

Development of Lycopene Loaded Nanoemulsion as Anti-UV Filter and Its Antimelanogenesis

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Abstract: Lycopene is one of the compounds found in plants, and it possesses broad pharmacological activity, including for skin problems. However, it has lower solubility. This study aimed to develop lycopene nanoemulsion (LNE) and evaluated its sun protection factor (SPF), anti-melanogenesis, and anti-collagenase activity. The LNE was characterized for its droplet size, polydispersity index (PDI), and zeta potential, followed by the determination of SPF, anti-melanogenesis, and anti-collagenase activity *in vitro*. It was found that LNE provides ultra protection against UV-B with an SPF value of 6.80 ± 0.00 and possesses anti-melanogenesis and collagenase activity with IC_{50} of 48.46 ± 3.86 $\mu\text{g/ml}$ and 77.94 ± 0.74 $\mu\text{g/ml}$, respectively. In conclusion, the LNE possesses potency as a delivery system for lycopene, which might be beneficial for solving skin problems, especially in skin aging.

Keywords: lycopene nanoemulsion; SPF; anti melanogenesis; anti collagenase.

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1. Introduction

As life expectancy increases, aging and aging-related complexities also increase. By 2050, it is estimated that the number of people aged 60 years and over will increase from 11% to 22% of the global population, potentially increasing from 605 million to 2 billion [1].

As one of the most visible organs of the body, maintaining skin condition is crucial, especially for women who desire youthful skin free from signs of premature aging [2]. Human skin consists of three structural layers, namely the epidermis, dermis, and subcutaneous tissue, that act as skin protectors and prevent damage in the human body. In the process of skin aging, these three layers undergo degenerative changes, with changes in the dermis layer, including the matrix and collagen, being the most visible part of the aging process. During the aging process, type I collagen, the most abundant type of collagen in the dermis, will undergo structural changes, Extracellular Matrix (ECM) protein synthesis will decrease, and matrix metalloproteinase degradation will increase, causing fragmentation of collagen fibers [2,3]. This fragmentation reduces elastin and collagen fibers, resulting in fine lines and wrinkles on the face and hyperpigmentation [4,5].

Additionally, maintaining homeostasis and protecting the skin from ultraviolet radiation (UVR) is essential, as imbalances can lead to wrinkles, hair loss, blisters, rashes, life-

threatening cancers, and disturbances in immune regulation. UV light is categorized into three bands: UV-A (320-400 nm), UV-B (290-320 nm), and UV-C (100-280 nm). UVC is less concerned because the ozone layer blocks its rays and does not reach the earth's surface. Protection from UVA and UVB radiation is of more concern to patients. UVA has a longer wavelength; therefore, its rays penetrate deeper into the skin through the epidermis and dermis. UVA can be further divided into UVA I (320–400 nm or "far UVA") and UVA II (320–340nm or "near UVA"). UVA rays are present throughout the day (morning to evening). UVA can penetrate window glass, so some low-dose UVA exposures in humans cause significant dermal and epidermal histological changes. UVB, also known as "burn rays", most car windows and glass block these rays [6,7]. UV-A (and UV-B, to some extent) generate reactive oxygen species (ROS) that cause oxidative stress that can damage many cellular targets, including proteins, lipids, and DNA, potentially resulting in skin cancer [7].

Skin aging is classified into two, namely intrinsic aging and extrinsic aging. Intrinsic or chronological aging is caused by increasing age and is influenced by genetic factors, while extrinsic aging or photoaging is mainly caused by exposure to sunlight [8]. Photoaging due to UV exposure can trigger free radical reactive oxygen species (ROS) so that oxidative stress can occur in the dermis, which causes structural changes in the skin, increased regulation of activator protein (AP-1) activity, and increased expression of matrix metalloproteinase (MMP). AP-1 activity increases the expression of MMP-1, MMP-3 and MMP-9. Although MMP does not digest collagen directly, this enzyme can degrade the extracellular matrix (ECM), decreasing collagen production and procollagen biosynthesis [9]. Collagen is one of the proteins widely found in humans and acts as a supporting component of connective tissue in the extracellular matrix to maintain skin structure [10]. Collagen administration can reduce the intensity of skin hydration due to UV rays, increase water content in the skin, especially the stratum corneum, reduce wrinkles and roughness, and reduce epidermal hyperplasia due to UV rays [11].

Nowadays, antioxidants from natural ingredients are widely sought to reduce oxidative damage. Several oils and plant extracts have been shown to have antioxidant potential because they can prevent biological oxidation reactions and reduce the formation of free radicals. Lycopene is a natural keratinoid that acts as an antioxidant against environmental damage and oxidation of proteins, lipids, and DNA, enhances the cellular antioxidant defense system [12], protects the skin from premature aging by strengthening the skin by increasing its ability to produce collagen and reducing wrinkles [1].

Previous studies showed that one of the active effects of lycopene is its photoprotective action against UV damage to human skin, which can also contribute to skin aging [13]. Lycopene also has pro-vitamin A activity and is very effective against singlet oxygen, which is potentially the most dangerous reactive oxygen species produced in the skin after exposure to sunlight [14,15]. Based on previous studies, lycopene has antioxidant and antiaging potential through collagenase inhibition. However, lycopene has disadvantages, such as hydrophobic compounds, and will undergo photo-oxidation when exposed to light, causing decreased bioavailability and degradation. Lycopene can be dispersed in oil-in-water emulsions, specifically nanoemulsions, to overcome the limitation [16]. In addition, lycopene on a nanometer scale optimizes its efficacy and increases its penetration into the basal layer of the epidermis. Indirectly, this substance can help the skin's natural protective mechanisms, scavenge free radicals, prevent severe cell damage, and improve the general condition of the skin [12].

Nanoemulsion is a nanotechnology that has been widely developed to improve the performance of drug substances, especially for drugs that are difficult to dissolve in water or those with limited solubility in other solvents. The particle size of nanoemulsions ranges from 20-200 nm. With a small particle size, nanoemulsions have various benefits, such as high optical clarity, long-term stability, absorption, and bioavailability. Lycopene nanoemulsion consists of a mixture of oil and water stabilized by surfactants and cosurfactants, which aim to facilitate the drug solution directly to the target organs in the body as an antioxidant [17,18].

Based on the description above and the limited research on lycopene nanoemulsion as an anti-collagenase agent, researchers are interested in evaluating lycopene nanoemulsion's anti-melanogenesis and anti-collagenase activity through *in vitro* testing.

2. Materials and Methods

2.1. Lycopene nanoemulsion (LNE) preparation.

Lycopene nanoemulsion (LNE) was prepared by using the microfluidization method. Briefly, 0.1 g of lycopene (Merck®, Germany) was dissolved in an oil mixture of oleic acid and caprylic/ capric triglyceride (1:1), tween 80 and span 80 (1:1), propylene glycol, and alpha-tocopherol. Then, they were added to distilled water containing paraben concentrate until 100 g and mixed with a homogenizer to obtain the coarse emulsion. The coarse emulsion was then subjected to a sonicator (Biologics, USA) to obtain the lycopene nanoemulsion with an intensity of 30% for 5 min.

2.2. Characterization of LNE.

The LNE was characterized by determining its droplet size, polydispersity index, and zeta potential following the previous [19]. Furthermore, the blank formulation was also characterized.

2.3. Determination of Sun protection factor (SPF).

The LNE sun protection was determined *in vitro* using a UV-Vis spectrophotometer (Shimadzu, Japan) at 290 to 320 nm with absorption set at 5 nm intervals. The SPF value was determined by using Mansur equation (1) and categorized as minimum if the SPF value ranges from 2 to 4, as moderate if the SPF value ranges from 4 to 6, as extra if the SPF value ranges from 6 to 8, maximum if the SPF value range of 8 to 15, and ultra if the SPF value range of more than 15 [20,21].

$$SPF = CF \times \sum_{290}^{320} EE(\lambda) \times I(\lambda) \times abs(\lambda) \quad (1)$$

CF is correction factor (10), $EE(\lambda)$ = erythmogenic effect of radiation with wavelength λ , and $Abs(\lambda)$ = spectrophotometric absorbance values at wavelength λ . The values of $EE \times I$ are constants, as listed in Table 1.

Table 1. The normalized values of $EE \times I$ in the calculation of SPF.

Wavelength	EE x I
290	0.015
295	0.0817
300	0.2874
305	0.3278

Wavelength	EE x I
310	0.1864
315	0.0839
320	0.018
Total	1

2.4. Anti-melanogenesis activity assay.

The antimelanogenesis activity assay was conducted by determining the samples' ability to inhibit the tyrosinase activity in vitro. Briefly, 100 µl of LNE at a concentration of 6.25 to 100 µg/ml) in phosphate buffer was mixed with tyrosinase at a concentration of 333 units/ml) and 2 mM of L-DOPA. Then, they were incubated for 30 min at 37°C before measuring their absorbance at a wavelength of 492 nm with a microplate reader (Biorad®, USA). Kojic acid was used as a control in this experiment.

The tyrosinase inhibitor activity (%) was calculated as follows:

$$\% \text{ tyrosinase inhibitor activity} = 100 \times \frac{\text{Abs control} - \text{Abs Sample}}{\text{Abs control}} \quad (2)$$

The percentage of tyrosinase inhibition at each concentration was calculated, and the result was expressed as IC₅₀ [22].

2.5. Anti-collagenase activity assay.

The anti-collagenase assay was performed by mixing the reaction mix containing collagenase (EC 3.4.24.3) 0.35 U/ml (100 µl) and various concentrations of LNE (6.25 to 100 µg/ml) in collagenase assay buffer, 40 µl of collagenase substrate (FALGPA), and 60 µl of collagenase assay buffer. This experiment used EGCG (epigallocatechin gallate) as a positive control. The mixture's absorbance was measured at a wavelength of 345 nm using a triplicate microplate reader. The anti-collagenase activity is expressed by the percentage of inhibition of the collagenase enzyme, which is calculated using the following equation [23].

$$\% \text{ Inhibition} = 100 \times \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \quad (3)$$

The percentage of tyrosinase inhibition at each concentration was calculated, and the result was expressed as IC₅₀ [23].

3. Results and Discussion

3.1. Lycopene nanoemulsion (LNE) characterization.

Lycopene belongs to the class II biopharmaceutical classification system (BCS), meaning it has low solubility and high permeability [24]. Thus, lycopene was formulated into nanoemulsion to improve the bioavailability of lycopene nanoemulsion and increase the physical stability of lycopene nanoemulsion preparations. The characterization of LNE, including the droplet size, PDI, and zeta potential, is tabulated in Table 2.

Table 2. The droplet size, PDI, and zeta potential.

	Lycopene nanoemulsion
Droplet size (nm)	218.67±6.66
PDI	0.523±0.04
Zeta potential (mV)	-0.31±0.65

3.2. Sun protection factor activity of LNE.

UVB ranges from 0 to 320 nm and is more carcinogenic than UVA, ranging from 320 to 400 nm. It can penetrate deeply into the skin and damage the DNA, thus impacting the skin more [25]. The sun protection activity of LNE was found to be 6.80±0.00 and categorized as extra protection against UVB [20].

3.3. Anti melanogenesis activity.

Tyrosinase is an enzyme that contributes to skin pigmentation [26]. Tyrosinase is essential in the initial step of melanin production, which is responsible for pigmentation, through catalyzation of tyrosine into L-DOPA (3,4-dihydroxy-l-phenylalanine), continued dopaquinone, and finally, melanin production. The inhibition of tyrosinase activity through rate-limiting steps inhibits melanogenesis [27]. However, UV light exposure affects the hyperpigmentation of the skin by inducing the melanogenesis process. This is important in reducing the dark spot-induced UV in the skin, which occurs in skin aging [12,28]. Figure 1 illustrates the anti-melanogenesis activity of LNE.

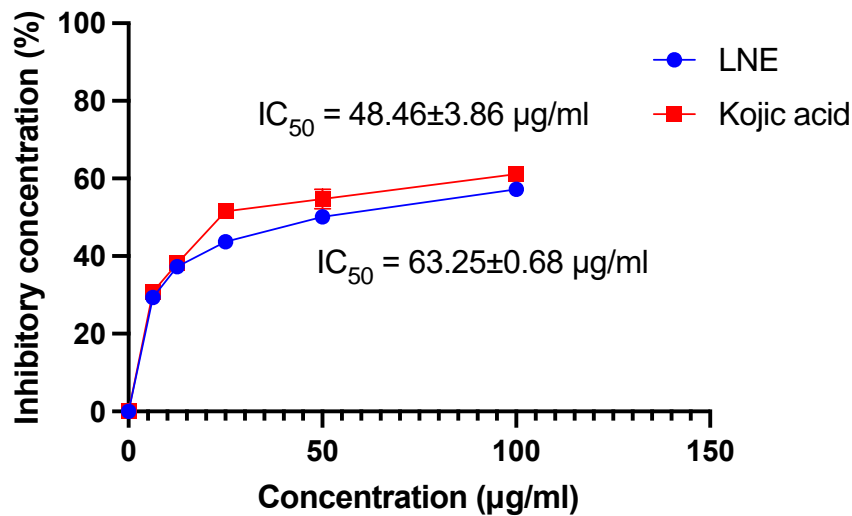


Figure 1. The anti-collagenase activity of LNE and kojic acid.

The anti-melanogenesis activity was performed by comparing the IC₅₀ value of LNE and kojic acid as control. Kojic acid was used as a control because it prevents the activation of tyrosinase, thus inhibiting melanin production [29]. According to the result, it was obtained that the IC₅₀ value of LNE was 63.25±0.68 µg/ml, while for kojic acid, it was 48.46±3.86 µg/ml, as shown in Figure 1. The possible mechanism of lycopene from LNE in suppressing the tyrosinase activity because of its activity to chelate the copper ions in the active site of tyrosinase or oxidize the tyrosinase [30,31].

3.4. Anti-collagenase activity.

Collagenase is essential in tissue structuring, remodeling, and development in normal conditions. However, it can be pathological, such as the tumor cell metastasis process. UV

exposure could increase collagenase expression, thus affecting skin aging [25]. The anti-collagenase activity of LNE was performed by comparing the IC_{50} of LNE and the positive control used, ECGC. The ECGC is an ester of epigallocatechin and gallic acid with the most abundant catechin content compared to other catechin types [23], which can inhibit collagenase activity at low concentrations [32]. The anti-collagenase activity is illustrated in Figure 2.

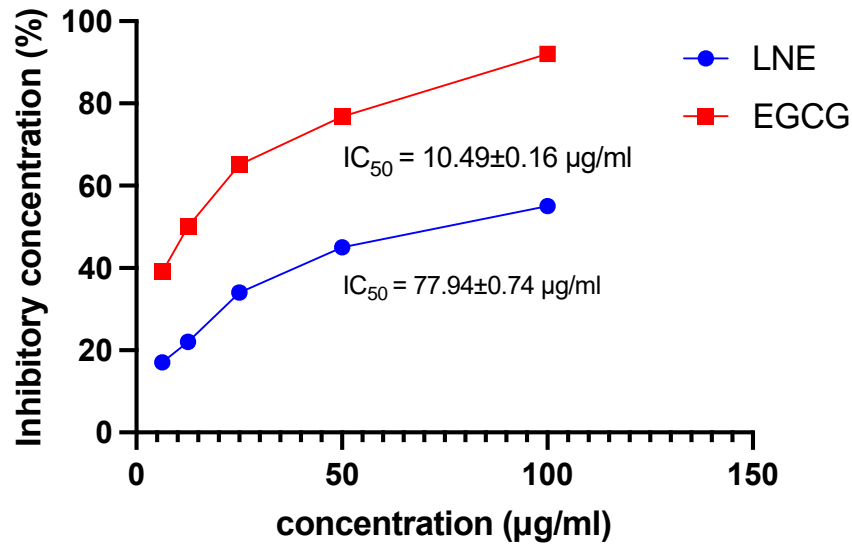


Figure 2. The anti-collagenase activity of LNE and ECGC.

As illustrated in Figure 2, the IC_{50} of LNE was 77.94 ± 0.74 µg/ml, and ECGC was 10.49 ± 0.16 µg/ml. It was found that ECGC possessed higher anti-collagenase activity than LNE. ECGC prevents the substrate binds to the enzyme by acting as a metal chelator [23,33]. At the same time, lycopene neutralizes the reactive oxygen species (ROS), which ROS promotes the matrix metalloprotease-1 (MMP-1), thus degrading the collagen [1].

4. Conclusions

The lycopene nanoemulsion (LNE) is a promising drug delivery system that has the potential for preventing UV-induced aging by providing ultra protection against UV-B with an SPF value of 6.80 ± 0.00 and possessing anti melanogenesis and collagenase activity with IC_{50} of 48.46 ± 3.86 µg/ml and 77.94 ± 0.74 µg/ml, respectively.

Author Contributions

Conceptualization, A.F., R.R.; methodology, L.S.; formal analysis, A.F., W.W.; investigation, L.S.; resources, A.F.; data curation, L.S., R.R.; writing—original draft preparation, A.F.; writing—review and editing, A.F., R.R.; supervision, A.F.; project administration, W.W.; funding acquisition, A.F. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

No conflict interested.

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