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Effect of Ajwa date extract cream (Phoenix Dactylivera L) on TGF-β and IL-6 expression in rats exposed to UV-B

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Abstract: Excessive exposure to ultraviolet B (UVB) rays can trigger acute inflammatory reactions and damage to skin structures, including shortening and thickening of collagen fibers, damage to elastic fibers, and changes in the proportion of collagen in the dermis. This study aims to evaluate the effect of Ajwa date (Phoenix dactylifera L.) extract cream on the expression of TGF-β and IL-6 cytokines in Wistar rats exposed to UVB rays. This study is an in vivo experimental study with a post-test only control group design using 30 male rats randomly divided into five treatment groups: healthy control group (K1), UVB group without intervention (K2), UVB + base cream group (K3), UVB + 4% Ajwa date cream group (K4), and UVB + 8% Ajwa date cream group (K5). The cream was applied topically for 7 days and IL-6 and TGF-β levels were measured on the 8th day using the ELISA method. The results of one-way ANOVA showed no statistically significant differences in TGF-β ($p = 0.150$) and IL-6 ($p = 0.902$) levels between groups. However, there was an increase in the number of fibroblasts in the 8% cream group (K5) which was biologically relevant, indicating a possible regenerative effect in the proliferative phase. This study is a preliminary study that provides an important basis for further exploration of the topical therapeutic potential of Ajwa date extract. Further studies with improved formulations, longer treatment durations, and pre–post designs are recommended to understand the biological efficacy more comprehensively.

Keywords: Ajwa date extract cream; TGF-β levels; IL-6 levels.

INTRODUCTION

Excessive exposure to ultraviolet rays could causes acute inflammatory reactions in the skin.[1,2] its cause impaired skin function and texture such as *sunburn* or *tanning*.[3,4] Morphing the structure of the skin, including shortening and thickening of collagen fibers, damage to elastic fibers, and changes in the proportion of collagen types in the dermis.[5] Causes wrinkles and loss of skin firmness and elasticity.[6] The most obvious clinical effects such as erythema/sunburn are complex processes, consisting of inflammatory cell infiltration, cell proliferation, and *tissue remodeling* phases to restore skin integrity and function.[7] Topical use is widely used in cosmetic products that are effective in anti-aging treatments. However, its use can cause skin irritation such as burning, peeling, and dermatitis.[8]

The increasing need to develop more effective alternative therapies is indispensable for reducing skin damage.[1] Natural ingredients are needed as an alternative with fewer side effects. The use of natural ingredients with high

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antioxidant properties can be a choice of cosmetic ingredients with immunostimulant capacity such as ajwa dates, currently there is still little data that reports research using ajwa date cream as a therapy for skin improvement.[9,10]

Exposure to ultraviolet rays is the most important environmental risk factor resulting in photoaging, and is also an exacerbation factor for several skin diseases.[11] Clinical and epidemiological evidence suggests a link between cumulative sun exposure intensity and sunburn frequency and skin damage.[12] Causes oxidative stress, inflammation, ROS-mediated DNA damage, and disruption of cellular signaling pathways, thereby accelerating skin aging.[13] Oxidative stress means that redox balance is disturbed and the body is in an oxidative environment that damages proteins, DNA, lipids and can eventually lead to photoaging.[3] The aging process is characterized by a decrease in the ability of cells to repair themselves. Symptoms that are clearly visible include the appearance of wrinkles, bulges, and the skin becomes rough and dry. Excess free radicals will damage collagen in the skin cell membrane, so that the skin loses its elasticity and causes wrinkles.[14]

The development of herbal ingredients is in great demand because of the more affordable price and minimizing side effects, maintaining the balance of oxidant and antioxidant in ajwa dates which are rich in compounds with anti-inflammatory, antioxidant, and anticarcinogenic properties both in *vivo* and *in vitro systems*.[15] Flavonoids and polyphenols are the most common compounds found in ajwa dates. These polyphenol compounds are mainly found in fruit peels in high concentrations and have enormous health benefits such as antioxidant activity and free radical repellent, it is effective in minimizing the effect on the proliferation of damaged cells.[16]

Studies report that ajwa dates contain phenolic compounds and flavonoids that have an effect on human health due to their powerful antioxidant properties.[16] Using an experimental design in rabbits with ajwa date ethanol extract showed increased serum antioxidant enzyme levels along with a reduction in lipid hydroperoxide in rabbits with lead poisoning.[16] Another study using a dose of date extract (4%) in the form of a cream significantly improved skin elasticity, reduced redness, increased brightness, and hydration and led to improved facial skin.[17] Date fruit extract serves as a skin care ingredient that significantly improves the characteristics for aging parameters and skin health. The efficacy of this treatment may be due to the combination of various active substances found in date extract.[17]

UV exposure induces pro-inflammatory cytokines including *interleukin-6* (IL-6) in the skin, activating *metalloproteinases* (MMPs) and other enzymes that can damage the skin.[18] The interaction between *Interleukin-6* (IL-6) signaling and many regulatory factors (IFN-γ, TGF-β, STAT3, NF-κB) is involved in the resolution of acute inflammation.[19] UV exposure stimulates TGF-β which contributes to collagen degradation.[20] Changes in collagen and elastin fibers are related to photoaging. This causes wrinkles and loss of skin firmness and elasticity. Collagen fiber atrophy is caused by increased expression of collagenase (MMP-1), gelatinase (MMP-2) and stromelysin-1, as well as increased expression of elastase and MMP-9 associated with the degradation of elastin fibers. ECM-producing cells in the skin are activated by retinol and cause its production in aging skin. Activation of fibroblast production is stimulated through the TGF-b/CTGF pathway. Connective tissue growth factor (CTGF) includes immunostaining TGF-b1, which is a regulator of ECM homeostasis.[6]

Ajwa date extract is linked to antioxidant and anti-inflammatory phytochemical components.[21] Research using lyophilized ajwa date extract (AJLE) has strong antioxidant, hypolipidemic, cardioprotective, anti-inflammatory, and antiapoptotic potential against myocardial damage. Ajwa date extract prevents the decline of important antioxidants such as glutathione peroxidase, superoxide dismutase and carnitine acyltransferase.[22] From various studies that show the potential of Ajwa dates as an alternative treatment for skin disorders, until now,

there has been no study evaluating the molecular effects of topical Ajwa date extract on cytokine expression (TGF-β and IL-6) after UV-B exposure. This study aims to evaluate whether topical Ajwa date extract modulates inflammatory and remodeling cytokines, namely TGF-β and IL-6 expression after UV-B-induced skin damage in a mouse model

MATERIAL AND METHOD

This study is an in vivo experimental study conducted from February to March 2024 at the Integrated Biomedical Laboratory of the Faculty of Medicine, Unissula Semarang. A total of 30 male Wistar rats (Rattus norvegicus), aged 2–3 months with a body weight of 190–250 grams, were used as research subjects and randomly divided into five treatment groups, each consisting of six rats. The five groups include: a healthy control group (without UVB exposure), a UVB exposure group without intervention, a UVB group with base cream, a UVB group with 4% Ajwa date extract cream, and a UVB group with 8% Ajwa date extract cream. The selection of 4% and 8% concentrations was based on literature showing the effectiveness of plant bioactive compounds at topical concentrations of 1–10% as well as preliminary test results showing the safety and anti-inflammatory potential of the cream. The group allocation process was carried out using a closed lottery method to avoid selection bias, and researchers who evaluated the results were blinded to the treatment groups. The examination was conducted on day 8 using skin tissue samples for analysis of IL-6 and TGF-β cytokine levels via the ELISA method. Although the measurements were performed at a single time point, this study can be strengthened in further studies with a pre-post design or the addition of gradual time points to evaluate the dynamics of biomarker changes more thoroughly. All animal procedures in this study adhered to the established guidelines for the care and use of laboratory animals and were approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia (Approval No. 57/II/2024/Komisi Bioetik)

Making ajwa date extract

The sample of Ajwa dates was 2 kg, the part used was the flesh of Ajwa dates. The samples were separated from the seeds, then dried in an oven at 50°C. The results are checked for moisture content with *moisture balance*, if the moisture content is below 10%, the drying results are considered good. Simplisia is then sorted, cut into small pieces and weighed. Then it is blended into powder. Then it is sifted with a sieve of 20 mesh size. 500 grams of Ajwa date simplicia powder was extracted using the maceration method with 70% ethanol solvent as much as 3,750 ml. Date simplicia powder is put into a dark-colored bottle separately. Then the simplicia is soaked using ethanol solvent for 5 days and occasionally shaken 3 times a day, after 3 days then filtered and the pulp is re-aacerated for 2 days with 70% ethanol as much as 1250 ml. The repetition was carried out three times. The collected filtrate is then thickened using a *rotary evaporator* at a temperature of 50o until a thick extract is obtained.

Preparation of a cream ajwa date (*Phoenix dactylifera .L*) extract

Prepared in advance *of vanishing cream*. Preparation of *vanishing cream* in 50 grams with a composition (*Stearate acid, Triethanolamine, Glycerine, Borax*, and *aquadest,* the final cream base had a pH of 6.8–7.0, suitable for topical application. Stability testing of the formulation stored at room temperature for 14 days showed no visible phase separation, discoloration, or odor change, indicating acceptable stability for experimental use.), . Heat water in a bekerglas, put 14.5g stearate acid in a porcelain cup and place it on top of boiling water, stir until melted. Add Potassium *hydroxide* 125mg sequentially then homogenize, add *Triethanolamine* 1.5 ml, *Glycerine* 10 ml, and aquadest 25ml until well mixed. The cream was made in 20 grams by weighing 0.6 grams of ajwa date ethanol extract

then put it in a mortar, then adding enough *Tween* to be homogenized. After homogeneously Add 20 grams of *vanishing cream*, mix well until homogeneous before Place the ajwa date extract cream into a pot..[23].

Preparation of animals test

This study used Wistar rat test animals that were 2-3 months old and weighed 190-250 grams. The rats were placed in a room with a temperature of about 28-32°C, with a sufficiently ventilated room. For one week the mice will be adapted first. The rats were given pellet food and enough water drinks. The randomly taken sample came from 30 male Wistar rats, which were divided into 5 groups. The mice were caged in 5 cages consisting of healthy controls, only UVB exposure, control with base gel, administration of 4% Ajwa date extract cream, and administration of 8% Ajwa date extract cream. Each cage contains 5+1 rats.

UV-B exposure

After a 7-day acclimatization period, the rats were anesthetized using a combination of ketamine (60 mg/kg body weight) and xylazine (20 mg/kg body weight). The fur of each Wistar rat was shaved clean within a 5 × 5 cm area. Subsequently, the shaved area was exposed to (UVB) r using a broadband light source with a 302 nm emission at a minimum erythema dose of 160 mJ/cm²/day for 15 minutes over a period of 7 consecutive days. Rats in treatment groups K4 and K5 received topical application of Ajwa date extract cream at concentrations of 4% and 8%, respectively, administered once daily, four hours after UVB exposure. The 7-day sampling window was selected to capture the acute to early subacute phase of UVB-induced cytokine response. Prior work in rodent models of injury has shown that inflammatory mediators such as IL-6 and members of the TGF-β family exhibit significant dynamic changes between early (1 day) and later (7 days) phases—reflecting shifts from inflammatory to regenerative signaling patterns [24]. In UVB-irradiated human dermal fibroblasts, TGF-β1 expression was observed to increase significantly by day 7 [25]. This makes day 8 (one week) a biologically relevant endpoint for assessing both inflammatory and early recovery processes following repeated UVB exposure.

Skin tissue sampling

On the 8th day, after the final treatment, tissue samples were collected. Prior to collection, all Wistar rats were euthanized using anesthesia. Incisions were made in the UVB-exposed skin area using sterile scissors and tweezers. The excised tissue samples were immediately placed into phosphate-buffered saline (PBS, pH 7.4) and then homogenized under cold conditions at 4°C. The homogenates were centrifuged at 2000–3000 rpm for 20 minutes. The resulting supernatant, representing the low-density fraction of the centrifuged sample, was collected and used for further analysis. If not analyzed immediately, the samples were stored at −20°C until use.

IL-6 and TGF-β expression analysis using ELISA method

The skin tissue samples that had been obtained were then analyzed for IL-6 and TGF-β expression using the ELISA method. IL-6 and TGF-β expression levels were quantified using rat-specific ELISA kits (Bioassay Technology Laboratory, Shanghai Korain Biotech Co., Ltd., China; IL-6: Cat. No. E0135Ra, standard curve range 0.1–40 ng/L, sensitivity 0.052 ng/L; 96-well format). All procedures followed the manufacturer's protocol. Absorbance was measured at 450 nm using a microplate reader, and concentrations were calculated from standard curves provided with the kit.

Validation of Hematoxylin–Eosin (H&E) staining for fibroblast identification

Hematoxylin and eosin (H&E) staining is one of the most common methods of staining specimens in the diagnosis of pathology due to its ability to show the morphological structure of tissues. Tissue evaluation with biopsy and examination of clinical pathology remains the gold standard for diagnosis. In the diagnosis of pathology, staining the specimen is an important process, where the color information obtained from the tissue components is useful for further pathological analysis. Hematoxylin and eosin (H&E) staining, which is one of the most common staining methods, is performed in almost all pathological diagnoses to observe the morphological structure of tissues. In the H&E-stained image, the fibers and cytoplasm are colored pink and the core is colored blue.[26] The reason why we performed this procedure is that this study did not consider the classification of the entire pathological element but only focused on the classification of elastic fiber and collagen potential in H&E staining specimens.[26]

RESULTS AND DISCUSSION

The results of the flavonoid content test of ajwa date extract with analysis of flavonoid levels and total phenols. The average result of flavonoid levels of ajwa date pulp was 58.99 mg/ml, while the average phenol content of ajwa date pulp extract was 16.6 mg/ml. In line with these results, dates are rich in vitamins (A, C, and B complex), fiber, minerals, and phenolic compounds that have strong antioxidant activity.[27] high antioxidant profile content inside awja date suggests the potential of Ajwa date extract for skin protection applications. Observations were conducted on mouse models exposed to broadband UV-B light with a peak emission of 302 nm with an erythema dose of 160 mJ/cm2 within 30 minutes/day for 7 days, a macroscopic picture of the skin of mice exposed to UV-B is in figure 1.

Observation results on samples with a mouse model exposed to UV light (broadband with peak emission 302 nm) with an erythema dose of 160 mJ/cm2/day for 7 days. On the 8th day, skin tissue samples were taken to be stained with hematoxylin and eosin (H&E) to assess the number of fibroblasts in each sample and the observation results were carried out by an anatomical pathology specialist. The average results of the analysis of the number of fibroblast cells as a marker of inflammation from UVB exposure are shown in figure 2.

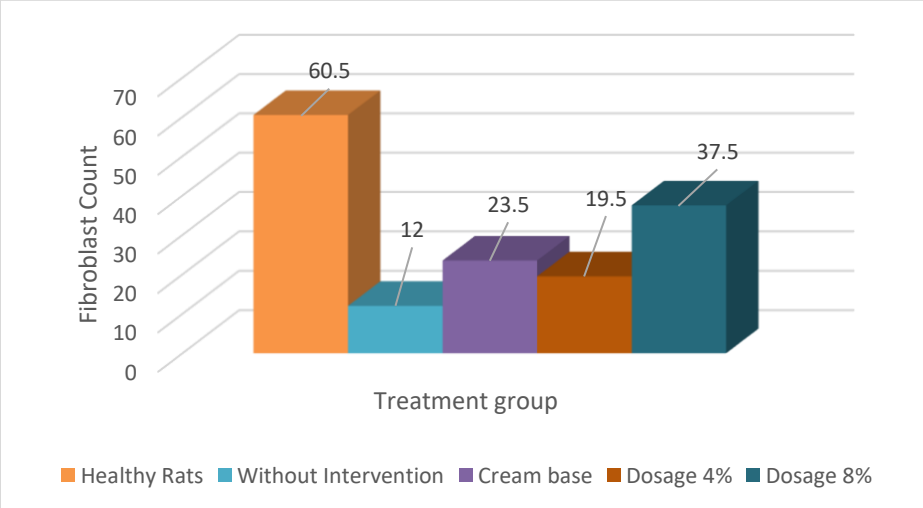

Figure 3. Graph of the results of the validation of the average number of fibroblasts between treatment groups

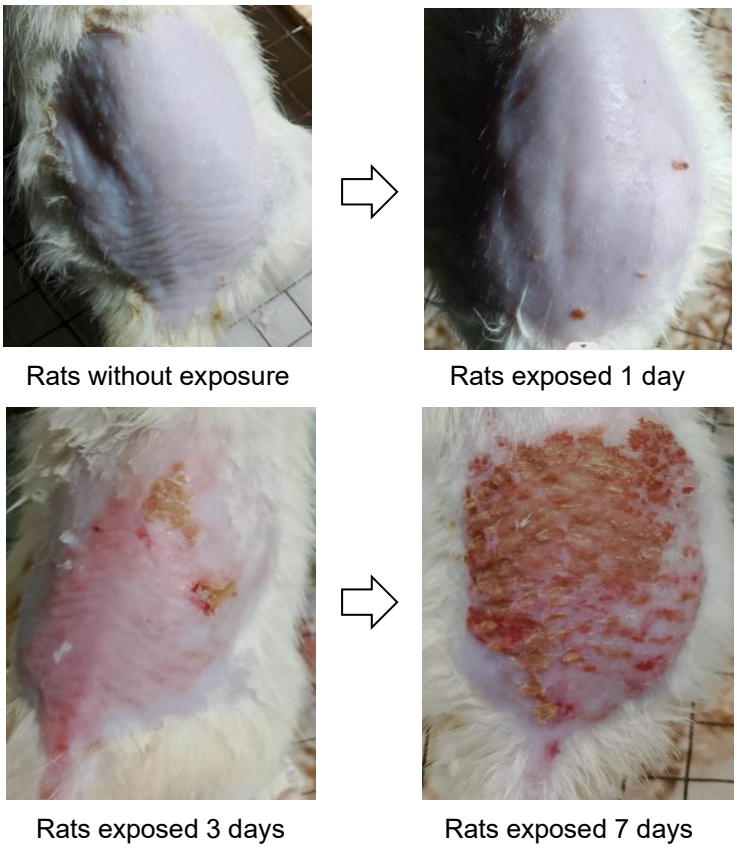

Figure 1. Comparison of rat skin exposed to UV-B rays

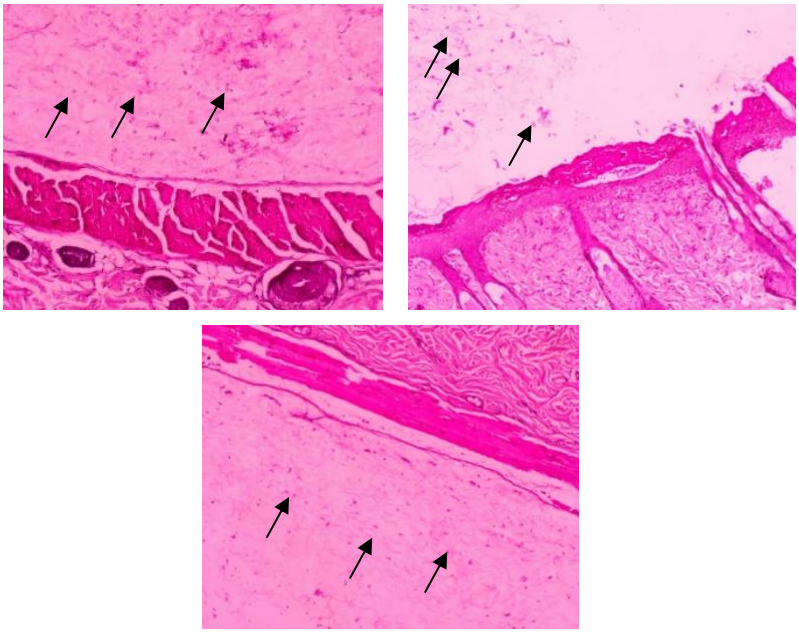

Figure 2. Distribution of fibroblast cells in the field of view of HE staining; Field of view of the Healthy Rats (KN) group (A), Field of view of group without intervention (K-) (B), Field of view of the group of rats who were given 8% ajwa date extract cream (K2) (C)

Analysis using Hematoxylin-Eosin (HE) staining demonstrated significant variations in the average number of fibroblast cells among the experimental groups. The healthy control group (K1) exhibited the highest mean fibroblast count, with an average of 60.5 cells per field of view. In contrast, the UVB-exposed group

without any treatment (K2) showed a substantial reduction, with a mean count of only 12 fibroblasts per field. Among the treated groups, the cream base group (K3) demonstrated an average of 23.5 fibroblasts per field, while groups treated with 4% (K4) and 8% (K5) concentrations of date extract cream showed mean counts of 19.5 and 37.5 fibroblasts per field, respectively (fig 3).

Statistical analysis confirmed a significant decrease in fibroblast counts in all UVB-exposed groups (K2, K3, K4, and K5) compared to the healthy control (K1), indicating the damaging effects of UVB exposure on fibroblast integrity. However, treatment with the 8% date cream (K5) resulted in a statistically significant increase in fibroblast numbers when compared to both the untreated UVB group (K2) and the lower dose treatment groups (K3 and K4), suggesting a dose-dependent protective or regenerative effect. These findings support the potential efficacy of date extract cream, particularly at higher concentrations, in promoting fibroblast proliferation following UVB induced skin damage.

The results of the average examination of TGF-β levels in each group using the ELISA method using rat skin tissue samples, are shown in Table 1 below:

Table 1. Descriptive Statistics and One-Way ANOVA Results for TGF-β Expression Levels Across Treatment Groups

Group	K1 Healthy Rats	K2 No Intervention	K3 Base Cream	K4 Dosage 4%	K5 Dosage 8%	*P value*
TGF-β Expression						
Mean	409.60	464.28	447.35	357.35	430.65	
±SD	±53.11	±95.92	±46.85	±63.82	±65.15	
Shapiro-Wilk	0.112*	0.112*	0.753*	0.813*	0.064*	
Lavene Test						0.669*
One way Anova						0.150

Description: * *Shapiro-Wilk* = Normal (p>0.05)
* *Leuvene Test* = Homogen (p>0.05)
* *One way Anova* = Significance (p<0.05)

The results of TGF-β levels were increased in the group without intervention (K2) and lowest in the 4% (K4) dose group of ajwa date extract. There was a decrease in TGF-β levels with the administration of ajwa date extract cream at a dose of 4%.

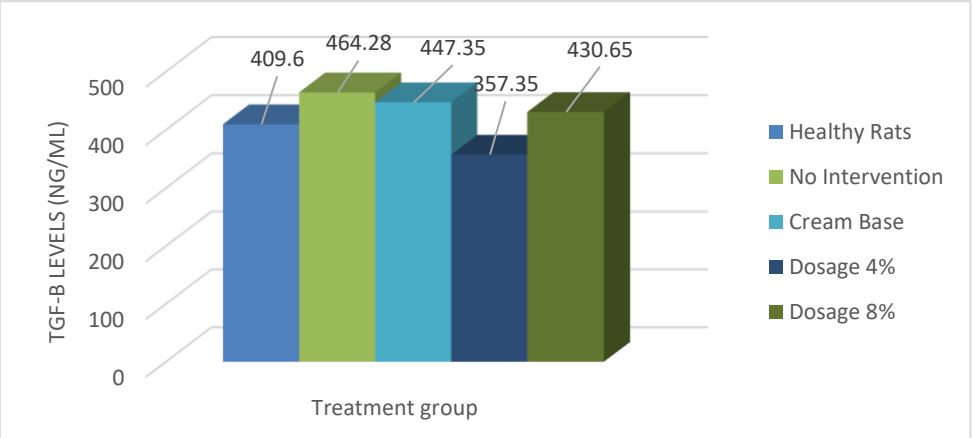

Figure 4. Mean of TGF-β levels between groups

The descriptive test of determining the normality of TGF-β levels with the Shapiro–Wilk test showed that the results of each group were normally distributed (p>0.05), and the determination of data homogeneity with the Levene's test

obtained a result of 0.669 (p>0.05). These results indicated that the data on TGF-β levels between groups had a homogeneous distribution and were eligible for one-way ANOVA testing. The results of the one-way ANOVA showed no statistically significant differences in the mean TGF-β levels between groups (p=0.150).

Although the one-way ANOVA did not show significant differences in TGF-β levels between groups (p = 0.150), the comparison between the 4% (K4 = 357.35 ± 63.82 ng/mL) and 8% (K5 = 430.65 ± 65.15 ng/mL) treatment groups showed an observable difference. The overall effect size was small-to-moderate (η^2 = 0.136; equivalent to Cohen's f = 0.397), and post-hoc power analysis (α = 0.05, N = 30, k = 5) indicated an observed power of 0.31, reflecting low sensitivity to detect group effects. Direct comparison of K4 and K5 showed a mean difference of 73.29 ng/mL (95% CI: –15.27 to 161.87 ng/mL). While this result was not statistically significant, the difference between the two treatment concentrations represents an interesting trend that should be regarded as exploratory and considered for further investigation in studies with larger sample sizes.

The average IL-6 levels were measured following UVB exposure and topical application of Ajwa date extract cream for 7 days and the 8th day of the skin tissue of Wistar rats were taken for analysis by the ELISA method. The results of the average examination of IL-6 levels in each group are shown in the table 2.

Table 2. Descriptive test results and *One way Anova* IL-6 levels

Group	K1 Healthy Rats	K2 No Intervention	K3 Base Cream	K4 Dosage 4%	K5 Dosage 8%	*P value*
IL-6 Expression (ng/mL)						
Mean	9.75	9.18	9.68	9.18	9.45	
±SD	±0.86	±1.21	±1.50	±0.59	±1.48	
Shapiro-Wilk	0.733*	0.540*	0.976*	0.632*	0.695*	
Lavene Test						0.393*
One way Anova						0.902

Description: * *Shapiro-Wilk* = Normal (p>0.05)
* *Lavene Test* = Homogen (p>0.05)
* *One way Anova* = Significance (p<0.05)

IL-6 levels were highest in the healthy control group (K1), while the lowest levels were observed in groups K2 and K4. Topical application of Ajwa date extract cream did not result in a statistically significant reduction in IL-6 levels among the treatment.

The descriptive test of determining the normality of the average results of IL-6 levels with *the Shapiro-Wilk test* showed the results of each group were normally distributed (p>0.05), and the determination of data homogeneity with *the Leuvene Test* obtained a result of 0.669 (p>0.05) the results showed that the data on IL-6 levels between groups had a homogeneous distribution of data. The average IL-6 levels were distributed normally and homogeneously and were eligible for the *One-way Anova test.* The results of *the One way anova* test showed an insignificant value of 0.902 (P<0.05). So it was concluded that there was no significant difference in the average IL-6 levels of each group.

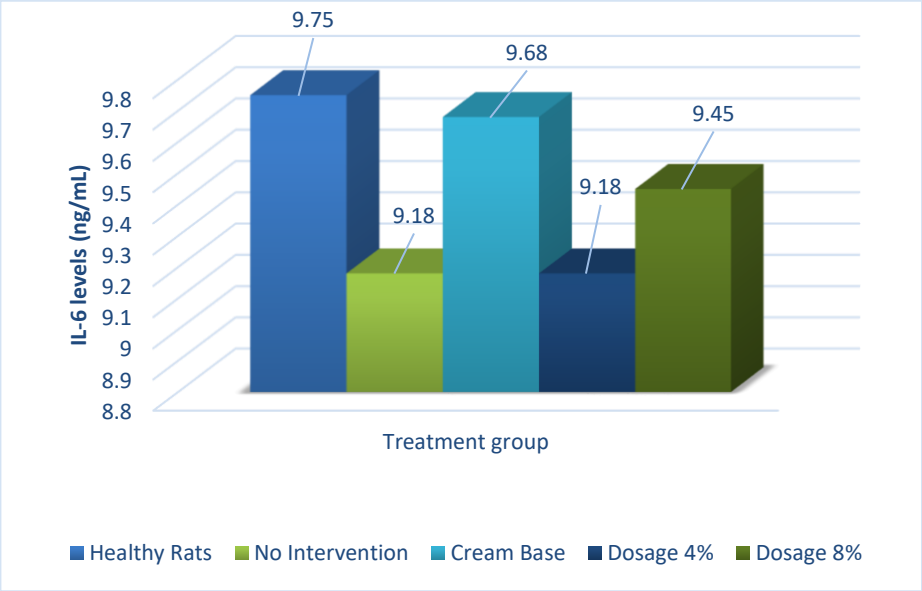

Figure 5. Mean IL-6 levels between treatment groups

The one-way ANOVA (table 2) did not show significant differences in IL-6 levels between groups ($p = 0.902$). Mean values across treatment groups were relatively similar, with the lowest observed in both the untreated UVB group (K2 = 9.18 ± 1.21 ng/mL) and the 4% cream group (K4 = 9.18 ± 0.59 ng/mL), while the 8% cream group (K5 = 9.45 ± 1.48 ng/mL) showed a slight increase. The overall effect size was $\eta^2 = 0.024$ (Cohen's $f = 0.157$), and post-hoc power analysis ($\alpha = 0.05$, $N = 30$, $k = 5$) indicated an observed power of 0.083, confirming very low sensitivity to detect effects of this magnitude. Direct comparison between K4 and K5 showed a mean difference of 0.27 ng/mL (95% CI: –0.77 to 1.31 ng/mL). These results were statistically non-significant and should be regarded as exploratory.

The validation of UVB exposure in this study confirmed a marked reduction in fibroblast counts in untreated animals, consistent with previous reports that UVB radiation induces DNA damage and apoptosis in dermal fibroblasts, thereby impairing tissue repair capacity [28]. Administration of Ajwa date extract cream at 8% (K5) was associated with a descriptive increase in fibroblast numbers compared to the UVB-only and base-cream groups (K2 and K3). Although this difference did not reach statistical significance, the observed trend is biologically relevant, as fibroblast proliferation plays a central role in wound healing and extracellular matrix remodeling. Similar findings have been reported with other plant-derived flavonoid-rich extracts, which promote fibroblast activity and tissue repair despite variable statistical outcomes in short-term studies [29,30]

By contrast, analysis of IL-6 and TGF-β levels showed no significant group differences. These null results should be interpreted cautiously, as cytokine dynamics are strongly time-dependent. IL-6 is typically elevated during the early inflammatory phase (within 24–72 h) and often subsides by one week [31,32], while TGF-β expression generally peaks later, between 2–3 weeks post-injury[29].

Accordingly, the 7-day sampling window used here may reflect a transitional phase between inflammation and remodelling, which could explain the absence of marked cytokine changes. A modest upward trend in TGF-β at the 8% dose group (K5) was observed, but given the study's limited sample size and statistical power, this should be regarded as exploratory. Comparable time-course studies have also reported non-significant cytokine fluctuations at intermediate time points, with clearer differences emerging over longer observation periods [28,33]

In addition to timing, formulation factors may have contributed to the findings. Although the vanishing cream base used here is suitable for topical

application, limited percutaneous penetration of bioactive compounds cannot be excluded. Other reports highlight the need for advanced delivery systems (e.g., liposomes, nanoparticles) to enhance dermal absorption and therapeutic efficacy [30,33]. Similarly, the sensitivity of the ELISA kits and the absence of pre-exposure baseline measurements constrain the ability to detect subtle changes in cytokine levels.

Taken together, while statistical significance was not achieved, the observed fibroblast trends and descriptive cytokine patterns suggest a potential pro-regenerative effect of higher Ajwa extract concentrations. These findings align with prior studies indicating flavonoid-mediated support of dermal repair mechanisms [29,30] but should be viewed as preliminary. Further research with larger sample sizes, improved delivery systems, and extended observation periods (2–3 weeks) will be necessary to clarify the therapeutic potential of Ajwa date extract against UVB-induced skin damage.

CONCLUSION

Administration of Ajwa date cream (*Phoenix dactylifera L*.) did not show a statistically significant effect on increasing TGF-β levels in UVB-induced Wistar rat skin tissue. Likewise, there was no statistically significant effect on decreasing IL-6 levels in UVB-exposed skin tissue after administration of Ajwa date cream. Nevertheless, this study is a preliminary study that provides an important basis for further exploration of the therapeutic potential of Ajwa date extract in topical applications. These results indicate the need for further research with a longer treatment duration, improved formulation, and a pre-post-test design approach, in order to obtain a more comprehensive understanding of its mechanism of action and biological effectiveness.

AUTHORS' CONTRIBUTIONS

Aria Nova Lisa: Data curation, Investigation, Writing-Original draf, Conceptualization; Prasetyowati Subchan: Reviewing, Supervision; Titiek Sumarawati: Validation, Reviewing, Supervision.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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