Research Article

Formulation, optimization, physicochemical characterization, and *in vivo* evaluation of ellagic acid topical serum against ultraviolet-induced skin inflammation in Wistar rats

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ABSTRACT

Background: Ultraviolet (UV) radiation induces skin inflammation and oxidative stress through reactive oxygen species generation, lipid peroxidation, and release of pro-inflammatory cytokines. Ellagic acid, a natural polyphenolic antioxidant, possesses antioxidant, anti-inflammatory, and photoprotective properties. **Objectives:** This study aimed to formulate, optimize, and evaluate an ellagic acid topical serum for its protective effect against UV-induced skin inflammation. **Materials and Methods:** Topical ellagic acid serums (1% and 2% w/v) were prepared using Carbopol 940 and evaluated for physical appearance, pH, viscosity, spreadability, drug content, and stability. Optimized formulations were evaluated in UV-induced skin inflammation models using Wistar rats. The effects were assessed through gross skin observation, inflammatory markers (interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]), oxidative stress markers (catalase and malondialdehyde [MDA]), and histopathological examination. **Results:** All formulations showed acceptable physicochemical properties with drug content above 95%. F2 was selected as the optimized formulation based on its balanced viscosity, spreadability, pH, and stability. UV exposure increased inflammatory and oxidative stress markers, whereas ellagic acid in serum significantly reduced IL-6 from 43.32 to 26.65 pg/mL and TNF-α from 91.81 to 34.37 pg/mL compared with the UV-induced control ($P < 0.001$). MDA levels were decreased, and catalase activity increased from 41.59 to 78.57 U/mg ($P < 0.001$). The 2% w/v formulation showed greater protective activity than the 1% formulation and exhibited effects comparable to hydrocortisone. **Conclusion:** Optimized ellagic acid serum demonstrated significant anti-inflammatory, antioxidant, and photoprotective activity against UV-induced skin injury, suggesting its potential as a topical therapeutic formulation for inflammatory skin disorders.

Keywords: Ellagic acid, oxidative stress, skin inflammation, topical serum, ultraviolet radiation

Introduction

The skin is the largest organ of the human body and serves as the primary protective barrier against environmental stressors, including ultraviolet (UV) radiation, microorganisms, pollutants, and chemical irritants. Among these factors, prolonged UV exposure is one of the major causes of skin damage, leading to erythema, edema, inflammation, oxidative stress, premature aging, immunosuppression, and carcinogenesis. Ultraviolet B radiation penetrates the epidermis and generates excessive reactive oxygen species (ROS), resulting in oxidative damage to cellular lipids, proteins, and nucleic acids.[1,2]

Oxidative stress plays a crucial role in the development of UV-induced skin inflammation. Excessive ROS production activates signaling pathways such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), leading to increased expression of inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), and prostaglandins. Persistent oxidative stress enhances lipid peroxidation, decreases endogenous antioxidant defenses, and promotes degradation of collagen and elastin, contributing to inflammatory skin disorders and photoaging.[3,4]

Topical drug delivery systems are widely used for the management of skin-related inflammatory conditions due to their ability to deliver

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active compounds directly to the site of action while reducing systemic exposure. Among topical formulations, serum preparations have gained importance because of their light consistency, rapid absorption, improved patient acceptability, and enhanced penetration of active ingredients into the skin.[5,6]

Ellagic acid is a naturally occurring polyphenolic compound found in pomegranate, berries, walnuts, and other medicinal plants. It exhibits significant antioxidant, anti-inflammatory, antimicrobial, and photoprotective activities. Its therapeutic effects are associated with free-radical scavenging, inhibition of lipid peroxidation, reduction of inflammatory cytokines, and enhancement of antioxidant enzymes. However, its poor aqueous solubility and limited bioavailability restrict its practical application, which can be improved through the development of suitable topical delivery systems.[7,8]

Therefore, the present study was designed to formulate and optimize 1% and 2% w/v ellagic acid serums using Carbopol 940 as a gelling polymer. The prepared formulations were evaluated for physicochemical characteristics, drug content, spreadability, viscosity, pH, and stability. Furthermore, the optimized formulations were investigated for their protective effect against UV-induced skin inflammation in Wistar rats through gross observation, estimation of inflammatory and oxidative stress biomarkers, and histopathological examination of skin tissues.

Materials and Methods

Ellagic acid was procured from Lab-Chem Corporation, Ahmedabad, Gujarat, India. Carbopol 940, propylene glycol, polyethylene glycol (PEG) 400, glycerin, ethanol, triethanolamine (TEA), disodium ethylenediaminetetraacetic acid (EDTA), methylparaben, propylparaben, and purified water were of analytical grade. All biochemical reagents were of analytical/enzyme-linked immunosorbent assay (ELISA) grade [Figure 1].

Preparation of ellagic acid serum

Topical ellagic acid serum (1% and 2% w/v) was prepared using Carbopol 940 as the gelling polymer. Three formulations (F1–F3) were developed by varying Carbopol concentration. Propylene glycol and PEG 400 were mixed and heated to 40°C, followed by dissolution of preservatives. Carbopol 940 was hydrated in purified water containing disodium EDTA. Ellagic acid was dissolved in ethanol and incorporated into the Carbopol dispersion with continuous stirring. Glycerin was added, and the final volume was adjusted with purified water. TEA was added dropwise to neutralize Carbopol and obtain the desired serum consistency. The formulations were stored in amber-colored containers [Table 1].

Physicochemical evaluation[9]

The formulations were evaluated for:

- Physical appearance: Color, clarity, homogeneity, grittiness, phase separation, and odor were examined visually

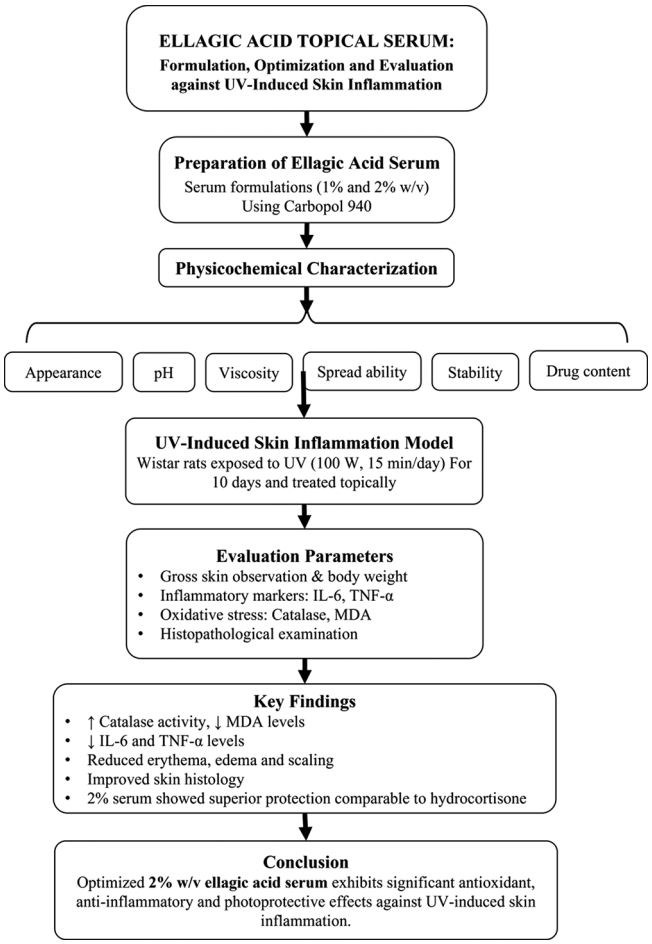

Figure 1: Graphical abstract. Schematic representation of the formulation, optimization, and *in vivo* evaluation of ellagic acid topical serum against ultraviolet-induced skin inflammation

- pH: pH was measured using a calibrated digital pH meter at room temperature
- Viscosity: Viscosity was determined using a digital rotational viscometer.

Spread ability: Spread ability was evaluated by the parallel plate method using:

$$S=(M\times L)/T$$

Where S is the spreadability, M is the weight on the upper slide, L is the distance traveled, and T is the separation time.

Drug content

Drug content was estimated using UV-visible spectrophotometry after the extraction of ellagic acid in ethanol.

Stability study

Optimized formulations were stored at 4 ± 2°C and 30 ± 2°C for 1 month and evaluated for changes in appearance, pH, viscosity, spread ability, and drug content.

Table 1: Composition of 1% and 2% w/v ellagic acid serum formulations

1% w/v ellagic acid serum			
Ingredients	**F1**	**F2**	**F3**
Ellagic acid (active)	0.3 g	0.3 g	0.3 g
Carbopol 940	0.03 g	0.12 g	0.24 g
Ethanol	4.5 mL	4.5 mL	4.5 mL
PEG400	3.3 mL	3.3 mL	3.3 mL
Propylene glycol	3.0 mL	3.0 mL	3.0 mL
Glycerin	1.9 mL	1.9 mL	1.9 mL
Methyl paraben	0.04 g	0.04 g	0.04 g
Propyl paraben	0.02 g	0.02 g	0.02 g
Disodium EDTA	0.03 g	0.03 g	0.03 g
Triethanolamine	QS	QS	QS
Purified Water	QS	QS	QS
2% w/v Ellagic acid serum			
Ingredients	**F1**	**F2**	**F3**
Ellagic acid (active)	0.6 g	0.6 g	0.6 g
Carbopol 940	0.03 g	0.12 g	0.24 g
Ethanol	5.1 mL	5.1 mL	5.1 mL
PEG400	4.5 mL	4.5 mL	4.5 mL
Propylene glycol	3.0 mL	3.0 mL	3.0 mL
Glycerin	1.5 mL	1.5 mL	1.5 mL
Methyl paraben	0.04 g	0.04 g	0.04 g
Propyl paraben	0.02 g	0.02 g	0.02 g
Disodium EDTA	0.03 g	0.03 g	0.03 g
Triethanolamine	QS	QS	QS
Purified Water	QS	QS	QS

F1–F3 represent different formulations with varying Carbopol 940 concentrations. Triethanolamine and purified water were added QS. w/v: Weight/volume, F1–F3: Formulation 1–3, QS: Quantity sufficient, EDTA: Ethylenediaminetetraacetic acid, PEG: Polyethylene glycol

Experimental animals

Healthy Wistar albino rats (200–250 g, 7–8 weeks old) were used. Animals were maintained under standard laboratory conditions and acclimatized for 7 days.

Ethical approval and experimental design

The study was approved by IAEC, Dr. Rajendra Gode Institute of Pharmacy (Approval No. 2240/IAEC/25–26/07), and conducted according to CPCSEA guidelines.

Thirty rats were divided into six groups ($n = 5$):

- Group I: Normal control (saline)
- Group II: UV-induced disease control
- Group III: Standard treatment (1% hydrocortisone cream)
- Group IV: UV + optimized 1% w/v ellagic acid serum
- Group V: UV + optimized 2% w/v ellagic acid serum
- Group VI: UV + placebo serum.

Induction of UV-induced skin inflammation[10,11]

The dorsal region was shaved, and animals were exposed to a 100-W UV lamp for 15 min daily for 10 days. Two hours after UV exposure, respective treatments were applied to the dorsal skin.

Evaluation of skin inflammation

Skin changes, including erythema, edema, scaling, and roughness, were recorded daily using standard scoring criteria. Body weight was measured on days 1, 7, and 14.

Biochemical analysis

- At the end of the study, skin tissues were collected and homogenized for biochemical analysis
- IL-6 and TNF-α: Estimated using rat ELISA kits, and absorbance was measured at 450 nm
- Catalase activity: Determined spectrophotometrically by hydrogen peroxide decomposition at 240 nm
- Malondialdehyde (MDA): Lipid peroxidation was estimated using the TBARS method at 532 nm.

Histopathological examination

Skin tissues were fixed in 10% formalin, processed, embedded in paraffin, sectioned (4–5 μm), and stained with hematoxylin and eosin. Histological changes, including epidermal integrity, inflammation, collagen organization, and follicular changes, were examined microscopically.

Statistical analysis

Results were expressed as mean ± standard error of the mean ($n = 5$). Statistical analysis was performed using one-way analysis of variance followed by Dunnett's test. Values of $P < 0.05$ were considered statistically significant.

Results

Formulation development and optimization

Ellagic acid serum formulations (1% and 2% w/v) were successfully prepared using Carbopol 940 as the gelling polymer. Three formulations (F1–F3) were developed for each concentration by varying the polymer concentration. All formulations showed smooth texture, uniformity, and absence of phase separation or precipitation.

Physicochemical evaluation

All formulations exhibited satisfactory physical characteristics with homogeneous appearance, smooth consistency, and no grittiness. The pH values ranged from 5.3 to 7.08, indicating acceptable skin compatibility. Viscosity increased with increasing Carbopol 940 concentration, while spreadability showed an inverse relationship with viscosity.

Drug content analysis showed uniform distribution of ellagic acid in all formulations, with values above 95%, indicating efficient drug incorporation. Based on overall physicochemical properties, formulation F2 of both 1% and 2% w/v ellagic acid serum showed optimum pH, viscosity, spreadability, and drug content and was selected as the optimized formulation.

Stability studies of optimized F2 formulations under refrigerated and room temperature conditions showed no significant changes in physical appearance, pH, viscosity, spreadability, or drug content after 1 month of storage, confirming formulation stability [Tables 2 and 3].

Gross dermatological evaluation

UV exposure produced visible inflammatory changes, including erythema, edema, dryness, and scaling in the disease control group. Treatment with ellagic acid serum progressively improved skin appearance. The 2% w/v ellagic acid serum showed a greater reduction in inflammatory changes compared with the 1% formulation and showed effects comparable to those of the standard hydrocortisone treatment [Table 4 and Figure 2].

Dermatological scores were recorded on days 1, 7, and 14. Erythema and edema were graded using a standardized semi-quantitative scoring system. Higher scores indicate greater severity of skin inflammation.

Scoring criteria

Erythema: 0 = absent; 1 = very slight; 2 = well-defined; 3 = moderate-to-severe; 4 = severe erythema/eschar. Edema: 0 = absent; 1 = very slight; 2 = slight elevation; 3 = moderate elevation; 4 = severe Edema.

Effect on body weight

The normal control group showed continuous weight gain, whereas UV-exposed animals showed reduced weight gain due to oxidative

Table 2: Physicochemical evaluation of 1% and 2% w/v ellagic acid serum formulations

Parameter	1% EA serum F1	1% EA serum F2	1% EA serum F3	2% EA serum F1	2% EA serum F2	2% EA serum F3
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
Grittiness	Non-gritty	Non-gritty	Non-gritty	Non-gritty	Non-gritty	Non-gritty
Appearance	Slightly translucent	Slightly translucent	Translucent	Translucent	Translucent	Translucent
Color	Off-white	Pale cream	Creamy beige	Light tan	Pale peach	Pale peach
Odor	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic
pH	5.8±0.04	6.4±0.03	6.97±0.02	5.3±0.04	6.5±0.03	7.08±0.02
Viscosity (cP)	1587	4254	12843	1243	4565	13532
Spreadability (g/cm/s)	11.0	8.2	5.3	10.75	7.98	4.8
Drug content (%)	95.84±0.62	96.12±0.58	96.42±0.55	97.18±0.50	97.74±0.46	98.16±0.44

Data are presented as mean±SD (n=3) for quantitative parameters. Qualitative parameters (homogeneity, grittiness, appearance, color, and odor) were assessed by visual inspection.
EA: Ellagic acid, F: Formulation, w/v: Weight/volume, cP: Centipoise, SD: Standard deviation

Table 3: Stability study of optimized F2 ellagic acid serum formulations

Formulation	Storage condition	pH	Drug content (%)	Spread ability (g/cm/s)	Viscosity (cP)	Physical appearance
1% EA serum F2	Initial	6.40±0.03	99.52±0.42	6.5±0.08	4254±12	Smooth and homogeneous
	Refrigerator (4±2°C)	6.36±0.04	98.94±0.40	6.4±0.07	4218±11	Stable
	Room temperature (30±2°C)	6.28±0.05	97.86±0.45	6.1±0.09	4146±14	Slightly stable
2% EA serum F2	Initial	6.5±0.03	99.54±0.41	7.98±0.08	4565	Stable
	Refrigerator (4±2°C)	6.4±0.02	99.02±0.38	7.82±0.07	4528	Stable
	Room temperature (30±2°C)	6.3±0.03	98.36±0.40	7.64±0.08	4472	Stable

Data are presented as mean±SD (n=3). Stability was evaluated after 1 month of storage under refrigerated (4±2°C) and room temperature (30±2°C) conditions. EA: Ellagic acid, F2: Optimized formulation 2, cP: Centipoise, SD: Standard deviation, °C: Degrees Celsius

Table 4: Gross dermatological observation and inflammatory scores of treatment groups

Treatment group	Gross observation	Erythema score (day 1/7/14)	Edema score (day 1/7/14)
Group I – Normal control	Healthy skin; no erythema, edema, or scaling	0/0/0	0/0/0
Group II – UV-induced group	Severe erythema, moderate edema, scaling, inflamed and rough skin	1/3/4	1/2/3
Group III – Standard (1% hydrocortisone cream)	Mild erythema and edema with slight scaling; improved skin condition	1/2/1	1/1/0
Group IV – 1% w/v ellagic acid serum (F2)	Moderate erythema, mild edema, slight scaling; reduced inflammation	1/2/1	1/1/0
Group V – 2% w/v ellagic acid serum (F2)	Mild erythema and edema with slight scaling; near-normal skin appearance	1/1/0	0/1/0
Group VI – Placebo serum	Moderate erythema and edema with persistent scaling; inflamed and rough skin	1/3/2	1/2/2

UV: Ultraviolet

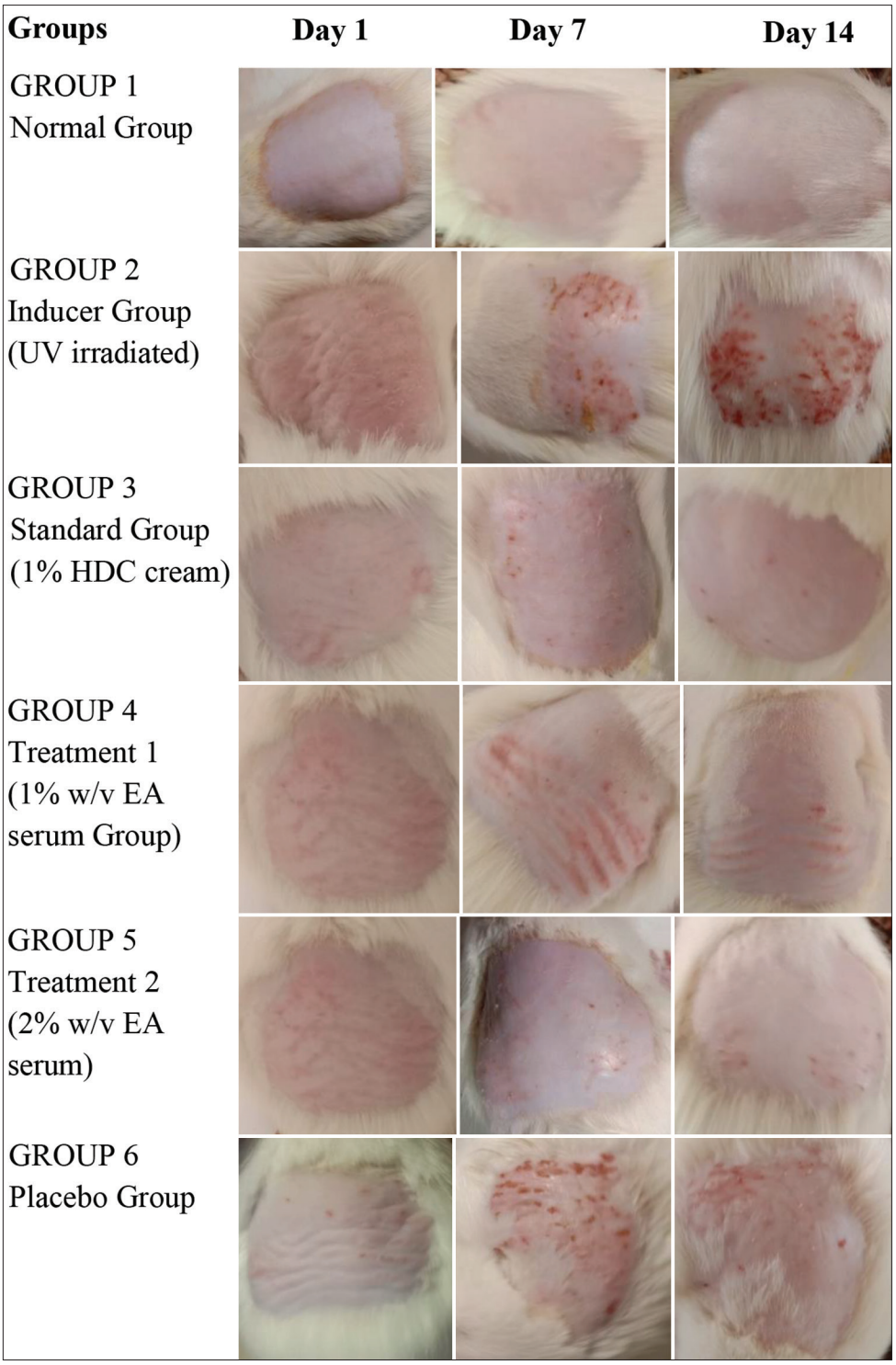

Figure 2: Weekly gross observation. EA: Ellagic acid, UV: Ultraviolet, F2: Optimized formulation 2, w/v: Weight/volume

stress. Ellagic acid treatment prevented weight reduction, with better improvement observed in the 2% w/v formulation group [Table 5].

Effect on oxidative stress biomarkers

UV exposure caused a significant decrease in catalase activity and increased lipid peroxidation, as indicated by elevated MDA levels. Ellagic acid serum significantly restored catalase activity and reduced MDA concentration compared with the UV control group. The 2% w/v formulation demonstrated superior antioxidant activity compared with the 1% formulation [Table 5; Figures 3 and 4].

Effect on inflammatory biomarkers

UV irradiation significantly increased IL-6 and TNF-α levels compared with the normal control group ($P < 0.001$). Treatment with ellagic

Table 5: Effect of ellagic acid serum treatment on body weight, oxidative stress biomarkers, and inflammatory cytokine levels

Day	Normal control (g)	UV control (g)	Standard (g)	1% EA serum (g)	2% EA serum (g)	Placebo (g)
1	235.0±2.14	243.0±2.36	220.0±1.95	240.00±2.08	228.00±1.84	230.0±2.11
7	248.0±2.42	237.6±2.17	232.0±2.06	240.10±2.24	235.00±2.12	228.1±1.96
14	262.0±2.65	230.6±2.03	243.0±2.28	248.86±2.31	240.32±2.15	234.3±2.04
Effect on oxidative stress biomarkers						
Catalase level (U/mg)	104.45±1.13	41.59±0.92	93.84±1.04	67.81±2.04	78.57±2.84	44.38±1.73
Lipid peroxidation level (nmol MDA/mg)	2.18±0.04	8.63±0.07	3.02±0.07	4.97±0.09	3.49±0.07	8.06±0.08
Effect on Inflammatory Biomarkers						
IL-6 level (pg/mL)	19.73±0.14	43.32±0.15	24.12±0.67	30.17±1.04	26.65±0.79	33.13±1.03
TNF-α level (pg/mL)	30.12±0.18	91.81±0.22	31.19±0.74	39.01±0.11	34.37±0.43	59.58±0.33

Data are presented as mean±SEM (n=5). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test. P<0.05 was considered statistically significant. EA: Ellagic acid, UV: Ultraviolet, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-alpha, MDA: Malondialdehyde, SEM: Standard error of the mean, ANOVA: Analysis of variance, w/v: Weight/volume

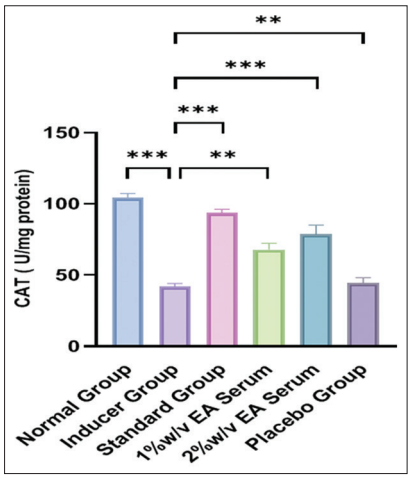

Figure 3: Effect of ellagic acid topical serum on skin catalase activity

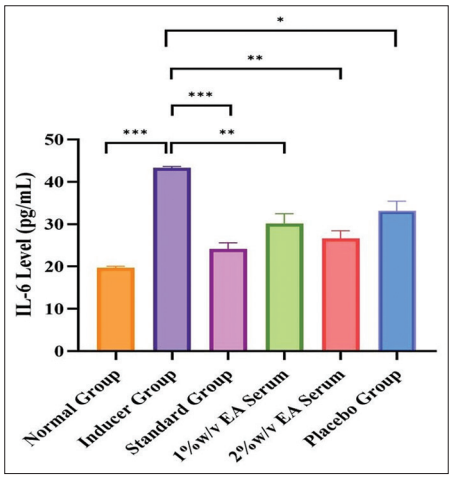

Figure 5: Effect of ellagic acid topical serum on skin interleukin-6 levels

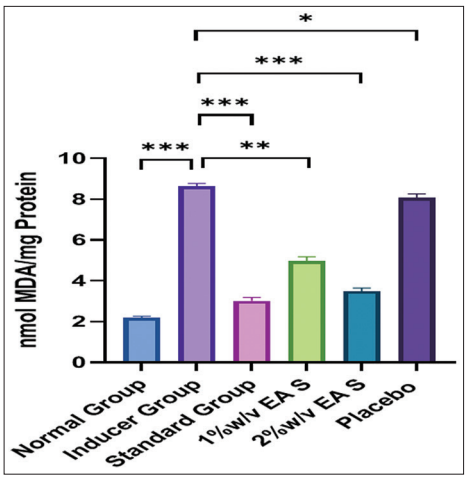

Figure 4: Effect of ellagic acid topical serum on skin malondialdehyde levels

acid serum significantly reduced both inflammatory markers. The 2% w/v formulation showed a greater reduction in IL-6 and TNF-α levels and produced results comparable to those of hydrocortisone treatment [Table 5; Figures 5 and 6].

Histopathological evaluation

Histopathological examination confirmed the protective effect of ellagic acid serum against UV-induced skin damage [Figure 7]. The UV control group showed epidermal disruption, inflammatory cell infiltration, dermal edema, collagen disorganization, and follicular damage. Treatment with 1% w/v ellagic acid serum produced moderate tissue recovery, whereas the 2% formulation showed marked restoration of epidermal structure, collagen organization, and reduction of inflammatory changes. The placebo group showed persistent pathological alterations similar to the disease control group.

Discussion

The present study demonstrated successful development and evaluation of an ellagic acid topical serum for protection against UV-induced skin inflammation. The optimized F2 formulations showed suitable physicochemical properties, including acceptable pH, viscosity, spreadability, drug content, and stability. Carbopol 940 provided desirable consistency and rheological properties required for

topical application. Recent studies have emphasized the importance of suitable delivery systems for improving ellagic acid stability, solubility, and skin penetration due to its limited aqueous solubility and bioavailability.[12,13]

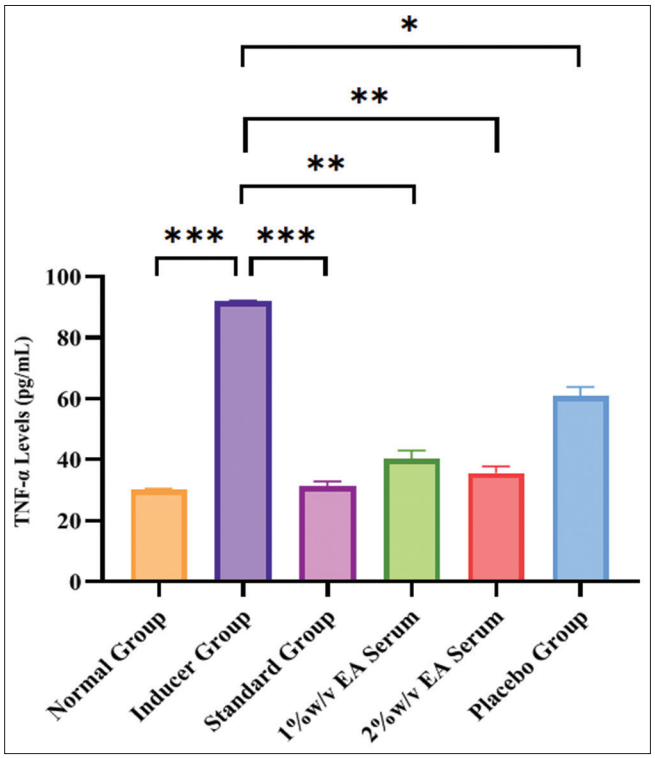

Figure 6: Effect of ellagic acid topical serum on skin TNF-α levels

UV irradiation produced significant inflammatory and oxidative changes, as indicated by erythema, edema, increased IL-6 and TNF-α levels, elevated lipid peroxidation, and reduced catalase activity. These findings confirm successful induction of UV-mediated skin injury. Treatment with ellagic acid serum significantly improved inflammatory changes, with the 2% w/v formulation showing a greater protective activity than the 1% formulation, indicating a concentration-dependent effect. Similar antioxidant and anti-inflammatory properties of ellagic acid have been reported in recent studies, supporting its role in skin protection.[8,14]

The increased IL-6 and TNF-α levels observed in UV-exposed animals were significantly reduced after ellagic acid treatment. The 2% w/v of ellagic acid serum showed effects comparable to those of hydrocortisone, suggesting strong anti-inflammatory potential. This activity may be related to the ability of ellagic acid to suppress oxidative stress-mediated inflammatory signaling and reduce the production of pro-inflammatory cytokines. Recent evidence has also reported the role of ellagic acid in regulating inflammatory and oxidative biomarkers.[8,15]

UV exposure causes excessive ROS generation, resulting in depletion of antioxidant enzymes and increased lipid peroxidation. In the present study, ellagic acid serum restored catalase activity and reduced MDA levels, demonstrating effective antioxidant protection. The superior activity of the 2% formulation may be attributed to higher availability of ellagic acid, leading to enhanced free radical scavenging and protection against oxidative membrane damage.[16]

The photoprotective activity of topical ellagic acid serum is likely mediated through multiple antioxidant and anti-inflammatory

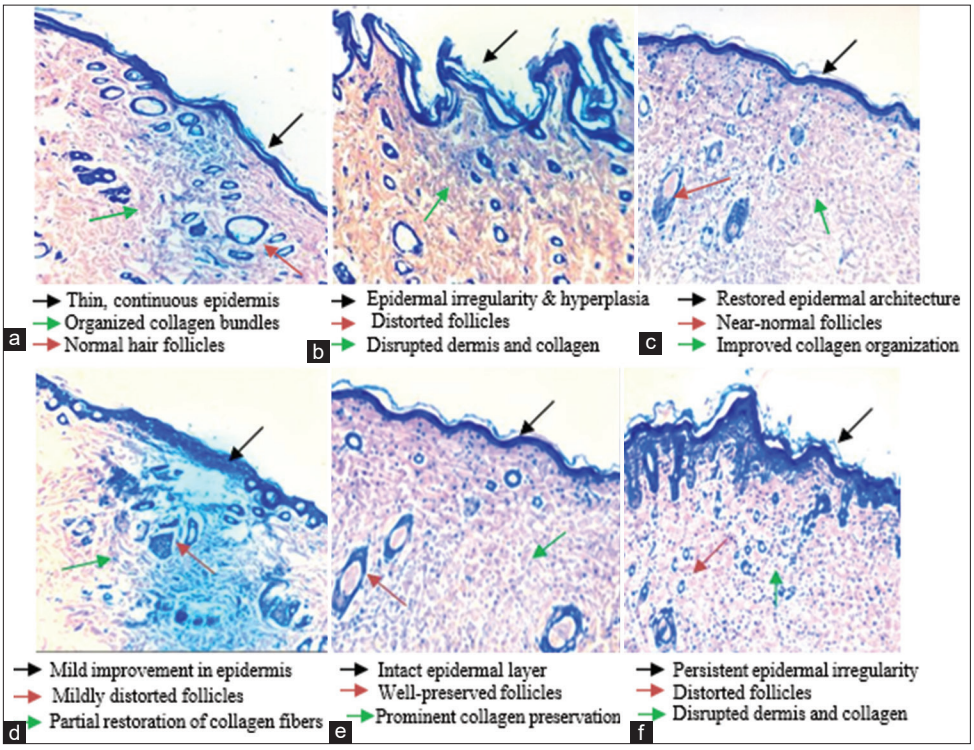

Figure 7: Histopathological observation of skin tissue. (a) Normal Group (b) Inducer Group (c) Standard Group (d) 1% w/v ellagic acid serum (e) 2% w/v ellagic acid serum (f) Placebo Group

mechanisms. Ellagic acid is a potent polyphenolic compound capable of directly scavenging ROS, thereby reducing oxidative stress induced by UV irradiation. Previous studies have further suggested that ellagic acid may activate the nuclear factor erythroid 2-related factor 2/antioxidant response element pathway, resulting in enhanced expression of endogenous antioxidant enzymes, including catalase. Attenuation of oxidative stress may subsequently suppress activation of pro-inflammatory signaling pathways such as NF-κB and MAPK, leading to reduced production of inflammatory mediators, including IL-6, TNF-α, and COX-2. Although these molecular pathways were not directly investigated in the present study, the observed reduction in inflammatory cytokines, restoration of catalase activity, decreased lipid peroxidation, and improved histopathological architecture are consistent with these previously reported mechanisms. The superior efficacy observed with the 2% w/v formulation further suggests a concentration-dependent pharmacological response and supports its potential as a promising natural topical therapeutic agent for preventing UV-induced inflammatory skin disorders.

Histopathological findings further supported the biochemical results. UV-treated animals showed epidermal disruption, inflammatory infiltration, dermal edema, collagen damage, and follicular alterations. Treatment with ellagic acid serum improved epidermal integrity and collagen organization, with the 2% formulation producing near-normal tissue architecture.

Overall, the findings indicate that optimized ellagic acid serum, particularly the 2% w/v formulation, exhibits significant anti-inflammatory, antioxidant, and photoprotective effects against UV-induced skin injury. The activity comparable to hydrocortisone suggests that ellagic acid serum may serve as a promising natural topical formulation for the management of UV-associated inflammatory skin disorders.

Conclusion

Ellagic acid serum was successfully formulated and optimized with suitable physicochemical properties and stability. The optimized 2% w/v ellagic acid serum showed significant anti-inflammatory, antioxidant, and photoprotective effects against UV-induced skin damage. It reduced inflammatory markers, oxidative stress, and histopathological changes, indicating its potential as a promising topical formulation for managing UV-induced skin inflammation.

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