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Research Article

Physicochemical Profile and Stability of Red Ginger (*Zingiber officinale* var. *rubrum*) SNEDDS as Potential Aphrodisiac

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Abstract

This study investigated the stability of a Self-Nanoemulsifying Drug Delivery System (SNEDDS) formulated with *Zingiber officinale* var. *rubrum* (red ginger) extract. SNEDDS formulations, composed of an oil phase, co-surfactant, and surfactant, are designed to create stable isotropic mixtures, critical for drug delivery systems. Prior to assessing long-term physical stability, the optimal *Z. officinale* var. *rubrum* SNEDDS preparation underwent comprehensive characterization, including evaluation of emulsification time, pH, particle size, polydispersity index (PDI), and zeta potential. Subsequent physical stability assessments involved rigorous centrifugation, hot-cold, and freeze-thaw cycles. The results demonstrated an emulsification time of $\leq$1 minute, a pH value of 5.04$\pm$0.05, and a particle size of 14.92±0.7 nm, indicative of a nanoscale dispersion. The PDI was 0.282, and the zeta potential was −18.57±1.30 mV, suggesting good colloidal stability. Crucially, throughout six cycles of centrifugation, hot-cold, and freeze-thaw stress tests, the *Z. officinale* var. *rubrum* extract SNEDDS exhibited no signs of phase separation, sedimentation, cracking, or creaming. These findings collectively confirm that the prepared *Z. officinale* var. *rubrum* extract SNEDDS meets critical physicochemical characteristics and demonstrates excellent physical stability, positioning it as a promising candidate for further development as a natural extract delivery system.

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INTRODUCTION

Male sexual dysfunction represents a major health issue in Indonesia, affecting approximately 10% of all age groups and impacting over 50% of men aged 50–70[1]. Consequently, there is a substantial trend towards seeking traditional herbal remedies for treatment. The reliance on medicinal plants, often cultivated in home gardens, is favored due to the generally lower potential for side effects compared to synthetic chemical pharmaceuticals[2,3]. One such traditional medicine is red ginger (*Zingiber officinale* var. *rubrum*), a tropical plant in the Zingiberaceae family. Traditionally valued for its therapeutic properties, *Z. officinale* var. *rubrum* shows significant promise as an aphrodisiac, with its extract proven to enhance male fertility parameters, including increasing sperm motility by 50%, viability by 58%, sperm count by 31 million/mL, and improving morphology by 61% after 35 days of oral administration[4,5].

However, the efficacy of oral administration, which is preferred for its practicality and patient compliance[6], is severely limited by the poor water solubility of many bioactive compounds, affecting nearly 40% of orally administered drugs[7]. Further challenges in herbal drug delivery include low oral bioavailability, inconsistent dosing, and significant inter-individual variability[8]. *Zingiber officinale* var. *rubrum* contains key lipophilic bioactive compounds, such as gingerol, shogaol, and zingerone, which possess poor water solubility.

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A highly promising solution to these challenges is the Self-Nanoemulsifying Drug Delivery System (SNEDDS). SNEDDS is an isotropic mixture of active substances, oil, surfactant (SA), and co-surfactant (Co-SA), designed to enhance the solubility and absorption of lipophilic drugs[9]. Formulating *Z. officinale* var. *rubrum* extract into SNEDDS can substantially improve its therapeutic effectiveness, particularly its aphrodisiac potential[10]. Developing a safe and effective SNEDDS formulation necessitates rigorous quality evaluation, including testing for emulsification time, transmittance, particle size, zeta potential, pH, organoleptic properties, and physical stability across various stress conditions (heating–cooling, freeze–thaw cycles, and centrifugation)[11]. This study, therefore, aims to evaluate the physicochemical properties and physical stability of a *Z. officinale* var. *rubrum* SNEDDS formulation. The results are intended to support the development of a stable and effective SNEDDS formulation of *Z. officinale* var. *rubrum*, ultimately improving male reproductive health.

MATERIALS AND METHODS

Materials

The study utilized a specific set of instrumentation and chemical reagents. The key instruments included Duran 50 mL Erlenmeyer flasks, 250 mL Iwaki CTE33 beaker glasses, a mortar and pestle for sample preparation, Iwaki CTE33 measuring cylinders, a hot plate, a magnetic stirrer, Nesco centrifuge tubes, a Hettich D-78532 Tuttlingen centrifuge, a Malvern Zetasizer Advance for particle analysis, a pH meter, and a rotary evaporator. The primary materials and chemicals used were polyethylene glycol 400 (Sigma-Aldrich), Tween 80 (Sigma-Aldrich), Virgin Coconut Oil (VCO) (Al-fiat), aquadest, sodium chloride (Emsure®), sodium hydroxide (Supelco®), potassium dihydrogen phosphate (Supelco®), hydrochloric acid (Riedel-de Haen), and 70% ethanol. The primary biological material, *Z. officinale* var. *rubrum* rhizomes, was procured from a market in Surabaya City and formally identified at the Pharmacognosy and Phytochemistry Laboratory, Faculty of Pharmacy, Universitas Airlangga.

Methods

Preparation of Z. officinale var. rubrum extract

About 1000 g of finely powdered *Z. officinale* var. *rubrum* simplicial material was subjected to maceration using 2.5 L of 70% ethanol for a duration of 24 hours. The mixture was then filtered, and the remaining solid residue was re-macerated twice more with 2 L of fresh solvent each time to maximize the yield of active compounds. The resulting filtrates were pooled and concentrated under reduced pressure using a rotary evaporator at a controlled temperature of 50°C to yield the viscous crude extract.

Preparation of SNEDDS from Z. officinale var. rubrum

The nanoemulsion formulation utilized in this study was based on the optimized methods previously established by Andriani *et al.*[12] as shown in **Table I**. The preparation involved the careful, stepwise mixing of excipients and the active ingredient. Initially, *Z. officinale* var. *rubrum* extract was gradually triturated with Tween 80 using a mortar and pestle until a homogenous mixture was achieved. Subsequently, PEG 400 and VCO were added while maintaining continuous stirring. This final mixture was then transferred to an Erlenmeyer flask and subjected to homogenization via a magnetic stirrer for 30 minutes, followed by sonication for an additional 30 minutes to ensure adequate particle reduction and stability[13].

Table I. Formulation of SNEDDS *Z. officinale* var. *rubrum* preparation.

Materials	Quantity	Functions
Zingiber officinale var. *rubrum* extract (mg)	500	Active compound
VCO (%)	10	Oil phase
Tween 80 (%)	67.5	Surfactant
PEG 400 (%)	22.5	Co-surfactant

Characteristics test of SNEDDS Z. officinale var. rubrum preparation

pH level: For pH determination, 10 mL of *Z. officinale* var. *rubrum* SNEDDS preparation was precisely diluted with 50 mL of distilled water. The pH of the resulting solution was then measured using a calibrated pH meter, ensuring the reading fell within the physiologically relevant range of 4.5 to 7[10].

Emulsification time: The emulsification time of *Z. officinale* var. *rubrum* SNEDDS was determined by introducing 1 mL of the preparation into a beaker glass containing 250 mL of either acidic gastric fluid (AGF), artificial intestinal fluid (AIF) (as detailed in **Table II**), or distilled water. The mixture was then stirred using a magnetic stirrer at a fixed speed of 100 rpm and maintained at a physiological temperature of 37°C[14]. A high-quality SNEDDS formulation is defined by its ability to rapidly and completely disperse, with a satisfactory emulsification time typically achieved in less than 1 minute[15].

Table II. Composition of AGF and AIF media.

Materials for AGF	Quantity	Materials for AIF	Quantity
NaCI (g)	1	Potassium phosphate (g)	3.4
HCI (mL)	3.5	NaOH 0.2 N (mL)	38.5
Distilled water (mL)	Up to 500	Distilled water (mL)	Up to 500
pH ≤1-2		**pH up to 6-7**	

Particle size, zeta potential, and PDI: To determine the size and uniformity of the self-nanoemulsifying droplets, 5 drops of the SNEDDS preparation were gently introduced into 5 mL of distilled water. Following brief mixing, a 3 mL aliquot of the resulting nanoemulsion was carefully withdrawn and immediately analyzed for mean droplet size and Polydispersity Index (PDI) using a ZetaSizer Advance (Malvern)[16].

Characteristics test of SNEDDS Z. officinale var. rubrum preparation

Centrifugation test: To assess the physical stability of the preparation, the formulation underwent a rigorous centrifugation test. Samples were centrifuged at 5000 rpm for 30 minutes, after which they were visually inspected for signs of phase separation, sedimentation, creaming, or cracking. Only preparations that demonstrated satisfactory stability under this stress test were then subjected to further evaluation via heating and freeze-thaw cycles to simulate real-world storage conditions and confirm long-term stability[17].

Heating-cooling test: The thermodynamic stability of the formulation was assessed through a temperature cycling test involving six alternating cycles. The samples were sequentially stored at 4°C (refrigeration) and 40°C (accelerated stability) for a duration of 48 hours at each temperature extreme. Formulations that successfully maintained their integrity—exhibiting no signs of phase separation, creaming, or cracking—were then advanced to the subsequent freeze-thaw test[17].

Freeze-thaw test: The stability of the formulation under thermal stress was evaluated using a freeze-thaw cycling test. Six complete cycles were performed, with each cycle involving 48 hours of alternating temperature exposure between −21°C (freezing) and 25°C (thawing). Throughout this process, the samples were meticulously observed for any signs of physical instability, including phase separation, sedimentation, creaming, or cracking[17].

Data analysis

The data acquired from the measurements of particle size, PDI, and zeta potential, alongside the results from the physical stability tests, were critically analyzed. These parameters were rigorously compared against established requirements derived from multiple relevant references. This comparative analysis was essential for precisely determining the overall stability and predicting the potential effectiveness of the final nanoemulsion preparation.

RESULTS AND DISCUSSION

The formulation of *Z. officinale* var. *rubrum* extract into SNEDDS was strategically selected to overcome the poor aqueous solubility and consequently low oral bioavailability of its primary lipophilic active constituents, such as gingerol. Conventional dosage forms fail to optimize the therapeutic potential of these compounds. SNEDDS addresses this by spontaneously forming nanoemulsions upon contact with gastrointestinal fluids, dramatically enhancing solubility, dissolution rate, and absorption, making it a superior delivery system. Previous research established *Z. officinale* var. *rubrum* aphrodisiac properties, demonstrating its ability to increase testosterone levels and improve sperm quality parameters—including count, motility, viability, and morphology—in male rats[18].

The enhanced therapeutic effectiveness of *Z. officinale* var. *rubrum* SNEDDS formulation, particularly its positive effect on male reproductive health, is directly attributable to its optimized physical characteristics and stability. The prepared

SNEDDS exhibited an ideal emulsification time, favorable nano-sized droplets, appropriate zeta potential, and confirmed thermodynamic stability. These properties are critical as they guarantee rapid, consistent dispersion and highly efficient absorption of lipophilic compounds like gingerol and shogaol in the gastrointestinal tract. Consequently, the 28-day administration of the optimized SNEDDS led to a significant increase in testosterone levels and substantial improvements across all measured sperm parameters[19]. This strongly indicates that the formulation's physical integrity and superior stability directly translate into enhanced pharmacodynamic effects.

Characterization and evaluation are crucial steps in formulating SNEDDS, as they define the quality and properties of the resulting nanoemulsion[20]. Parameters such as particle size, PDI, zeta potential, emulsification time, and pH must be rigorously assessed before stability testing can proceed[21]. In this context, the formulation optimized by Andriani *et al*.[12] met all initial SNEDDS characterization requirements. However, a crucial re-evaluation of the emulsification time, pH, particle size, zeta potential, and PDI was performed immediately prior to the physical stability test. Despite the demonstrated potential, research specifically on using SNEDDS for aphrodisiac purposes remains scarce. Therefore, further development is essential to thoroughly investigate and optimize the absorption kinetics of the active compounds from this advanced delivery system to fully unlock its pharmacological potential as an aphrodisiac agent.

The results presented in **Table III** demonstrate that SNEDDS containing *Z. officinale* var. *rubrum* extract achieved an emulsification time of less than 1 minute across all tested media (distilled water, AGF, and AIF), successfully meeting the predetermined formulation criteria[22]. This rapid dispersion is crucial, as an emulsification time under one minute signifies the spontaneous formation of a transparent emulsion upon contact with gastric and intestinal fluids. A slower rate, leading to a cloudy emulsion, would render the formulation unsuitable[23]. The efficiency of this rapid emulsification is largely attributed to PEG 400 acting as a co-surfactant. PEG 400 enhances the flexibility and penetration of the primary surfactant into the oil phase, thereby increasing the overall solubility of the preparation by filling the spaces between surfactant molecules[24]. This swift *in situ* nanoemulsion formation is key to achieving optimal drug absorption.

Table III. Emulsification time using AGF and AIF.

Replications	AGF (s)	AIF (s)	Distilled water (s)
1	16.11	17.07	13.57
2	17.10	17.27	13.97
3	17.46	17.99	13.98
Average±SD	**16.89±0.70**	**17.44±0.48**	**13.84±0.23**

The measurement of the system's pH was a crucial step to ensure the safety, acceptability, and comfort of the final preparation upon entering the body. An inappropriate pH range can lead to localized irritation and discomfort during use. As presented in **Table IV**, the tested preparation exhibited a pH value of 5.04. This result falls squarely within the generally accepted physiological range of 4.5 to 6[25], confirming that the formulation is non-irritating and suitable for administration.

Table IV. pH level.

Replications	pH
1	5.00
2	5.04
3	5.09
Average±SD	**5.04±0.05**

The final product was confirmed to be a nanoemulsion, characterized as a thermodynamically stable oil-in-water system with an average droplet size typically ranging from 5 to 100 nanometers[26]. The data presented in **Table V** confirms the successful formulation, showing that the obtained mean particle size was 14.95 nm, which falls well within the required size criteria for SNEDDS. This result is highly consistent with previous research; for instance, a study optimizing a wualae extract SNEDDS using the same components—VCO as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co-surfactant—yielded an almost identical particle size of 14.6 nm[12]. This small, uniform droplet size is crucial, as it enhances the surface area for absorption, predicting superior bioavailability and therapeutic efficacy of the final preparation.

Table V. Particle size, zeta potential, and PDI.

Replications	Particle Size (nm)	Zeta Potential (mV)	Poly Dispersity Index
1	14.22	-17.36	0.233
2	14.95	-18.40	0.283
3	15.68	-19.95	0.328
Average±SD	**14.95±0.73**	**-18.57±1.30**	**0.281±0.04**

The prepared *Z. officinale* var. *rubrum* SNEDDS exhibited favorable physicochemical properties necessary for a stable nanoemulsion. The formulation utilizes Tween 80 as the primary surfactant, which acts by adsorbing onto the oil globule surface, forming a monolayer that significantly reduces the interfacial tension between the oil and water phases, thereby influencing globule size[27]. The co-surfactant, PEG 400, further stabilizes this layer; as a medium-chain hydrocarbon, it resides in the interstitial spaces of the system, using hydrogen bonds to maximize the emulsification efficiency[28]. Virgin coconut oil was selected as the oil phase due to its high content of Medium Chain Triglycerides (MCTs). MCTs are preferred over Long Chain Triglycerides (LCTs) as they possess more polar groups, offering greater solubility and more effective interaction with other components, leading to a more stable and clearer nanoemulsion[29,30].

The *Z. officinale* var. *rubrum* SNEDDS demonstrated excellent uniformity, yielding a PDI of 0.281. This value, being close to zero, signifies a narrow and uniform particle size distribution, which is indicative of a quality preparation[31]. The zeta potential was measured at −18.57 mV, a value slightly below the ideal threshold of ±30 mV typically associated with high electrostatic stability[32]. This lower magnitude is likely attributed to the use of Tween 80, a non-ionic surfactant that lacks charge in its hydrophobic groups and thus reduces the net surface charge[12,33]. Despite this, the nanoemulsion was deemed acceptable because no precipitation was observed during the stability assessment. The overall stability and desirable nanometer size of the particles are largely attributed to the sonication process, which utilizes ultrasonic waves to induce a cavitation effect, breaking down larger particles into the nanometer range[34]. Furthermore, the preparation's thermodynamic stability, assessed through standard cycles such as centrifugation, heating-cooling, and freezing-thawing, serves as a crucial indicator of the system's long-term kinetic stability and its resistance to chemical degradation[35].

As presented in **Table VI**, the prepared nanoemulsion formulation exhibited exceptional physical stability over a one-year storage period, with no observable phase separation under the influence of gravity. This prolonged stability is primarily attributed to the effective action of the non-ionic surfactant, Tween 80, incorporated during preparation. Non-ionic surfactants contribute to stabilization not through a strong electrostatic potential, but via the formation of a surface charge resulting from either the adsorption of ions from the aqueous phase or frictional interactions between the dispersed droplets and the medium. The resulting adsorbed layer forms an electric double layer on the droplet surface, generating sufficient repulsive forces to effectively prevent droplet aggregation and maintain the system's nano-scale integrity over time[36].

Table VI. Centrifugation test results.

Parameters	Results	Description
Separation	-	Stable
Sedimentation	-	Stable
Creaming	-	Stable
Cracking	-	Stable

Note: (-) No sedimentation, separation, creaming, or cracking was observed

In the oil-in-water nanoemulsion system utilizing a non-ionic surfactant, the surfactant molecules critically organize to form a thin interfacial layer around each dispersed oil droplet (**Figure 1**). This protective layer is essential for maintaining the stability of the system by physically preventing adjacent droplets from merging, a process known as coalescence. This stabilizing phenomenon, whereby the membrane layer actively impedes droplet aggregation, is technically termed steric hindrance[37].

Table VII presents the results of the storage stability test under hot-to-cold temperature cycles, a crucial indicator of the nanoemulsion's long-term integrity. The observed stability is fundamentally governed by the synergistic action of the surfactant and co-surfactant in significantly reducing the interfacial tension between the oil and aqueous phases. This reduction directly mitigates phase separation; essentially, the greater their ability to lower interfacial tension, the more stable the resulting nanoemulsion. Specifically, the surfactant molecules localize effectively at the droplet surface, which decreases the interfacial free energy and creates a robust mechanical barrier that prevents droplet coalescence. The co-surfactant further

enhances this effect by integrating into the interfacial spaces between the surfactant molecules. This integration leads to the formation of a dense, highly structured interfacial film, which collectively ensures low surface tension and contributes to the spontaneous and sustained stability of the nanoemulsion[38].

Figure 1. *Zingiber officinale* var. *rubrum* SNEDDS preparation.

Table VII. Heating-cooling and freeze-thaw results.

Cycles	Creaking	Creaming	Separation	Description
1	-	-	-	Stable
2	-	-	-	Stable
3	-	-	-	Stable
4	-	-	-	Stable
5	-	-	-	Stable
6	-	-	-	Stable

Note: (-) No separation, creaming, or cracking was observed

Our findings offer a more efficient drug delivery pathway for *Z. officinale* var. *rubrum* bioactive compounds compared to previous studies, such as the work by Anggraini *et al*.[5], which demonstrated improvements in sperm quality and testosterone levels following conventional *Z. officinale* var. *rubrum* extract administration. The successful development of a stable SNEDDS is highly relevant to the purported aphrodisiac claims because formulation stability is directly linked to the consistent release, optimal absorption, and superior bioavailability of key active compounds like gingerol and shogaol. These compounds are widely believed to be the primary mediators of enhanced male reproductive function. Therefore, the stable SNEDDS formulation developed here is anticipated to support more reliable and potentially enhanced therapeutic outcomes *in vivo*. While these stability results are promising, dedicated further research is essential to evaluate if the improved stability and delivery of *Z. officinale* var. *rubrum* SNEDDS can translate into a significant, clinically relevant enhancement of aphrodisiac effects through subsequent *in vivo* and clinical studies.

CONCLUSION

The SNEDDS formulation containing *Z. officinale* var. *rubrum* extract successfully met all critical physicochemical criteria, demonstrating its suitability as a stable nanocarrier. The preparation exhibited an emulsification time of $\leq$1 minute, a pH of 5.04±0.05, an optimal nanoscale particle size of 14.92±0.7 nm, a low PDI of 0.282, and a Zeta potential of −18.57±1.30 mV. Furthermore, the formulation demonstrated excellent physical stability across rigorous stress tests, including centrifugation, heating-cooling, and freeze-thaw cycles over six periods, showing no signs of phase separation, precipitation, creaming, or cracking. It is thus concluded that the SNEDDS preparation of the *Z. officinale* var. *rubrum* extract possesses desirable physical characteristics and high stability, confirming its potential for development as a nanoemulsion-based drug delivery system. However, to fully validate its therapeutic promise as an aphrodisiac, comprehensive *in vivo* studies are essential to evaluate the effects of the *Z. officinale* var. *rubrum* SNEDDS on testosterone levels and sperm quality parameters, thereby confirming that the enhanced physicochemical properties translate into superior biological activity and pharmacodynamic efficacy for male reproductive health.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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