

The safety and efficacy of 3% *Cannabis* seeds extract cream for reduction of human cheek skin sebum and erythema content

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Abstract: Escalated sebum fabrication is seen with an unattractive look and adds to the growth of acne. We aimed to investigate the efficacy and safety of 3% *Cannabis* seeds extract cream on human cheek skin sebum and erythema content. For this purpose, base plus 3% *Cannabis* seeds extract and base (control) were prepared for single blinded and comparative study. Healthy males were instructed to apply the base plus 3% *Cannabis* seeds extract and base twice a day to their cheeks for 12 weeks. Adverse events were observed to determine skin irritation. Measurements for sebum and erythema content were recorded at baseline, 2nd, 4th, 6th, 8th, 10th and 12th week in a control room with Sebumeter and Mexameter. Base plus 3% *Cannabis* seeds extract was found to be safe in volunteers. Measurements demonstrated that skin sebum and erythema content of base plus 3% *Cannabis* seeds extract treated side showed significant decrease ($p < 0.05$) compared with base treated side. Base plus 3% *Cannabis* seeds extract showed safety. It was well tolerated for the reduction of skin sebum and erythema content. Its improved efficacy could be suggested for treatment of acne vulgaris, seborrhea, papules and pustules to get attractive facial appearance.

Keywords: *Cannabis sativa*, cream, irritation, sebum, erythema.

INTRODUCTION

Sebum secreted by sebaceous glands (Zouboulis, 2004) is complicated mixture of lipids, that is, triglycerides, cholesterol esters, squalene, free fatty acids and wax esters. These sebaceous lipids play vital functions under physiological conditions for integrity of the skin which influence inflammatory activities, passage antioxidants to the skin surface, and have inborn antimicrobial activity (Zhang *et al.*, 2011). Human face exhibits highest rate of sebaceous glands with 300-1500 glands/cm². Men exhibit a higher rate of sebum production compared to women (Peirano *et al.*, 2012). The outcomes of surplus sebum may be associated with unfavorable psychological and community consequences acquired from associated acne and the manifestation of skin shine and oiliness (Arbuckle *et al.*, 2008; Wójcik *et al.*, 2011).

Oily skin is a public complaint upsetting men and women, typically occurred puberty and about 60 years of age. 66% to 75% of the population aged between 15 and 20 years bear from an escalated sebum production, leading to subsided self-confidence and a weakening of quality of life (Arbuckle *et al.*, 2008). Out of these intentions seek is concentrating towards sebum reducing plants and their constituents (Aburjai and Natsheh 2003). Another truth is that sunlight is the foremost back supplier of UV radiation for human beings (Alena *et al.*, 2003). Safety of skin against detrimental effects of seasonal changes is big challenge for researchers (Takashi *et al.*, 1980). There is also support that ROS are concerned in allergic and

irritant contact dermatitis and erythema (Rates, 2001). In this view, antioxidants and phenolic compounds from natural products offer novel potentials for the remedy of oxidative stress-mediated skin diseases when they are used in topical form (Foldvari, 2000). A little is known about skin physical property like sebum and erythema content in asian especially in males.

Recent developments on the medical remedies of *Cannabis sativa* (Cannabaceae) has been commenced, mostly Asian and European countries move towards a more non-interventionist on the exploitation of *Cannabis* as a treatment (Hazekamp *et al.*, 2004; Zuardi *et al.*, 2010). Clinical advancements appear an acceptable benefit; the UK Government is likely to reconsider legalization, but only for medical use (Baker, 2003). *Cannabis* seeds have been omitted from legal regulations under *Cannabis* Control Law in Japan (Yotoriyama, 2005). The massive number of *Cannabis* constituents and their likely interaction with each other concoct this plant chemistry precious and composite. Phyto-chemistry of *Cannabis* characterize the chemical classes like phenolic compounds, phyto-cannabinoids, mono and sesquiterpenes, hydrocarbons, steroids, flavonoids, nitrogenous compounds, sugars, fatty acids and amino acids, among others (Radwan *et al.*, 2008; Elsohly and Slade, 2005).

Cannabis can be used for cosmetic preparations. *Cannabis* seed oil is favorable as an ingredient in light body oils and lipid-enriched creams, known for their adeptness to pierce the skin. Currently, *Cannabis* oil is used for skin care products in the form of moisturizers,

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shampoos, lotions and lip balms (Anwar *et al.*, 2006). But none of the scientific studies are available of this useful plant; therefore, we aimed to investigate the efficacy and safety of 3% *Cannabis* seeds extract cream for reduction of human cheek skin sebum and erythema content.

MATERIALS AND METHODS

Seeds of *C. sativa* were purchased from local market of Islamabad, Pakistan on August, 2011. *Cannabis* seeds were identified by Cholistan Institute of Desert Studies and specimen (Voucher No. CS-SD-01-11-32) was deposited by Herbarium, the Islamia University of Bahawalpur, Bahawalpur- Pakistan. ABIL EM 90 was procured from Franken Chemicals Germany, Paraffin oil was procured from Merck, Germany and Methanol was procured from BDH, England.

Preparation of the extract

The plant material, crushed (40g) was extracted with solvent-aqueous methanol (methanol: water, 80:20 v/v) (1L) in mechanical mixer for 6 hours at room temperature (Euro-Star, IKA D 230, Germany). The extract by filtering through Whatman No. 1 filter paper was removed from the residues. The residues with the same fresh solvent were extracted twice and extracts combined. The combined extracts were concentrated under reduced pressure at 45°C, using a rotary evaporator (Eyela, Co. Ltd. Japan) and freed of solvent up to one tenth. The concentrated extract was stored for further experiment at -4°C. (Sultana *et al.*, 2009).

Preparation of the Base plus 3% Cannabis Seeds

Extract

2% ABIL EM 90, 14% Paraffin oil, 3% *Cannabis sativa* seeds aqueous methanolic extract. 1% fragrance and deionized water were consumed for formulation. Both oily phase and aqueous phase were heated up to 75°C±1°C and then combined by adding extract and fragrance using homogenizer (Euro-Star, IKAD 230, Germany). The same method was adopted to prepare the base.

Determination of anti-oxidant activities

Anti-oxidant activities of the plant extract alone and after addition in the extract cream were determined. The free radicals scavenging of The H-donor capability was evaluated by consuming a methanol solution of DPPH. The DPPH discloses maximum absorbency at 517 nm. The DPPH stable free radical was used to determine free radical scavenging of extract. In 5 microliter of aqueous methanolic plant extract, added DPPH to fabricate the volume up to 100µl in 96 well plates. Admixed the contents and incubated for 30 minutes at 37°C and determined the optical density at 517nm. Ascorbic acid, as standard, had a strong antioxidant property that's why it was used as standard to evaluate the antioxidant activity of substances. Experiments were done in triplicates.

Results were taken as mean and standard error of mean of three independent experiments.

% DPPH scavenging activity = (100-OD of test sample/OD of controlled x100)

Subjects

Eleven asian and healthy males with an age between 20 to 35 years (Rasul and Akhtar, 2011), with no identified skin diseases or allergy to substances in formulations, joined in the single blinded and comparison study, in accordance with Declaration of Helsinki. Informed consent was signed before start of this study from all volunteers. The volunteers were instructed not to utilize any skin care products on cheeks 24 hours earlier and then, throughout the experiment.

Safety evaluations

We conducted single blinded and comparison study of 3% *Cannabis* seeds extract cream for reduction of skin sebum and erythema content during the winter season (October, 2011 to January, 2012) at the Faculty of Pharmacy and Alternative Medicine which is located at latitude 29.4° and longitude 71.683°. All instrumental measurements were made by the researcher as guidelines of manufacturer. At the baseline visits, each volunteer was then given two products that were similarly packaged: one contained base plus 3% *Cannabis* seeds extract and other contained base. The volunteers were educated about the appropriate use of the both base and 3% *Cannabis* seeds extract cream. Skin sebum and erythema content evaluations were done in a control room every second week up to end study period of three months.

For primary irritation potential of base and base plus 3% *Cannabis* seeds extract, patch test was accomplished on both left and right forearms of each volunteer on the first day of skin assessment. A 5×4cm area was marked on the forearms. The patch (Bandage disc) for the left and right forearm was drenched with 1.0g base and base plus 3% *Cannabis* seeds extract respectively with surgical dressing after application on marked areas. After 48 hours, both left and right forearms were observed for any skin irritation by an experienced dermatologist and also using Mexameter. The quantification of the skin irritation is given through a numeric scale; was used to quantify the skin irritation (visual scoring). The average irritant score of the base and base plus 3% *Cannabis* seeds extract calculated from the average of the quotations obtained for each volunteer, allowing ranking from "non-irritant to very irritant". The reactions were evaluated according the following arbitrary scale. No erythema: 0, Light erythema (hardly visible): 1, Clearly visible erythema: 2, Moderate erythema: 3, Serious erythema (dark red with possible formation of light eschars): 4.

No edema: 0, Very light edema (hardly visible): 1, Light edema: 2, Moderate edema (about 1 mm raised skin): 3, Strong edema (extended swelling even beyond the application area): 4. The index of average irritation was classified according amended Draize system: Non irritating: 0.5, 0.5-2.0: Slightly irritating, 2.0-5.0: moderately irritating, 5.0-8.0 (highly irritating (Varvaresou *et al.*, 2011). Approximately 500 mg of both base plus 3% *Cannabis* seeds extract and base were instructed to apply to the right cheek and left cheek of face respectively by using their fingertips; twice a day (mornings, 7:00-9:00; Evenings, 19:00-21:00) by volunteers. The region around the eyes was neglected.

Effectiveness of the two products (Rasul *et al.*, 2011) that is, base plus 3% *Cannabis* Seeds Extract and base were assessed in this study by giving questionnaire to answer consisting of seven parameters after 12 weeks application of products from the initiation of the study:

1. Ease of application
2. Spreadability
3. Sense just after application
4. Sense on long term
5. Irritation
6. Shine on skin
7. Sense on softness

Instrumental assessment

Three successive of non-invasive measurements were made on human cheeks of 3% *Cannabis* seeds extract cream right treated side and base left treated side. The sebum levels of both cheeks were revealed with a photometric device, Sebumeter (Courage and Khazaka, Germany). Special opaque plastic tape (64mm²) was pressed onto the skin for 30 sec with a slight pressure to collect the skin sebum. The consequential spread in transparency of the tape was calculated and the displayed values tally to the sebum amount on the skin surface in µg sebum/cm². The erythema measurements were performed with reflectance spectrophotometer, Mexameter from Courage and Khazaka Electronics GmbH, Cologne Germany. It has arbitrary units (Courage and Khazaka, 2004).

Ethical standards

The approval of this study was given by the Advanced Study and Research Board (ASARB), The Islamia University of Bahawalpur and The Institutional Ethical Committee, Faculty of Pharmacy and Alternative Medicine (Ref. No. 3715/Acad), the Islamia University of Bahawalpur, Bahawalpur- Pakistan.

STATISTICAL ANALYSIS

For statistical analysis, the data obtained was then explored and analyzed by the SPSS 17.0 by using the two-way ANOVA for variation between different time

intervals and the paired sample t-test for the variation between the two formulations. *P*-values<0.05 were considered statistically significant.

RESULTS

Antioxidant activities determination of the plant extract and after addition of plant extract of the 3% *Cannabis* seed extract cream was found to be 87% and 79% respectively.

Evaluation of irritancy testing was based on visual scoring only as shown in Table 1. It was found by performing patch testing on forearms skin of volunteers for 48 hours for both the base and 3% *Cannabis* seeds extract cream that skin erythema level after application of base was slightly decreased while the skin erythema level after application of 3% *Cannabis* seeds extract cream was pronouncedly decreased after 48 hours (fig. 1). But with paired sample t-test, it was apparent that the effects of 3% *Cannabis* seeds extract cream treated side and base treated side were insignificant regarding the skin erythema even though the 3% *Cannabis* seeds extract cream decreased the skin erythema content more than the base.

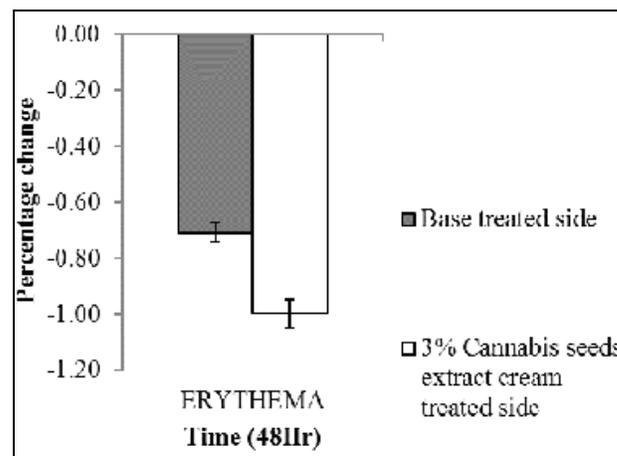


Fig. 1: Change (%) in skin erythema values on forearms

The percent change in the calculated skin sebum of base treated side and 3% *Cannabis* seeds extract cream treated side of volunteers have been given represented in fig. 2. Mean skin sebum values, standard deviation and standard errors are given in table 2. It was found that there was decrease in skin sebum contents regularly throughout the investigation. After applied ANOVA test, it was found that there was insignificant effect of base treated side with respect to time while it was evident that 3% *Cannabis* seeds extract cream treated side was significant effect with respect to time. When the paired sample t-test was applied, it was found that the base treated side and 3% *Cannabis* seeds extract cream treated side showed significant variations regarding the skin sebum with respect to time.

Table 1: Values and classification of average irritation indexes of base treated side and 3% Cannabis seeds extract treated side on forearms

Volunteer	Erythema	Edema	Total readings 48 hours
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
Total irritation			0
Irritation index			0.00
Result			Non irritant

Table 2: The changes of the sebum values the base treated side and the 3% Cannabis seeds extract treated side

Time	Base treated side (p>0.05)			3% Cannabis seeds extract cream treated side (p<0.05)		
	Mean	STD Dev	SEM	Mean	STD Dev	SEM
0 hr	73.88	28.05	8.48	74.09	13.66	4.13
2 week	66.55	22.24	6.72	59.09	19.22	5.81
4 week	66.72	15.26	4.61	57.00	9.47	2.86
6 week	63.90	15.08	4.56	56.45	18.14	5.48
8 week	61.67	10.61	3.20	48.64	11.11	3.36
10 week	65.62	42.68	12.89	46.45	13.59	4.11
12 week	62.77	20.66	6.24	46.00	21.15	6.39

Table 3: The changes of the erythema values with base treated side and the 3% Cannabis seeds extract cream treated side

Time	Base treated side (p>0.05)			3% Cannabis seeds extract cream treated side (p<0.05)		
	Mean	STD Dev	SEM	Mean	STD Dev	SEM
0 hr	523.45	75.42	22.79	412.09	59.09	17.85
2 week	537.36	69.42	20.97	381.00	81.26	24.55
4 week	545.91	66.79	20.18	378.91	73.23	22.12
6 week	525.00	59.40	17.95	376.45	64.14	19.38
8 week	530.00	75.44	22.79	373.91	54.46	16.45
10 week	497.09	53.55	16.18	366.82	54.34	16.42
12 week	501.00	51.91	15.68	364.91	51.73	14.33

Table 4: Average values ± SEM for Panel Test

	Average points for base treated side ± SEM	Average points for 3% Cannabis seeds extract cream treated side ± SEM
Ease of application	4.14±0.05	4.21±0.11
Spreadability	4.31±0.08	4.25±0.03
Sense just after application	4.02±0.07	4.21±0.05
Sense in long term	4.23±0.08	4.12±0.12
Irritation	0.00±0.00	0.00±0.000
Shine on skin	4.13±0.08	4.12±0.04
Sense of softness	4.35±0.08	4.67±0.03

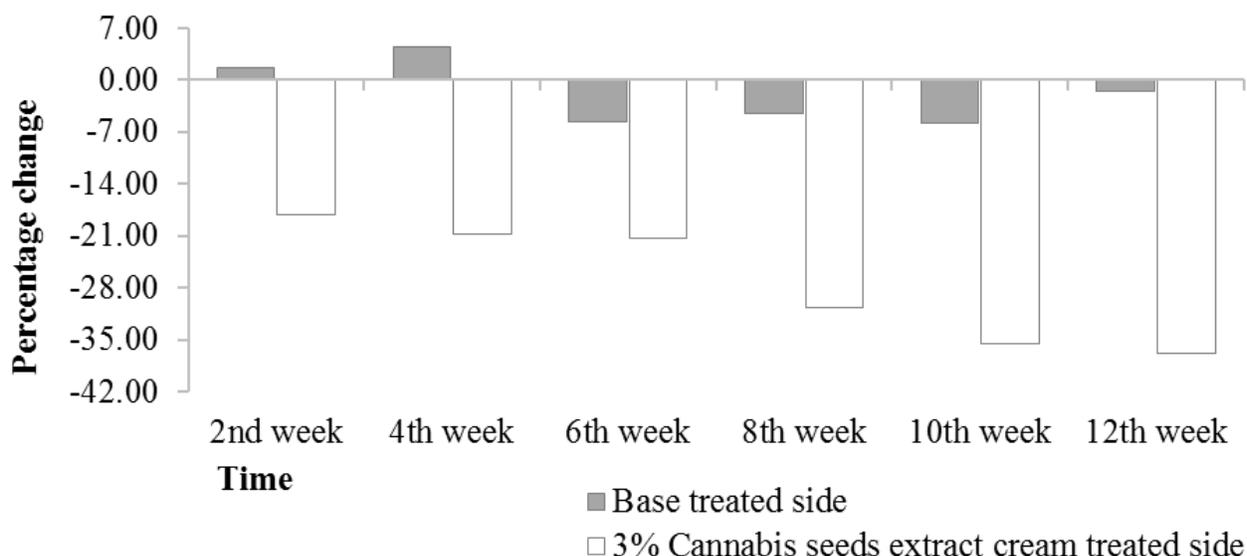


Fig. 2: Change (%) in skin sebum values with base treated side and 3% Cannabis seeds extract cream treated side

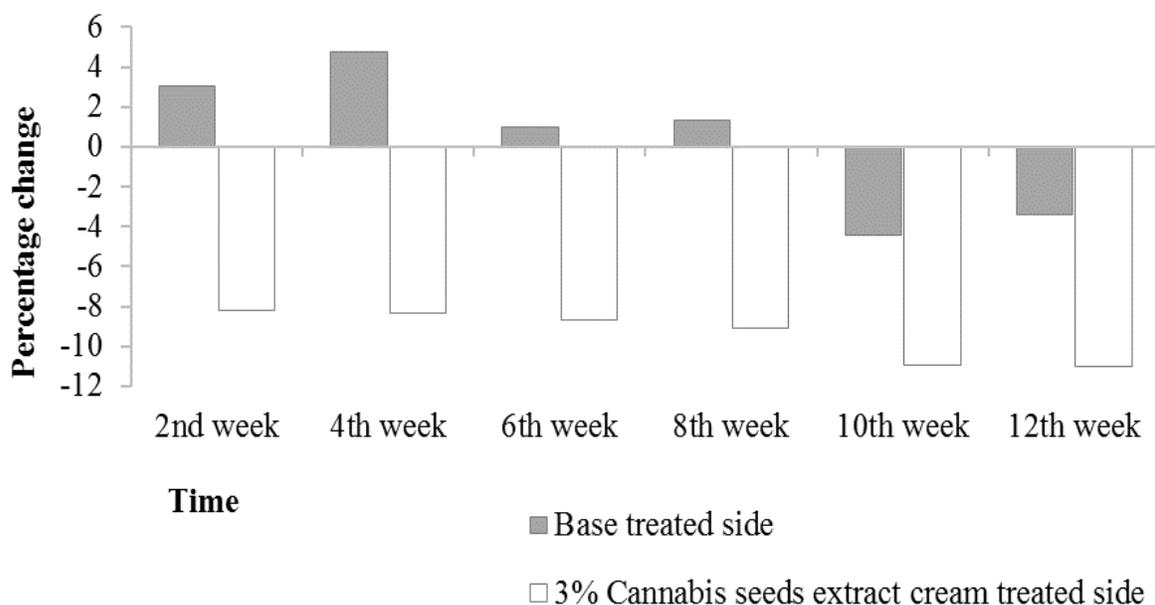


Fig. 3: Change (%) in skin erythema values with base treated side and 3% Cannabis seeds extract cream treated side

The percent change with respect to time in skin erythema with base treated side and 3% Cannabis seeds extract cream treated side has been presented in fig. 3. Mean skin erythema values, standard deviation and standard errors are given in table 3. It was found that there was gradual decrease in skin erythema values to 12th weeks. With the help of ANOVA test, it was found that changes in erythema values produced by 3% Cannabis seeds extract cream treated side were significant and base treated side were insignificant with respect to time. When the paired sample t-test was applied, it was found that the base

treated side and 3% Cannabis seeds extract cream treated side showed significant variations regarding skin erythema values with respect to time.

For efficacy assessment, average points for each parameter were shown in table 4 for both base and 3% Cannabis seeds extract cream. It was found from paired sample t-test that there was an insignificant difference between the average points of sensitivity for base and their respective 3% Cannabis seeds extract cream at different time intervals. All statistical evaluations are provided in table 5.

DISCUSSION

Phenolic compounds extensively occurring in the plant kingdom have been stated to influence strong antioxidant activity (Sultana *et al.*, 2009) and it is expected that the activity of the extract may be due to these compounds (Almeida *et al.*, 2008). The change in absorbency made by reduced DPPH was expended to assess the antioxidant ability of the plant extract and cream containing CS extract. The result behaved strong antioxidant activities.

Assessment of irritancy was centered on ocular scoring. This assessment can be a sensitive, trustworthy and reproducible method. Patch testing after a single application is a widely used method to assess irritant reactions (Gaspa *et al.*, 2008). The mean skin erythema values on forearms before application of the base and 3% Cannabis seeds extract cream were found to be 431.64 and 533.45 respectively. After 48 hours, the mean skin erythema values on forearms after application of base and 3% Cannabis seeds extract cream were found to be 428.18 and 528.45.

No irritant or allergic reactions were documented during the test period. So 3% Cannabis Seeds Extract cream can be used safely on human skin for *in vivo* evaluation.

Androgens receptors and 5- α -reductase are responsible for conversion of testosterone into dihydrotestosterone (the most active form stimulating skin sebum secretion) (Ali *et al.*, 2012). One of the reason behind to increase the sebum secretion is dihydrotestosterone DHT is a testosterone metabolite synthesized with the use of 5- α -reductase type I (Wójcik *et al.*, 2011).

The mean skin sebum values on baseline visit of the base treated side and 3% Cannabis seeds extract cream treated side were found to be 73.88 and 74.09 respectively. At the end of study, the mean skin sebum values on human cheeks base treated side were found to be 62.77 with variable tendency. Whereas the mean skin sebum values on human cheeks 3% Cannabis seeds extract cream treated side were observed decreasing gradually. At the end of study, the mean skin sebum values on human cheeks 3% Cannabis seeds extract cream treated side were found to be 46.00.

Many botanical compounds are thought to inhibit 5- α -reductase, like Saw palmetto extract, essential fatty acids (α -linolenic acid, γ -linolenic acid, linoleic and oleic acids), and phytosterols (β -sitosterol) (Dobrev, 2006; Zaman *et al.*, 2012). These constituents have the ability to inhibit the enzyme 5- α -reductase, which may inhibit the excessive skin sebum secretion. It is assumed that these constituents are present in Cannabis seeds extract so they may be responsible to attribute for the decrease of skin sebum values with application of 3% Cannabis seeds extract cream.

The inflammatory reaction behind acute UV irradiation and the degenerative progressions accompanying to chronic UV radiation skin experience are principally facilitated by the over-production of reactive oxygen species (Almeida *et al.*, 2008; Bissett, 2009). The mean skin erythema at baseline visit of the base treated side and 3% Cannabis seeds extract cream treated side were found to be 523.45 and 412.09 respectively. At the end of study, the mean erythema values on human cheeks with base treated side were found to be 501.00 with variable tendency. Whereas the mean skin erythema values with 3% Cannabis seeds extract cream treated side were observed decreasing gradually. At the end of study, the mean skin erythema values with 3% Cannabis seeds extract cream treated found were found to be 364.

UV- tempted oxidative stress, skin inflammation and DNA damage etc., with a focus on mechanisms underlying the CB_{1/2} double knockout display attenuated UVB-induced skin inflammation (Tamas *et al.*, 2009). Decline in erythema level provided the evidence against inflammation, which leads to collagen efficiency and offer protection against photo-damage in our results after application of 3% Cannabis seeds extract cream.

For efficacy assessment, it was disclosed that there was no immense variation between base and 3% Cannabis seeds extract cream regarding the irritancy evaluation. Both of the creams have similar performance. It is reported subjective analysis of applications after panel test, cream provided acceptable and appropriate for topical use (Gaspar *et al.*, 2008).

CONCLUSION

In conclusion, 3% Cannabis seeds extract cream showed significant efficacy as compared with base alone and it has good tolerability for reduction of skin sebum and erythema content. Most skin diseases are alleged to be connected with oxidative stress, involving psoriasis, and acne. Hence, it is suggested that 3% Cannabis seeds extract cream may speculate the results against acne vulgaris, papules, pustules, acne rosocca, acne infantum, and acne tarda.

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