JURNAL ILMU KEFARMASIAN INDONESIA
Indonesian Journal of Pharmaceutical Sciences
ISSN p-ISSN 1693-1831 (Print) e-ISSN 2614-6495 (Online) PUBLISHER : Faculty of Pharmacy Universitas Pancasila

Safety and efficacy test of a cream combination containing jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts

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Received: 29 November 2024 / Accepted: 22 October 2025

ABSTRACT: Excessive free radicals accelerate skin degradation by causing oxidative damage to keratinocytes and fibroblasts, leading to structural protein breakdown (collagen, elastin, keratin), lipid peroxidation, and DNA damage. This process compromises skin barrier integrity, reduces elasticity, and promotes premature aging. Antioxidants play a crucial role in protecting the skin by neutralizing reactive oxygen species (ROS) and preventing lipid peroxidation. This study aimed to develop a topical cream containing jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts and evaluate its antioxidant activity and dermal safety. Extracts were obtained through kinetic maceration using 70% ethanol and formulated into oil-in-water creams at two concentration levels. The creams were assessed for physical characteristics (organoleptic properties, cream type, pH, homogeneity, spreadability, rheology, viscosity), stability under room and accelerated conditions (40°C for 4 weeks), antioxidant activity via DPPH assay, and irritation potential using albino rabbits. All formulations exhibited good physical properties, stability, and homogeneity. Irritation testing showed no erythema or edema, confirming the cream's safety for topical application. Antioxidant testing revealed strong free radical scavenging activity, with IC_{50} values of 119.705 ppm (F1) and 66.938 ppm (F2). Accelerated storage slightly reduced antioxidant activity, while higher extract concentrations enhanced antioxidant effects compared to the base formulation. These findings indicate that jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts synergistically enhance antioxidant activity in a safe topical cream formulation, demonstrating potential as a natural preparation for skin protection against oxidative damage.

KEYWORDS: Antioxidant activity; dermal safety; synergistic bioactivity; topical cream.

INTRODUCTION

The skin is continuously subjected to environmental stressors, including ultraviolet (UV) radiation and atmospheric pollutants, this exposure triggers the overproduction of reactive oxygen species (ROS), which subsequently leads to oxidative stress [1]. These ROS contribute to oxidative stress, which plays a pivotal role in skin aging, hyperpigmentation, and the development of various skin disorders [1], [2]. This is where the role of antioxidants becomes crucial. Antioxidants plays a crucial role in preventing and reducing hyperpigmentation by neutralizing reactive oxygen species (ROS), inhibiting lipid peroxidation, protecting skin cells from oxidative damage, and enhancing skin defense mechanisms [3]. In recent years, plant-derived antioxidants have received growing interest due to their efficacy and safety compared to synthetic agents [4], [5]. Plant-based antioxidants have gained considerable attention due to their safety profile and multiple biological activities [6].

A topical cream was selected as the delivery system because it allows prolonged contact with the skin, enhances absorption of active compounds, and provides moisturizing benefits [7]. The oil-in-water cream base are widely used in cosmetic preparations due to their favorable sensory characteristics and safety profile [7]. They are non-greasy, provide good spreadability, and do not cause skin irritation, making them suitable for various skin types, including sensitive skin [7]. To maximize absorption and effectiveness, a topical cream based on an oil-in-water (O/W) emulsion was selected as the delivery system. This formulation type is particularly advantageous for antioxidant-based products intended as skin-brightening cosmetics because it

How to cite this article: Shaliha KF, Taurhesia S, Swandiny GF. Safety and efficacy test of a cream combination containing containing jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts. JIFI. 2025; 23(2): 268-276.

https://doi.org/10.35814/jifi.v23i2.1688
ISSN: 2614-6495

allows even distribution of active compounds, reduces the risk of clogged pores, and promotes skin tone improvement [8].

Jujube (*Ziziphus mauritiana* L.) leaves are rich in bioactive compounds such as flavonoids, phenolic acids, and alkaloids, which exhibit strong antioxidant activity [9]. Similarly, perilla (*Perilla frutescens* L. Britton) leaves contain rosmarinic acid, luteolin, and various flavonoids known for their potent free radical scavenging properties [10]. Previous studies have shown that both jujube and perilla leaf extracts demonstrate very strong antioxidant activity, with IC_{50} values of 18.80 and 23.11 ppm [9], [10], respectively. Although both plants individually exhibit strong antioxidant properties, combining different plant extracts can potentially produce synergistic effects, enhancing their overall bioactivity.

However, no previous research has formulated a cream combining jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts and evaluated its antioxidant effectiveness. This study developed such a formulation and comprehensively assessed its safety and efficacy. The cream was evaluated for organoleptic properties, cream type, pH, homogeneity, spreadability, rheology, viscosity, and antioxidant activity. Accelerated stability testing (40°C for 4 weeks) and irritation testing on albino rabbits were also conducted to ensure product reliability and safety.

▪ MATERIALS AND METHODS

Materials

Jujube leaves were collected from Kebun Qur'an, Lembang, Bandung, Jawa Barat, Indonesia. Perilla leaves were collected from Perbawati Village, Sukabumi, Jawa Barat, Indonesia. The plants were determined at the Biopharmaceutical Cultivation Conservation Unit of the Tropical Biopharmaceutical Study Center, LRI-PGK IPB with No. 401/IT3.L.P13/TA.00.03/M/B/2024. Adeps lanae (Sigma-Aldrich, USA), stearic acid (PT Brataco, Indonesia), triethanolamine (Sigma-Aldrich, USA), liquid paraffin (Sigma-Aldrich, USA), alpha tocopherol (Sigma-Aldrich, USA), glycerin (Sigma-Aldrich, USA), phenoxyethanol (Sigma-Aldrich, USA), purified water (Sigma-Aldrich, USA), DPPH (2,2-diphenyl-1-picryl-hydrazyl) (Sigma-Aldrich, USA), and methanol pro analysis (Sigma-Aldrich, USA).

Instruments

The instruments used in this research included agitator mixer (IKA RW20, Germany), analytical balance (Sartorius, Germany), centrifuge (MPW MScience, Poland), cuvettes, hair clipper (Enchen, China), kinetic macerator (IKA RW20, Germany), laboratory glassware (Pyrex, USA; Iwaki, Indonesia), micropipettes (Socorex, Switzerland), oven (Memmert, Germany), pH meter (Hanna Instruments, USA), rotary vacuum evaporator (Büchi, Switzerland), UV–Visible spectrophotometer (Shimadzu UV-1900, Japan), viscometer (Brookfield DV-II+ Pro, USA), and water bath (Julabo, Germany).

Preparation of the cream

The extraction technique employed in this study was kinetic maceration utilizing 70% ethanol as the solvent. The formulations consisted of various concentrations of jujube (*Ziziphus mauritiana* L.) (BLE) and perilla (*Perilla frutescens* L. Britton) (PLE) leaf extracts. Details of the formulations can be found in Table 1.

Table 1. Cream formulation.

No.	İngredients	Function	F0	F1	F2
1	BLE (*Ziziphus mauritiana* L.)	Active	-	0.6	1.2
2	PLE (*Perilla frutescens* L. Britton)	Active	-	0.4	0.8
3	Stearic acid	Emulsifier	6	6	6
4	Triethanolamine	Emulsifier	3	3	3
5	Adeps lanae	Emollient	2	2	2
6	Liquid paraffin	Emollient	25	25	25
7	Glycerin	Humectant	15	15	15
8	Alpha tocopherol	Antioxidant	0.05	0.05	0.05
9	Phenoxyethanol	Presservative	1	1	1
10	Purified water	Solvent	Ad 100	Ad 100	Ad 100

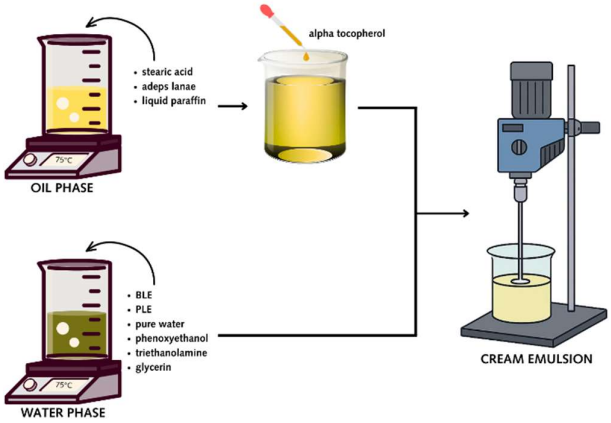


Figure 1. Schematic illustration of the cream preparation process (created by authors using Canva).

Evaluation of cream preparations

Organoleptic

The formulations were evaluated through organoleptic assessment, encompassing their morphology, coloration, and olfactory characteristics [11].

Cream type

Cream type testing is performed using the dye dispersion method. The test cream preparation is placed on a glass slide, then a few drops of methylene blue solution are added. If the blue color is immediately dispersed throughout the emulsion, then the emulsion type is oil-in-water (O/W). Whereas if the blue color is not dispersed throughout the emulsion, the emulsion type is water-in-oil (W/O) [7].

pH

The pH measurement was performed using a calibrated pH meter. Prior to analysis, the electrode was standardized with buffer solutions at pH 4 and pH 7. Subsequently, the electrode was immersed into the tested formulation and allowed to equilibrate until a stable reading was obtained, after which the displayed pH value was recorded [12].

Homogeneity

Homogeneity assessment was performed by spreading the cream formulation onto a glass slide, followed by visual examination to evaluate its uniformity [12].

Spreadability

Spreadability testing was conducted using a glass plate. The cream was placed onto a glass plate and the second glass plate was gently positioned on top of the cream, and a specified weight was added onto the top glass plate, allowed to sit for one minute. After this, the initial spread diameter of the cream was measured [12].

Rheology and viscosity

Rheological and viscosity analyses of the cream formulations were performed utilizing a Brookfield DV-II+ Pro viscometer. The samples were positioned beneath the designated spindle of the instrument, and the corresponding measurements were subsequently recorded [13].

Stability test

The objective of this study is to evaluate the physical stability of cream formulations under varying storage temperatures. The formulations were examined on a weekly basis through organoleptic assessments, determination of cream type, pH measurement, homogeneity analysis, spreadability evaluation, as well as rheological and viscosity profiling. The stability testing was performed on samples stored at 25 °C±2 °C and 40 °C±2 °C over a 4-week observation period [12].

Irritation test

The irritation test was performed on male New Zealand White rabbits in duplicate. A 0.5 g sample was topically applied to the shaved skin of the rabbits. Skin responses were evaluated at 24, 48, and 72 hours post-application. In the absence of observable dermal damage, the assessment was extended up to day 14 to evaluate the reversibility of potential reactions [14]. This study received ethical approval from the Health Research Ethics Committee of Universitas Pancasila (Approval No. 137/KEPK-FFUP/VI/2025).

Table 2. Criteria for skin irritation tests.

Reaction Type	Observation	Score
Erythema Formation	No erythema	0
	Very slight erythema (barely perceptible)	1
	Slight erythema (skin appears slightly reddish)	2
	Moderate erythema (skin appears red with small red spots)	3
	Severe erythema (skin appears intensely red with crust formation)	4
Edema Formation	No edema	0
	Very slight edema (barely perceptible)	1
	Slight edema (clearly defined area)	2
	Moderate edema (raised area approximately 1 mm)	3
	Severe edema (raised area greater than 1 mm and extending beyond the exposure site)	4

Antioxidant activity assay

The antioxidant potential was assessed through the DPPH free radical scavenging assay, adapted from the procedure reported by Rosiana et al. with minor modifications [15]. In brief, 1.0 mL of each sample solution prepared in methanol at varying concentrations was combined with 1.0 mL of 0.4 mM DPPH solution in methanol. The resulting mixtures were incubated at ambient temperature for 30 minutes, followed by absorbance measurement at 515.8 nm using a Shimadzu UV-1900 spectrophotometer (Kyoto, Japan). The percentage of free radical scavenging activity was calculated using the formula below:

$$\%\ \text{DPPH Scavenging Activity} = \frac{\text{Absorbance of blank} - \text{Absorbance of sample}}{\text{Absorbance of blank}} \times 100$$

▪ RESULTS

Organoleptic

Figure 2. Physical appearance of cream formulations containing different concentrations of extract.

Organoleptic observations showed that all formulations (F0, F1, and F2) maintained a semi-solid consistency. The color varied according to extract composition, with F0 appearing white and odorless, F1 light brown with a typical extract odor, and F2 dark brown with a similar extract odor.

Cream type

The determination of cream type using the dye dispersion method showed that all formulations produced a uniform blue color when mixed with methylene blue solution. This observation confirms that the emulsions were of the oil-in-water (O/W) type.

pH

The pH values ranged from 6.28 ± 0.01 to 6.50 ± 0.01. The ANOVA results showed significant difference among formulations ($p<0.05$). The pH decreased slightly with the addition of extract combinations, yet all remained within the acceptable skin pH range.

Homogeneity

All formulations appeared homogenous without phase separation, aggregation, or granule formation.

Spreadability

The spreadability values ranged from 6.54 ± 0.01 cm to 7.03 ± 0.01 cm. The ANOVA results showed significant differences between formulations ($p<0.05$), where increasing extract concentration tended to reduce spreadability. Nevertheless, all values were within the ideal range for topical application.

Rheology and viscosity

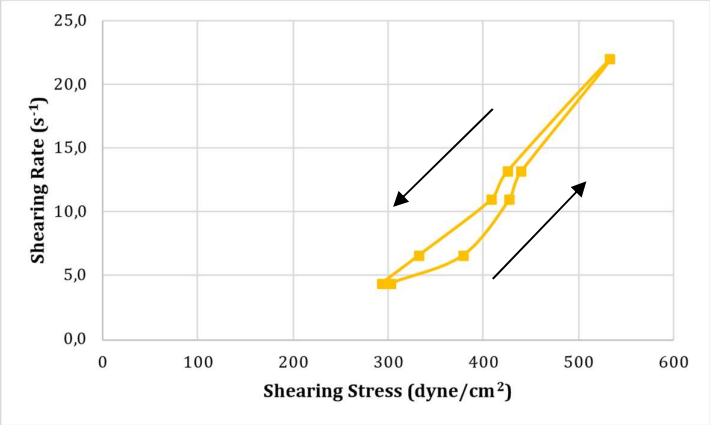


Figure 3. Rheological test results of the cream.

All formulations exhibited thixotropic flow behavior. The viscosity values increased from 9,454 cP in F0 to 11,398 cP in F2. Based on ANOVA analysis, viscosity differences among the formulations were statistically significant ($p<0.05$). The increasing viscosity correlated with the concentration of added extracts.

Stability test

Physical stability evaluation over four weeks showed that all formulations retained their organoleptic characteristics, homogeneity, and cream type without visible physical instability. Only minor variations were observed in pH, spreadability, and viscosity values throughout the storage period. However, the ANOVA results revealed that storage time and temperature significantly affected these parameters ($p<0.05$), indicating measurable changes in pH, spreadability, and viscosity from week 1 to week 4 under both room (25 °C) and elevated (40 °C) storage conditions.

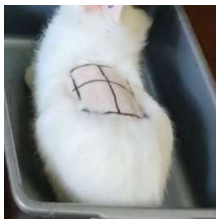
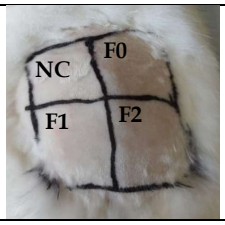
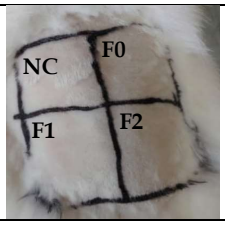
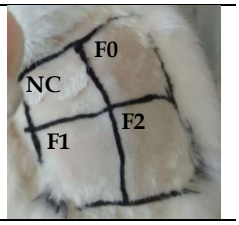
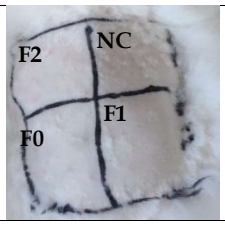
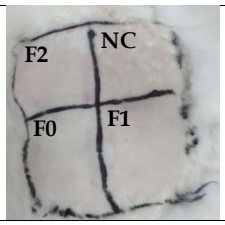
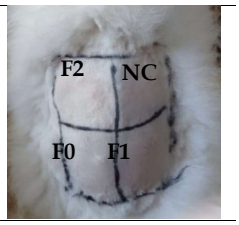
Irritation test

The primary dermal irritation test conducted on albino rabbits demonstrated that all cream formulations were safe for topical application. As summarized in Table 4, every formulation achieved an irritation index score of 0, confirming the absence of dermal irritation. Throughout the 72-hour observation period, no visible signs of erythema (skin redness) and edema (swelling) were detected on the dorsal skin of the rabbits. This outcome suggests that the excipients used in the cream base, as well as the incorporated jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts, do not induce inflammatory or allergic skin reactions. The lack of irritation may be attributed to the biocompatibility of the natural extracts and the mild nature of the oil-in-water emulsion system, which provides good skin tolerance. These findings emphasize the safety of the developed cream formulation and support its potential for long-term topical use without causing adverse dermal effects.

Table 3. Calculation of irritation index of cream formulas.

Group test	Irritation index
F0 (Base)	0
F1 (Combination of BLE 0.6% with PLE 0.4%)	0
F2 (Combination of BLE 1.2% with PLE 0.8%)	0

Table 4. Skin irritation test on albino rabbits observed at 24, 48, and 72 hours.

Before the test	24-hour	48-hour	72-hour
	Rabbit 1		
			
	Rabbit 2		
			

Information: NC : Negative control (without any treatment)
F0 : Base
F1 : Combination of BLE 0.6% with PLE 0.4%
F2 : Combination of BLE 1.2% with PLE 0.8%

Antioxidant activity assay

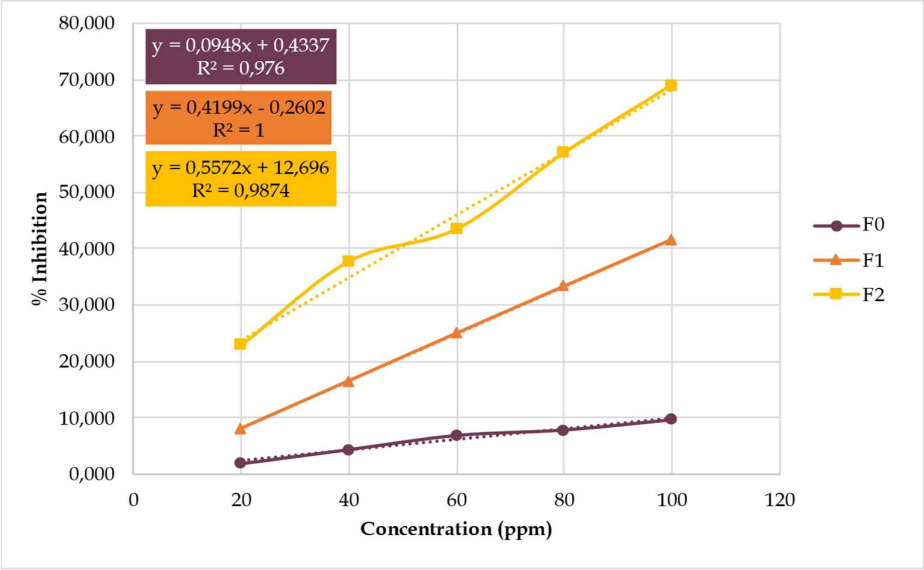


Figure 4. The antioxidant activity of the cream formulations.

Antioxidant activity testing was conducted based on the principle of quantitatively scavenging the free radical compound DPPH (2,2-diphenyl-1-pycrylhydrazyl) by antioxidant agents, namely jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts. DPPH radical compounds have unpaired electrons, so antioxidants will provide electrons to neutralize DPPH radicals [18].

Based on Figure 4, the antioxidant activity of the cream formulations varied significantly depending on the presence and concentration of jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf

extracts. Formula 0, which served as the base formulation without plant extracts, exhibited the weakest antioxidant capacity, indicated by the lowest percentage of free radical inhibition and the highest IC_{50} value of 523.900 ppm. Incorporation of the extracts in F1 (0.6% jujube and 0.4% perilla) significantly enhanced antioxidant activity with an IC_{50} of 119.705 ppm. F2, containing higher concentrations of both extracts, demonstrated the strongest antioxidant effect with the lowest IC_{50} of 66.938 ppm. The linear regression analysis indicated steeper inhibition curves for F1 and F2 compared to F0, confirming a dose-dependent increase in free radical scavenging ability. ANOVA analysis showed significant differences among the three formulations ($p<0.05$), indicating that extract concentration strongly influenced antioxidant activity.

Furthermore, increasing the concentration of jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts enhanced antioxidant efficacy in a dose dependent manner while maintaining stability under storage conditions of 25 °C (ambient) and 40 °C (accelerated). ANOVA analysis also confirmed that storage time and temperature significantly affected the antioxidant activity of all formulations ($p<0.05$). The synergistic antioxidant effect observed in the combined extract formulations is likely attributed to the complementary phytochemical profiles of both plants, which are rich in phenolics and flavonoids that act through multiple free radical scavenging mechanisms, thereby improving overall antioxidant capacity.

▪ DISCUSSION

A critical factor influencing the safety and efficacy outcomes in the present formulation is the choice of the oil-in-water (O/W) cream base, which differs in composition and functional properties from the bases reported [8], [12]. The formulation incorporated an O/W base with a higher proportion of fatty alcohols and waxes, providing enhanced viscosity and occlusivity, potentially improving moisturization but with a heavier skin feel [12]. The base contained a greater variety of non-ionic emulsifiers and emollients, optimizing active ingredient dispersion but with slightly lower viscosity stability at elevated storage temperatures [8]. In contrast, the current study employed a balanced O/W system with moderate oil-phase content, lightweight sensory properties, and emulsifiers optimized for botanical extract incorporation, which likely contributed to both active compound stability and user comfort.

From an efficacy perspective, the optimized base in this study appears to have supported higher antioxidant compared to the referenced formulations. This may be attributed to improved solubilization and retention of flavonoids, phenolic acids, and rosmarinic acid within the emulsion matrix, ensuring consistent delivery to the skin surface [8], [10]. Additionally, the stable rheological properties maintained pH, viscosity, and spreadability likely enhanced the bioavailability of actives over time. Importantly, unlike certain heavier or wax-rich bases, the lighter O/W system reduced the risk of pore occlusion and mechanical skin stress, indirectly contributing to the absence of irritation in safety testing [12].

The safety assessment using albino rabbits confirmed that all formulations were non-irritant, as indicated by an irritation index of 0 with no erythema or edema observed during 72 hours of observation. These results demonstrate that the cream components including emulsifiers, humectants, and emollients were dermally compatible and did not disrupt the stratum corneum integrity. The absence of irritation can be attributed to the mild O/W base, neutral pH, and the presence of soothing agents such as glycerin and natural plant constituents with antioxidant properties. Similar findings were reported by [12], who observed no irritation in herbal cream formulations containing non-ionic emulsifiers and moderate oil-phase concentrations. Therefore, the formulation approach used in the present study effectively balanced dermal safety with functional performance, ensuring suitability for prolonged topical use.

The comparative analysis suggests that the present cream base not only provides a favorable sensory profile and physicochemical stability but also plays an active role in preserving the functional integrity of the incorporated plant extracts. By combining these formulation advantages with verified safety and bioactivity, this cream represents a refined approach to natural skincare product design balancing stability, efficacy, and consumer acceptability more effectively than the bases employed in [8], [12].

▪ CONCLUSION

This study evaluated the safety and efficacy of an oil-in-water cream containing a combination of jujube (*Ziziphus mauritiana* L.) and perilla (*Perilla frutescens* L. Britton) leaf extracts. The formulations exhibited

desirable physical characteristics and stability under both room and accelerated conditions. Primary dermal irritation testing confirmed that the cream was non-irritant and safe for topical application. Antioxidant assays demonstrated significant and dose-dependent free radical scavenging activity, with the combination of both extracts producing a synergistic enhancement of efficacy compared to the base cream. The IC_{50} values were 119.705 ppm for the low-concentration formula (F1) and 66.938 ppm for the high-concentration formula (F2). Overall, the results confirm that the developed herbal cream is both safe and effective as a natural antioxidant formulation for protecting the skin against oxidative damage.

Acknowledgements: The authors would like to express their gratitude to all the collaborators for their contributions in conducting this research

Funding: This research was funded through personal funds.

Conflict of interest statement: The authors declared no conflict of interest.

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