (66%)	Carbopol 940 (0.8%)	Viscosity: 1715 ± 5.29 Cp pH: 6.89 ± 0.02
(Djajadisastra et al., 2014)	Caffeine (1.5%)	Oil: Liquid Paraffim (5%) Surfactant: Tween 20 (1.5%) and Span 60 (1%) Co-Surfactant: Propylene glycol (10%)	HPMC (2%)	Droplet size: 185.4 nm Viscosity: 78000 cPs pH: 5.5-6.5
(Sintov & Greenberg, 2014)	Caffeine (1%)	Oil: Isopropyl palmitate (11%) Surfactant: Polyoxyglycerides and glyceryl oleate (3:1 dengan total 74.17%) Co-Surfactant: Propylene carbonate (14.83%)	CAB-O-SIL TS-530 (Aerosil) 10% Water 20%	Droplet size: 3.97 – 4.55 nm

skin adhesion, allowing the anti-cellulite agent to remain in contact with the skin for a longer period. The emulgel formulation can improve the permeation of hydrophilic agents like caffeine, increasing their bioavailability and efficacy in reducing cellulite (Priani et al., 2021; Sintov & Greenberg, 2014). Nicotinamide has the potential to improve skin surface structure, smooth wrinkles, and inhibit photocarcinogenesis (Mehta et al., 2018). Essential oils and herbal tea extracts have been found to decrease lipogenesis and increase lipolysis in 3T3-L1 adipocytes. Furthermore, herbal tea extracts have been shown to reduce cellulite, skin fold thickness, and thigh circumference (Ngamdokmai, Waranuch, et al., 2021). The research suggests that the nanoemulgel formulation may improve the effectiveness of active compounds, such as caffeine, niacinamide, and botanical extracts. The clarification of caffeine's log P and its effect on skin penetration provides a strong scientific basis for the use of nanoemulgel. This formulation enhances skin adhesion and optimizes the absorption of active ingredients. Thus, this strategy is very relevant for enhancing the effectiveness of topical anti-cellulite products. Future investigations may explore the integration of active ingredients in nanoemulgel formulations to achieve improved synergistic effects. This study, augmented with further insights into molecular characteristics and clinical data, can serve as a valuable reference for researchers and manufacturers in improving anti-cellulite formulations.

Anticellulite Nanoemulgel Formulation

Table 1 summarizes the various oils, surfactants, and co-surfactants employed in different studies. The selection of oil, surfactants, and co-surfactants is critical, as these components significantly influence the stability of the nanoemulsion formulation. Surfactants function to decrease the interfacial tension between two immiscible phases, facilitating their mixing due to the hydrophilic and hydrophobic characteristics of their respective head and tail groups (Rai et al., 2018). Thus, surfactants are pivotal in the formulation of nanoemulsions. Co-surfactants further enhance this process by lowering interfacial tension and imparting flexibility to the interfacial layer, enabling it to accommodate the varying curvatures essential for effective nanoemulsion formation (Mulleria et al., 2021). Collectively, these components play a vital role in ensuring the stability and efficacy of nanoemulgel formulations.

The choice of oil for the nanoemulsion is primarily influenced by its solubility with the active compounds. Notably, caffeine exhibits the highest solubility in liquid paraffin oil (Djajadisastra et al., 2014) and the lowest in isopropyl myristate (Sintov & Greenberg, 2014). Liquid paraffin is a mineral oil characterized by low viscosity, chemical inertness, resistance to oxidation, and its ability to form stable emulsions (Zhao et al., 2021). Conversely, isopropyl myristate (IPM), despite its lower solubility in caffeine, enhances the penetration of active ingredients through the stratum corneum by modifying the lipid structure of the skin. IPM also contributes to the thermodynamic stability of nanoemulsions and facilitates the formation of smaller droplet sizes, thereby increasing the therapeutic efficacy and skin permeability of active compounds (Abdullah et al., 2021; Sintov & Greenberg, 2014). Nicotinamide at a concentration of 1.2% can be effectively dissolved in 30% peppermint oil (Mehta et al., 2018). However, caution is warranted when using peppermint oil on sensitive skin due to the potential for irritation from its menthol content (Rys et al., 2022). Furthermore, the incorporation of a blend of seven essential oils in nanoemulgel formulations of tea and coffee extracts is anticipated to yield a synergistic effect on anti-lipogenesis. Rice bran oil is added to address the issues of water insolubility, instability of short-chain hydrocarbon molecules present in the essential oils, and high volatility (Ngamdokmai, Ingkaninan, et al., 2021).

The surfactants and co-surfactants utilized in this study, as detailed in **Table 1**, predominantly include various nonionic surfactants. These nonionic surfactants are favored in cosmetic formulations due to their low toxicity and minimal irritation potential (Nanda et al., 2020). The selection of surfactants is critical; they must effectively reduce interfacial tension while ensuring skin compatibility.

Nonionic co-surfactants are particularly advantageous in cosmetic applications because they enhance solubility and stability, exhibit low toxicity and irritation risk, and promote the release and penetration of active ingredients into the skin. The strategic combination of

Table 2. Penetration test method using Franz diffusion cell

Author / Year	Anti-cellulite Effectiveness Testing Method							Result
	Methods	Membrane	Donor Compartment	Receptor Compartment	Temperature (°C)	Time (h)	Analysis Instruments	
(Mehta et al., 2018)	Ex vivo / Franz diffusion cell	Pig auricular skin	Nicotinamide Nanoemulgel	26 mL of phosphate buffer solution pH 7.4	37	9	UV-Vis Spectrophotometer λmax 262 nm	% Penetration: 1. Nicotinamide nanoemulgel with Carbopol gel base: 32.38% 2. Nicotinamide solution: 10.65%
(Priani et al., 2021)	In-vitro / Franz diffusion cell	HT-Tuffryn	Caffeine (3; 5; 7; 9; 11; and 13 µg/mL)	15 mL of phosphate buffer solution pH 7.4	37 ± 0.5	3	UV-Vis Spectrophotometer λmax 272.6 nm	The kinetic release of caffeine from emulgel formulations follows the Higuchi model
(Djajadisastra et al., 2014)	In-vitro / Franz diffusion cell	Female rat skin	1. Caffeine nanoemulgel + HPMC 2% 2. Caffeine nanoemulgel + HPMC 2% + NaHA 0.5%	Phosphate buffer solution pH 7.4	37	8	UV-Vis Spectrophotometer λmax 273.5 nm	Permeation Percentage (%): 1. Emulgel Caffeine + HPMC 2%: 10.47 ± 0.19%. 2. Emulgel Caffeine + HPMC 2% + NaHA 0.5%: 13.41 ± 0.12% Flux (µg/cm^2/h): 1. Emulgel Caffeine + HPMC 2%: 97.19 ± 1.97 2. Emulgel Caffeine + HPMC 2% + NaHA 0.5%: 151.04 ± 5.57
(Sintov & Greenberg, 2014)	In-vitro / Franz diffusion cell	Rat, pig, and rabbit skins	Caffeine nanoemulgel	Phosphate buffer solution pH 7.4	37	24	HPLC λmax 273 nm	The percentage of caffeine nanoemulgel that penetrated through various skin types is presented below: 1. Rat skin: 55.7% ± 19.4% 2. Pig skin: 24.9% ± 5.1% 3. Rabbit skin: 62.1% ± 4.0%

surfactants and co-surfactants not only improves the interaction between dispersed droplets and the external phase but also prevents the formation of liquid crystals that can impede the nanoemulsification process. Additionally, these components facilitate the broader distribution of molecules across surfaces, thereby enhancing the overall efficacy of the formulation (Krstić et al., 2018).

The gelling agent is a crucial excipient in nanoemulsion gel systems, playing a significant role in enhancing viscosity, which in turn improves contact time and adhesion (Priani, 2022). As shown in **Table 1**, Carbopol is the most commonly utilized gelling agent in these formulations. Notably, Carbopol 940 exhibits a higher molecular weight compared to Carbopol 934, resulting in increased viscosity (Mehta et al., 2018; Ngamdokmai, Ingkaninan, et al., 2021). This gel base is characterized by its clear appearance, excellent spreading properties on the skin, and a cooling effect. Additional benefits of Carbopol include its non-comedogenic nature, enhanced release of active substances compared to other gel bases, improved drug penetration, and stability of the formulation (Apriani et al., 2023). Furthermore, the formulation of a nanoemulgel using a 2% HPMC gel base yields the highest viscosity. This increase is attributed to the higher concentration utilized and the role of hydrogen bonding in polymer development, which elevates the viscosity by increasing the bound -OH groups (Daud et al., 2018; Djajadisastra et al., 2014). The viscolam MAC gel base presents several advantages, including ease of mixing due to its liquid form, stability at room temperature, a pH level that is close to that of human skin, and its functionality as both an emollient and moisturizer (Anugraheni et al., 2023; Priani et al., 2021; Ulfa et al., 2024).

The presented literature review elucidates the roles of key components in nanoemulgel formulation, specifically the oil, surfactant, co-surfactant, and gelling agent. Not only does the oil serve as a solvent for the active substances, but it also influences the stability and skin penetration. Choosing the right surfactant and co-surfactant combinations is important for making sure that the formulation works well and that the active ingredients can get deep into the skin. Surfactants are responsible for reducing interfacial tension, while co-surfactants provide additional flexibility to the interfacial layer. The gelling agent not only increases viscosity but also improves the contact time of the formulation with the skin. Considering the analysis of these components, nanoemulgel offers an innovative solution in enhancing stability, skin compatibility, and therapeutic potential.

Characterization of Nanoemulgel

The effectiveness of the nanoemulgel formula for anti-cellulite purposes must be ensured by evaluating its physicochemical parameters. According to the review findings, key parameters to consider include droplet size, viscosity, and pH value, as shown in **Table 1.** These physicochemical properties not only influence the formulation's stability but also enhance the bioavailability of active ingredients and improve user comfort.

Droplet size

Nanoemulgels, with average droplet sizes below 200 nm, offer significant advantages for enhancing drug delivery. According to Priani et al., (2021), the formulation's components, particularly surfactants and co-surfactants at higher concentrations, play a pivotal role in improving drug penetration. The nanoscale droplet size increases the surface area available for drug release, thereby accelerating the drug release rate. **Table 1** confirms that nanoemulgels in this study exhibited droplet sizes under 200 nm, with the smallest ranging between 3.97 and 4.55 nm (Sintov & Greenberg, 2014). Nanoemulgels with droplets around 4 nm demonstrated significantly higher skin permeability compared to those with larger droplet sizes, suggesting a direct correlation between droplet size and skin permeability, potentially influenced by water content. Sintov & Greenberg (2014) further noted that cumulative drug permeation decreased as water content increased from 60% to 80%, likely due to the corresponding increase in droplet size. Stokes' law supports these findings, as larger globules tend to sediment faster, reducing viscosity (Djajadisastra et al., 2014). Additionally, Djajadisastra et al., (2014) emphasized that droplet size is a critical factor in predicting emulsion stability, with larger droplets more prone to separation phenomena such as creaming or even complete phase separation ("breaking").A literature study of droplet size in nanoemulgel formulations for anti-cellulite applications establishes a robust scientific foundation for the advancement of pharmaceutical and cosmetic products. Nanoemulgel systems with droplet sizes below 200 nm show better potential for treating cellulite because the smaller size makes a lot more surface area available for drug release. This improvement makes it easier for active ingredients to get deeper into the dermal layer, which is where subcutaneous fat deposits are found and treated for cellulite. Moreover, droplet

size plays a critical role in determining the stability of nanoemulgel formulations. To further substantiate these findings, comprehensive studies on the interactions between active ingredients and the nanoemulgel matrix, as well as rigorous clinical trials, are essential.

Viscosity

The emulgel formulation offers several advantages over traditional emulsions, primarily due to the addition of gelling agents that enhance stability by increasing the viscosity of the aqueous phase. Viscosity testing is crucial for determining the consistency and thickness of the final emulgel product. The concentration of the gelling agent plays a significant role in influencing the viscosity; higher concentrations directly increase the viscosity of the formulation (Ulfa et al., 2024). Nanoemulgel was specifically developed to address the low viscosity of nanoemulsions, which limits their efficacy for topical applications (Sengupta & Chatterjee, 2017). Critical factors such as particle size, surface charge, and viscosity are essential for effective delivery of active ingredients through the skin (Taha et al., 2022). Mehta et al., (2018) highlighted that while nanoemulsions improve drug permeation, their low viscosity reduces retention time, necessitating conversion to nanoemulgel for optimal topical application. The highest recorded viscosity in the study was 78,000 cPs, achieved with a 2% HPMC gel base. After standing for approximately 24 hours, HPMC forms a random polymer structure that traps significant amounts of solvent, resulting in increased viscosity. However, after 8 weeks of storage, the viscosity decreased to 66,000 cPs. Despite this reduction, the change did not affect the flow or rheological properties of the emulgel, which retained pseudoplastic behavior (Djajadisastra et al., 2014). In a study by Ngamdokmai et al., (2021), the physical characteristics of anti-cellulite nanoemulgel (such as color, odor, pH, viscosity, and phase separation) remained stable after 12 weeks of storage, with no notable changes. However, after undergoing freeze-thaw stability testing, only minor changes in the appearance or organoleptic properties were observed.

The optimal viscosity for nanoemulsions typically ranges from 6,000 to 50,000 cPs at a stirring speed of 50 rpm or from 500 to 10,000 cPs at 100 rpm (Andini et al., 2023; Hidayanti et al., 2015). Beyond meeting these ranges, ideal viscosity balances physical stability, skin retention, and ease of application. For topical applications, a formulation that doesn't change much in viscosity when stored for a long time or exposed to high or low temperatures and still has pseudoplastic properties can effectively stop phase separation, ensure skin adhesion, and improve spreading. One of the primary limitations of nanoemulsions, low viscosity, can compromise skin retention and reduce the penetration efficacy of active ingredients. However, the incorporation of gelling agents like HPMC addresses this issue. However, while increased viscosity improves skin adherence, excessive thickness may negatively impact user comfort and application ease. Consequently, the ideal viscosity for nanoemulgels must account not only for formulation stability and effectiveness but also for usability and consumer satisfaction.

pH

Ensuring the pH of nanoemulgel formulations aligns with skin compatibility is essential for safe application. According to the data in **Table 1**, the nanoemulgel has a pH range of 5.5-6.95, which falls within the skin's natural pH range of 4.5-7 (Ulfa et al., 2024). A pH that is too low may cause irritation, while a high pH can lead to dry skin (Ismayanti et al., 2021). In studies by Priani et al., (2021) and Ngamdokmai, Ingkaninan, et al., (2021), nanoemulgel formulations were adjusted with triethanolamine (TEA) to reach a target pH range of 5.5–7. Ngamdokmai, Ingkaninan, et al., (2021) further demonstrated that there was no statistically significant difference between the initial pH (6.89 ± 0.02) and the final pH (6.65 ± 0.03) following freeze-thaw stability testing, indicating that the formulation is thermodynamically stable. Djajadisastra et al., (2014) observed that the pH of a caffeine nanoemulgel increased after 8 weeks of storage, likely due to sodium hyaluronate (NaHA) ionization. As NaHA binds with water, Na+ ions are released, forming OH- ions and increasing alkalinity. NaHA's hygroscopic nature further contributes to pH shifts by enhancing water absorption, which promotes ionization and a rise in pH.

Cosmetic and pharmaceutical formulations commonly use TEA as a pH regulator due to its effectiveness in maintaining pH within the desired range. Ideal pH regulation is important to ensure that the formulation does not cause

Table 3. Anti-cellulite effectiveness (adipocyte-lipolysis test on 3T3-L1 adipocytes and clinical trials)

Author/year	Object	Instrument or analytical Method Used	Observation	Results
(Ngamdokmai, Paracha, et al., 2021)	Positive control (adrenaline 0.1 mM or 18.3 µg/mL and caffeine 1 mM or 194.2 µg/mL), lemongrass (25 µg/ mL), ginger (50 µg/ mL), black pepper (100 µg/mL), long chili (50, 100 µg/ mL) and mixed oil (100, 200 µg/mL)	1. Adipocyte differentiation using 3T3-L1 lipolysis kit. 2. Total triglyceride content.	1. Lipid accumulation in cells was quantified using Oil Red O staining, with absorbance measured at 500 nm via a microplate reader and visualized by microscopy. 2. Cells were lysed by sonication, and total triglyceride content was assessed using a Triglyceride Assay Kit.	1. The positive controls, adrenaline and caffeine, exhibited adipogenesis inhibition percentages of 24 ± 5% and 25 ± 2%, respecttively. Meanwhile, lemongrass, ginger, black pepper, long chili, and blended oil significantly inhibited lipid accumulation within the range of 12-24%. 2. The positive controls (caffeine and adrenaline) decreased triglyceride content by 41 ± 2% and 67 ± 4%, respectively. The lowest concentration that significantly reduced triglyceride levels was lemongrass oil, which decreased triglyceride content by 53 ± 3%.
(Ngamdokmai, Waranuch, et al., 2021)	1.Thigh circumference 2.Skin elasticity 3.Cutaneous blood flow	1. Marking reference points on the anterior thigh surface (10 and 20 cm above the midpoint). 2. Cutometer® MPA 580 on the posterior thigh. 3. PeriCam PSI using laser speckle contrast analysis	1. Changes in thigh circumference over 12 weeks. 2. Probe-dependent values ranging from 0 (fluid surface) to 1 (non-deformable solid surface). 3. Blood perfusion calculated by analyzing pixel-wise variations in speckle patterns. This provides an estimate of the heterogeneity of skin blood flow.	1. Thigh circumference decreases by 0.8–1 cm during the second week, followed by a reduction of 0.5 cm between weeks 2 and 12. 2. Skin tightening is observed on the anterior thigh, with no significant effect on the posterior thigh. 3. An increase in blood flow is noted beginning in the second week.

irritation or disrupt the skin layer. However, excessive or inappropriate use of TEA can potentially lead to side effects like increased skin sensitivity. Therefore, the addition of appropriate TEA is needed to avoid excessive adjustment and ensure pH stability under various storage conditions. NaHa is a hygroscopic compound and increases skin hydration. However, its impact on pH needs to be considered. NaHa will undergo ionization during storage, especially in the presence of water. The release of sodium ions (Na+) and the formation of hydroxide ions (OH-) can increase the pH of the preparation. This pH shift can compromise

the stability and compatibility of the preparation if not properly controlled. Therefore, the formulation must take into account the buffer capacity and water content in the system.

The Effect of Membranes on Penetration Test using Franz Diffusion Cells

The in vitro evaluation of anti-cellulite efficacy using Franz Diffusion cells provides a comprehensive understanding of in vivo absorption, as the precise control of the donor dose allows for direct comparison with the concentration per square centimeter in clinical applications. The Franz diffusion cell method, which employs a semipermeable membrane between the donor and receptor compartments (Djajadisastra et al., 2014). Notably, a study by Mehta et al., (2018) utilized the ex vivo diffusion method with pig ear skin to analyze the release and retention of nicotinamide nanoemulgel drugs, revealing zero-order release kinetics and enhanced drug release and retention compared to nicotinamide solution **(Table 2).**Similarly, Priani et al., (2021) demonstrated that caffeine nanoemulgel can significantly enhance diffusion compared to caffeine in gel preparations, with release kinetics following the Higuchi kinetic model **(Table 2).** The Higuchi model, which is based on simple diffusion laws, is unaffected by matrix erosion or swelling. Furthermore, the study by Djajadisastra et al., (2014) highlighted the importance of membrane selection, with the skin of 2-3 month old female Sprague-Dawley strain rats being used due to its permeability similarity to human skin **(Table 2).** The results showed that caffeine nanoemulgel with enhancers significantly increased caffeine penetration compared to without sodium hyaluronate (NaHA). Moreover, NaHA dissolved in various anti-cellulite gel formulations, including hydrogels, hydroalcoholic gels, and nanoemulgels, was found to significantly enhance caffeine penetration. Consistently, Sintov & Greenberg, (2014) reported that drug penetration through the skin was significantly increased when the preparation was in the form of nanoemulgel compared to drug permease dissolved in water. The highest penetration results (62.1% ± 4.0%) were obtained in rabbit skin membranes, likely due to the higher cholesterol ester content and relatively low ceramide levels in the rabbit stratum corneum compared to the rat and pig stratum corneum.

In Vitro Evaluation of Anticellulite Activity using Lipid Accumulation Test in 3T3-L1 Adipocytes

As shown in **Table 3**, both the positive controls (caffeine and adrenaline) and all test samples significantly reduced lipid accumulation in 3T3-L1 adipocytes in a dose-dependent manner. Caffeine was selected as the positive control due to its known ability, along with other key coffee components (caffeic acid, chlorogenic acid, and trigonelline), to enhance glycerol release and reduce lipid accumulation during adipocyte differentiation in 3T3-L1 cells. Coffee consumption also inhibits the expression of peroxisome proliferator-activated receptor γ (PPARγ), a transcription factor that regulates adipocyte differentiation. Additionally, the study demonstrated that triglyceride accumulation in 3T3-L1 cells was reduced, indicating an in vitro lipolytic effect. Since excessive triglyceride accumulation in adipocytes is associated with an increased risk of metabolic diseases, the observed reduction in triglycerides in the positive control and test samples **(Table 3)** at all tested concentrations, compared to untreated controls, is particularly significant (Ngamdokmai, Paracha, et al., 2021). The effectiveness of anti-cellulite agents through adipogenesis and lipolysis testing in 3T3-L1 cells has been demonstrated with nutritional supplements. These supplements contain *Ananas comosus* (L.) Merr, *Oryza sativa* (L.), *Actinidia chinensis* Planch, and *Citrus sinensis* (L.) Osbeck, and have shown a significant 51% reduction in lipid accumulation at a concentration of 0.2% (Nobile et al., 2020). Additionally, a concentration of 1 µg/ml of *Annona squamosa* extract led to a substantial decrease in lipid accumulation in 3T3-L1 cells by 68.8% (Abuzaid et al., 2020). Adipogenesis and lipolysis assays in 3T3-L1 cells thus provide an effective method for evaluating anti-cellulite potential. Despite these promising findings, few anti-cellulite formulations have advanced to the adipogenesis lipolysis stage with 3T3-L1 cells; most current research only reaches penetration testing with Franz diffusion cells. This highlights the need for further investigation to develop products with proven efficacy for cellulite treatment.

Clinical Trial for Anticellulite Activity

A follow-up study by Ngamdokmai, Waranuch, et al., (2021) involved a randomized

clinical trial to evaluate the effectiveness of a coffee and tea extract nanoemulgel. The study demonstrated significant improvement in the appearance of cellulite on the back of the thighs, the primary outcome, following application of the nanoemulgel. Additionally, secondary outcomes such as thigh circumference, skin firmness, and blood flow also showed improvement. Using the coffee and tea extract nanoemulgel twice daily resulted in a reduction in cellulite severity scores from 13.4 ± 0.3 to 12.1 ± 0.3 at week 2, and further to 9.9 ± 0.6 at week 12. However, the anti-cellulite efficacy was limited without accompanying lifestyle changes.

CONCLUSIONS

Nanoemulgel as a topical formulation has demonstrated superior efficacy in drug delivery compared to drugs that are only dissolved in water. The development of nanoemulgel enhances the penetration of active compounds, as indicated by increased penetration percentages or flux values. Caffeine, a widely used anti-cellulite agent, owes its effectiveness to its methylxanthine content, which reduces cellulite by inhibiting lipogenesis and phosphodiesterase. The potential of nanoemulgel in treating cellulite is further supported by studies showing inhibition of lipid accumulation in 3T3-L1 adipocyte cells and reductions in triglyceride levels. Research on the potential of nanoemulgel formulations for anti-cellulite treatment remains limited primarily to lipolysis analysis in 3T3-L1 cells. This presents a significant opportunity for researchers to develop and evaluate formulations with proven anti-cellulite efficacy.

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AUTHORS' CONTRIBUTIONS

HFU contributed to the research design and concept, conducted the literature search, developed the data search strategy, and screened articles based on inclusion and exclusion criteria. HFU was also responsible for data analysis, interpretation of results, and drafting the initial manuscript, as well as making revisions based on feedback from the supervising lecturer.

ERW provided guidance on the research methodology design and input on the development of the literature search strategy. ERW also critically reviewed the literature selection, validated the analysis results, and provided feedback at each stage of manuscript revision until final submission

CONFLICT OF INTERESTS

This manuscript is original, has not been published previously, and is not presently under consideration for publication elsewhere. We, the undersigned, state that.

ETHICAL CONSIDERATION

Ethical issues (including plagiarism, data fabrication, double publication, etc) have been completely observed by the author .

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