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Tolerability profile of topical cannabidiol and palmitoylethanolamide: a compilation of single-centre randomized evaluator-blinded clinical and *in vitro* studies in normal skin

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Abstract

Background. An increasing number of studies have investigated the adverse effect profile of oral cannabinoids; however, few studies have provided sufficient data on the tolerability of topical cannabinoids in human participants.

Aim. To assess the tolerability profile of several commercial topical formulations containing cannabidiol (CBD) and palmitoylethanolamide (PEA) on the skin of healthy human participants.

Methods. Three human clinical trials and one *in vitro* study were conducted. The potential for skin irritation, sensitization and phototoxicity of several products, were assessed via patch testing on healthy human skin. The products assessed included two formulations containing CBD and PEA, one containing hemp seed oil and four concentrations of CBD alone. Ocular toxicity was tested using a traditional hen's egg chorioallantoic membrane model with three CBD, PEA and hemp seed oil formulations.

Results. There was no irritation or sensitization of the products evident via patch testing on healthy participants. Additionally, mild phototoxicity of a hemp seed oil product was found at the 48-h time point compared with the negative control. The *in vitro* experiment demonstrated comparable effects of cannabinoid products with historically nonirritating products.

Conclusion. These specific formulations of CBD- and PEA-containing products are nonirritating and nonsensitizing in healthy adults, and further encourage similar research assessing their long-term safety and efficacy in human participants with dermatological diseases. There are some limitations to the study: (i) external validity may be limited as formulations from a single manufacturer were used for this study, while vast heterogeneity exists across unregulated, commercial CBD products on the market; and (ii) products were assessed only on normal, nondiseased human skin, and therefore extrapolation to those with dermatological diseases cannot be assumed.

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Introduction

The impact of topical cannabinoids on skin health and potential anti-inflammatory modulation of the immune system has become a focus of attention as insight into the pathological roles of endogenous cannabinoids has increased.[1–3] Although data from animal studies are

promising, the safety and tolerability of topical cannabinoid-containing products remain largely unexplored in humans.[4]

Cannabidiol (CBD) and hemp oils are extracted from the flowers and leaves of the *Cannabis sativa* (hemp) plant. 'CBD oil' and 'hemp oil' are interchangeable terms to denote products with high levels of CBD and other smaller-quantity phytocannabinoids, but which notably lack intoxicating levels of tetrahydrocannabinol.[5] Hemp seed oil, derived from the plant's seeds, alternatively contains little to no CBD or phytocannabinoids, instead being rich in omega-6 and omega-3 fatty acids, as well as antioxidants.[5] Palmitoylethanolamide (PEA), an endocannabinoid-like lipid used in several topical products, may have analgesic properties and may synergistically enhance the effect of endogenous cannabinoids.[6,7] Using three clinical human studies and a single *in vitro* experiment, we explored the irritation, sensitization and phototoxic potential of products containing CBD, PEA and hemp seed oil.

Methods

The studies were conducted by Princeton Consumer Research Corporation (PCR Corp). Where relevant, aspects of the studies were performed in accordance with the principles of Good Clinical Research Practice. The studies conformed to the requirements of the 1964 Declaration of Helsinki and its subsequent amendments. All participants provided written informed consent before participating in the studies, and were free to withdraw from the study at any time.

Participants

For each clinical study (A, B and C), participants were volunteers recruited at a research centre in Chelmsford, UK. We enrolled health adults aged > 18 years. The exclusion criteria for all studies were: (i) use of any prescribed anti-inflammatory, immunosuppressive or antihistamine medications; (ii) presence of damaged skin (sunburn, tattoos, other disfiguration) or use of topical drugs at patch site; (iii) current skin disease of any type apart from mild acne; (iv) lactation, pregnancy or risk of becoming pregnant; (v) other significant medical history (including immunological disorders, cancer and/or insulin-dependent diabetes). Additional exclusions for Study C were: (i) previous severe phototoxic reactions, current heavy alcohol consumption or use of drugs with increased risk of phototoxicity; and (ii) Fitzpatrick skin types V and VI.

Four distinct studies explored the cutaneous effects of CBD, PEA and hemp seed oil-containing products (Tables 1 and 2), detailed below. Table 3 provides full ingredients lists for each de-identified test product.

For all clinical studies (A, B and C), skin reaction was evaluated on a numerical scale from '0' (no evidence of irritation) to '7' (strong reaction spreading beyond test site) according to the methods of Berger and Bowman.[8] Letter grades were appended to numerical scores to further describe response severity (Table 1). Unless irritation was severe (score ≥ 3), the patch test was reapplied to the same site, with final clinic evaluation on day 22.

Study A: skin irritation

Study A assessed skin irritation using a modified patch testing protocol. Three formulations were evaluated: a gel (1% CBD and PEA), a balm (0.1% CBD and PEA) and a cream (hemp seed oil only, no CBD) (all CQuell, Denver, CO, USA). Study A was unique in also assessing isolated CBD at four concentrations (0.1%, 1%, 5% and 10%) in a simple grapeseed oil vehicle. Patches 20×20 mm in size containing 0.2 mg (solid) or 0.2 mL (liquid) of the tested ingredients were applied to each participant's upper back, on either side of the spine. Saline 0.9% and sodium lauryl sulfate were 0.1% w/v were used as negative and positive controls, respectively. A 21-day cumulative test was conducted with patches applied on Days 1–5, 8–12 and 15–19, while clinic visits were performed daily to assess skin irritation.

Study B: skin irritation and sensitization

Study B explored both skin irritation and sensitization using cutaneous patch testing of the same three formulations (gel, balm and cream) used in Study A. Based on the Study A patch methods, Study B added an induction period followed by a sensitization period. This is a modified Draize protocol, also called the Human Repeated Insult Patch Test (HRIPT), to support consumer-oriented claims such as 'dermatologically tested', 'clinically proven', 'safe for skin' and 'dermatologist approved'.[9–11] Patches were applied and worn for 47 h, and this procedure was repeated for a total of nine inductions with irritation assessed after each induction period. To measure sensitization, participants were given a 14-day rest period following the induction phase and subsequently challenged with a patch application for 48 h, with the area examined

Table 1 Characteristics and results of clinical and experimental studies assessing tolerance profiles of various topical cannabinoid-containing formulations and controls.

Study title	Type of study	Total participants, *N* (*n*, % who completed study)	Irritation scoring	Test products	Irritation score results		Comparisons and summary
					Observed range	Mean (95% CI)	
(A) A 21-day cumulative irritation patch study (modified) in a panel of participants with normal skin	Single-centre, randomized, evaluator-blinded	20 (20, 100%)	Berger and Bowman skin scoring, numerical grade may be appended by letter grade[a]	(1) Gel (1% CBD and PEA)	0–0	0 (0)	No differences in irritation vs. negative control over 21 days for all products
				(2) Cream (hemp seed oil, no CBD)	0–0	0 (0)	
				(3) Balm (0)1% CBD and PEA)	0–0	0 (0)	
				(4) Oil (0)1% CBD)	0–0	0 (0)	
				(5) Oil (1% CBD)	0–0	0 (0)	
				(6) Oil (5% CBD)	0–0	0 (0)	
				(7) Oil 1(0% CBD)	0–0	0 (0)	
				(8) 0.9% saline (negative control)	0–0	0 (0)	
				(9) 0.1% w/v SLS (positive control)	0–3	1.4 (0.4)	Expected irritation response to positive control over 21 days
(B) A modified Draize repeat insult patch test in healthy volunteers, of either sex, to investigate the irritation and sensitization potential of one test article following repeated cutaneous patch applications (Human Repeated Insult Patch Test, HRIPT)	Single-centre, single-blind	57 (53, 93%)	As for Study A	(1) Gel (1% CBD and PEA)	Inductions: 0–1A; challenge 1 h: 0–0a; challenge 48 h: 0–0	Induction patch 7: 0.02 (0.04), induction patch 8: 0.06 (0.06), induction patch 9: 0.06 (0.06), all other patches: 0 (0)	Minimal irritation by test article, no sensitization
		57 (54, 95%)		(2) Cream (hemp seed oil, no CBD)	Inductions: 0–0A; challenge 1 h: 0–0; challenge 48 h: 0–0	All patches: 0 (0)	No irritation by test article, no sensitization
		58 (53, 91%)		(3) Balm (0)1% CBD and PEA)	Inductions: 0–0A; challenge 1 h: 0–0; challenge 48 h: 0–0	All patches: 0 (0)	No irritation by test article, no sensitization

Table 1 continued

Study title	Type of study	Total participants, *N* (*n*, % who completed study)	Irritation scoring	Test products	Irritation score results		Comparisons and summary
					Observed range	Mean (95% CI)	
(C) Study in healthy volunteers to examine the potential for phototoxicity of two sun-protection products when compared with negative controls after the sites are exposed to an artificial 'sun' light source	Evaluator-blinded study using a within-participant randomized design	22 (22, 100%)	As for Study A	(1) Balm (0)1% CBD and PEA) (2) Cream (hemp seed oil, no CBD)	1 h irradiated 0–0; shielded 0–0	1 h irradiated 0 (0); shielded 0 (0)	1 h irradiated vs. shielded NS; balm phototoxicity NS vs. negative control
					24 h irradiated: 0–2; shielded 0–2	24 h irradiated: 0.91 (0.29); shielded 0.82 (0.31)	24 h irradiated vs. shielded NS (two-tailed *t*-test $P = 0.16$, 95% CI 0.12); balm phototoxicity NS vs. negative control ($P = 1$, 95% CI 0.34)
					48 h irradiated: 0–2; shielded 0–2	48 h irradiated: 0.77 (0.26); shielded: 0.73 (0.26)	48 h irradiated vs. shielded NS ($P = 0.33$, 95% CI 0.089); balm phototoxicity NS vs. negative control ($P = 0.06$, 95% CI 0.38)
					72 h irradiated: 0–1; shielded 0–1	72 h irradiated: 0.32 (0.20); shielded 0.23 (0.18)	72 h irradiated vs. shielded NS ($P = 0.16$, 95% CI 0.12); balm phototoxicity NS vs. negative control ($P = 0.10$, 95% CI 0.27)

Table 1 continued

Study title	Type of study	Total participants, *N* (*n*, % who completed study)	Irritation scoring	Test products	Irritation score results		Comparisons and summary
					Observed range	Mean (95% CI)	
					1 h irradiated 0–0; shielded 0–0	1 h irradiated 0 (0); shielded 0 (0)	1 h irradiated vs. shielded NS; cream phototoxicity NS vs. negative control
					24 h irradiated: 0–2; shielded 0–2	24 h irradiated: 0.86 (0.27); shielded 0.73 (0.26)	24 h irradiated vs. shielded NS (P = 0.08, 95% CI 0.15); cream phototoxicity NS vs. negative control (P = 0.77, 95% CI 0.32)
					48 h irradiated: 0–2; shielded 0–2	48 h irradiated: 0.77 (0.26); shielded: 0.73 (0.26)	48 h irradiated vs. shielded NS (P = 0.33, 95% CI 0.09); Cream phototoxicity potentially significant vs. negative control (P = 0.042, 95% CI 0.35)
					72 h irradiated: 0–1; shielded 0–1	72 h irradiated: 0.23 (0.18); shielded 0.18 (0.16)	72 h irradiated vs. shielded NS (P = 0.33, 95% CI 0.089); cream phototoxicity NS vs. negative control (P = 0.19, 95% CI 0.21)

Table 1 continued

Study title	Type of study	Total participants, *N* (*n*, % who completed study)	Irritation scoring	Test products	Irritation score results		Comparisons and summary
					Observed range	Mean (95% CI)	
				(3) 0.9% saline (negative control)	1 h irradiated 0–0; shielded 0–0	1 h irradiated 0 (0); shielded 0 (0)	1 h irradiated vs. shielded NS
					24 h irradiated: 0–1; shielded 0–0	24 h irradiated: 0.91 (0.12); shielded 0 (0)	24 h irradiated vs. shielded significant ($P < 0.001$, 95% CI 0.12)
					48 h irradiated: 0–1; shielded 0–0	48 h irradiated: 0.41 (0.21); shielded 0 (0)	48 h irradiated vs. shielded significant ($P = 0.001$, 95% CI 0.21)
					72 h irradiated: 0–1; shielded 0–0	72 h irradiated: 0.09 (0.12); shielded 0 (0)	72 h irradiated vs. shielded NS ($P = 0.16$, 95% CI 0.12)
(D) The hen's egg test: utilizing the chorioallantoic membrane (HET-CAM)	*In vitro* experimental	36 CAMs (36, 100%)	Observed CAM reaction[13] type[b]	(1a) Gel (1% CBD and PEA)	1–3	2.5 (1.0)	Practically no ocular irritation potential *in vivo*. No differences vs. negative controls
				(1b) L'Oréal cream (negative control)	0–5	2.75 (2.02)	–
(1c) Alpha hydrox lotion (negative control)	1–1	1 (n/a)	–				
				(2a) Cream (hemp seed oil, no CBD)	0–0	0 (0)	Practically no ocular irritation potential *in vivo*. No differences vs. negative controls
				(2b) Lancôme Niosome (negative control)	1–3	2.5 (1.0)	–

Table 1 continued

Study title	Type of study	Total participants, *N* (*n*, % who completed study)	Irritation scoring	Test products	Irritation score results		Comparisons and summary
					Observed range	Mean (95% CI)	
				(2c) Lancôme Noctosome (negative control)	1–3	2.0 (1.1)	–
				(3a) Balm (0.1% CBD and PEA)	1–3	2.5 (1.0)	Practically no ocular irritation potential *in vivo*. No differences vs. negative controls
				(3b) Nivea Lotion (negative control)	1–1	1 (n/a)	–
				(3c) Vaseline Dermatology Lotion (negative control)	1–5	2.00 (1.96)	–

CAM, chorioallantoic membrane; CBD, cannabidiol; NS, not significant; PEA, palmitoylethanolamide; SLS, sodium lauryl sulfate. [a]Berger and Bowman[1] score: numerical grade: 0, no evidence of irritation; 1, slight, confluent or patchy erythema, barely perceptible; 2, definite erythema, readily visible; or minimal oedema; or minimal papular response; 3, erythema and papules; 4, definite oedema; 5, erythema, oedema and papules; 6, vesicular eruption; 7, strong reaction spreading beyond test site; letter grades (numerical equivalent); A (0), slight glazed appearance; B (1), marked glazing; C (2), glazing with peeling and cracking; F (3), glazing with fissures; G (3), film of dried serous exudate covering all or portion of the patch site; H (3), small petechial erosions and/or scabs. [b]Score at 0.5/2/5 min: hyperaemia (5/3/1); minimal haemorrhage or 'feathering' (7/5/3); haemorrhage or obvious leakage (9/7/5); coagulation or thrombosis (11/9/7). Numerical time-dependent scores were summed for each CAM. Each reaction type can be recorded only once for each CAM, with the maximum score being 5 + 7 + 9 + 11 = 32. Average scores for each test article over four CAMs were then classified as follows: 0.0–4.0, practically no irritation; 5–9.9, slight irritation; 10.0–14.9, moderate irritation; and 15.0–32.0, severe irritation.

at 1 and 48 h post-removal. As per the HRIPT protocol, Study B was a single-blind study.

Study C: phototoxicity

Study C investigated the phototoxicity of two of the aforementioned formulations (balm and cream) using ultraviolet (UV)A irradiation following application of the products.

For each patient, we measured their minimal erythema dose (MED), defined as the UV exposure that produces a just-noticeable erythema following full-spectrum irradiation on the back. Individuals with mean MED $\leq$ 1.67 times the standard erythema dose[12] were excluded; participants showing no reactivity remained eligible.

Simultaneous testing of four patches [0.2 mL balm, 0.2 mL cream, negative control (sodium chloride 0.9%) and placebo (saline)] was performed by placing the patches on each participant's back with duplicates on either side of the spine, giving a total of eight patches. The patches were removed after 24 h. For each participant, one side of the back was randomized to receive a total combined dose of UVA irradiation (16.5 J/cm^2) while the other side was shielded as a within-participant control. Blinded reviewers assessed each site for erythema and irritation, 1, 24, 48 and 72 h, post-irradiation. Paired two-tailed *t*-tests examined differences in assessment between the irradiated vs. shielded sites, as well as the phototoxic potential of the test articles compared with negative controls.

Study D: *in vitro* toxicity

Study D was an *in vitro* experiment assessing irritation of hen's egg chorioallantoic membrane (CAM) with testing of the same gel, balm and cream products used in the clinical studies against historically nonirritating control products (Table 1). This test provides a corollary for potential *in vivo* ocular toxicity and has been validated as a sensitive methodology to measure the irritant potential of medications and cosmetics.[13]

Eggs were incubated at 37 °C for 10 days, then incised at the air-sac level to expose the shell-membrane junction. The inner egg membrane was then hydrated and removed, leaving an intact CAM. The gel, balm or cream, dosed at 0.3 g (solid) or 0.3 mL (liquid), was administered to individual CAMs for 20 s. Physiological saline was used to rinse off any residual product and CAMs were evaluated at 30 s, 2 min and 5 min following exposure. Steps were repeated for a total of four CAMs per product.

CAM reactions (including irritant effects on blood vessels, capillaries and albumin) to the tested products were scored and compared with historically nonirritating controls. Scoring was based on hyperaemia and degree of blood vessel damage. Specific numerical time-dependent scores were summed for each CAM (maximum score 32 points; Table 1). Mean scores for similarly tested CAMs were classified as follows: 0.0–4.0, practically no irritation; 5–9.9, slight irritation; 10.0–14.9, moderate irritation; and 15.0–32.0, severe irritation.

Results

Study A: skin irritation

In Study A, patch test irritation was assessed for 20 participants (Table 2) for the gel, balm and cream, as well as four concentrations (0.1%, 1%, 5% and 10%) of isolated CBD in oil (Table 2). Over a 21-day period, the mean irritation scores of the saline negative control and all seven tested products were 0, indicating no evidence of irritancy. As expected, the positive control sodium lauryl sulfate yielded a slight irritant response, with a mean score of 1.4 (Table 1).

Study B: skin irritation and sensitization

In total, 160 separate participants completed patch testing with the irritation and sensitization protocol (Table 2) for the gel, balm and cream.

For the gel (1% CBD and PEA), most participants scored '0' (no evidence of irritation) throughout induction, but three participants (3/53; 6%) demonstrated mild to barely perceptible cutaneous erythema at the sites of induction patches 7, 8 and 9. The mean irritation scores of all participants were therefore 0.02, 0.06 and 0.06 for induction patches 7, 8 and 9, respectively, and 0 for all other patches. Induction irritation scores were uniformly '0' for both the cream and balm, indicating no evidence of irritation with either.

Sensitization did not occur with any of the products in any of the participants, as indicated by the consistent nonirritation scores of '0' after application and the assessment of the challenge patches at 1 and 48 h after the 14-day post-induction rest period.

Study C: phototoxicity

Photopatch testing of the balm and cream was ultimately assessed in 22 participants (Table 2).

Table 2 Demographics of human participants in three clinical studies of topical cannabinoid-containing formulations.

	Demographics						
			Age group, years				
Study title	Total participants, *N* (*n*, % who completed study)	Sex, M/F, *n*	18–20 (M/F)	21–30 (M/F)	31–40 (M/F)	41–50 (M/F)	51–70 (M/F)
(A) A 21-day cumulative irritation patch study (modified) in a panel of participants with normal skin	20 (20, 100%)	7/13	1 (0/1)	9 (4/5)	7 (3/4)	3 (0/3)	0
(B) A modified Draize repeat insult patch test in healthy volunteers, of either sex, to investigate the irritation and sensitization potential of one test article following repeated cutaneous patch applications (Human Repeated Insult Patch Test, HRIPT)	Total: 172 (160, 93%) (1) Gel: 57 (53, 93%) (2) Cream: 57 (54, 95%) (3) Balm: 58 (53, 91%)	61/111 20/37 22/35 19/39	 8 (3/5) 4 (0/4) 3 (0/3)	 20 (8/12) 23 (10/13) 30 (13/17)	 16 (4/12) 18 (9/9) 9 (1/8)	 10 (4/6) 10 (3/7) 10 (4/6)	 3 (1/2) 2 (0/2) 6 (1/5)
(C) A study in healthy volunteers to examine the potential for phototoxicity of two sun-protection products when compared with negative controls after the sites are exposed to an artificial 'sun' light source	22 (22, 100%)	10/8[a]	4 (2/2)	3 (3/0)	6 (3/3)	5 (2/3)	0

[a]Missing demographics from four participants.

After balm application, the mean irritation scores were not significantly different ($P > 0.05$) for irradiated and shielded sites respectively (Table 1). No significant differences ($P > 0.05$) in skin irritation were observed for the balm vs. negative control (0.9% sodium chloride) after irradiation at all time points.

For the cream, the mean irritation scores for irradiated vs. shielded sites were not significantly different. However, in contrast to the observations for the balm (containing 0.1% CBD, PEA and hemp seed oil), the cream (containing hemp seed oil and no CBD) demonstrated a potentially significant increase in phototoxicity compared with the negative control at 48 h post-irradiation ($P = 0.04$); the greatest response for any one participant was a '2' denoting 'definite erythema readily visible, or minimal oedema or minimal popular response'. There were no statistically significant differences in the degree of phototoxicity between the cream and negative control at 1, 24 and 72 h ($P > 0.05$). Notably, irradiation vs. shielding of the negative control alone showed significant differences in irritation scores at 24 h ($P = 0.001$) and 48 h ($P = 0.001$) due to presence of minimal erythema.

Study D: *in vitro* toxicity

Hyperaemia was observed in all four CAMs after gel application (mean score 2.50), similar to the historically nonirritating negative controls (Table 1). The balm formulation also achieved a mean score of 2.50, with hyperaemia detected at the 2- and 5-min intervals. The cream did not result in irritation, scoring 0 for all CAMs at all time points.

Based on the scoring classification system, the irritation potential of the gel, cream and balm were all in the 'practically none' range (0–4.9).

Discussion

To our knowledge, this is the first comprehensive study providing evidence of the tolerability of topical CBD and PEA. Healthy human participants demonstrated no increase in skin irritation or sensitization at varying concentrations of CBD (from 0.1% up to 10%), with no additional differences based on the presence of PEA.

It is interesting to note that mild phototoxic reactions (limited, at 48-h timepoint) were seen for the

Table 3 Complete lists of ingredients for tested topical cannabinoid-containing formulations.

Product formulation	Ingredient list of product[a]
Daily Eczema Cream [Cannabis Sativa (Hemp) seed oil, does not contain CBD]	Active ingredient: Colloidal Oatmeal 1% Other ingredients: Water (Aqua), Petrolatum, Caprylic/Capric Triglyceride, Cetearyl Olivate, Sorbitan Olivate, Caprylyl Methicone, Propanediol, Squalene, Glyceryl Stearate, **Cannabis Sativa (Hemp) Seed Oil**, Caprylyl Glycol, Ethylhexylglycerin, Behenyl Alcohol, Helianthus Annuus (Sunflower) Seed Oil, Carthamus Tinctorius (Safflower) Seed Oil, Benzyl Alcohol, Tocopherol, Cetearyl Alcohol, Hippophae Rhamnoides (Sea Buckthorn) Seed Oil, Xanthan Gum, Sorbitan Stearate, Bisabolol, Disodium EDTA Optional ingredients for pH balancing: Sodium Hydroxide, Citric Acid
Oil (0.1%, 1%, 5%, 10% CBD in Grapeseed Oil Vehicle)	Vitis Vinifera (Grape) Seed Oil, **Cannabis Sativa (Hemp) Oil**, Tocopherol (Vitamin E)
Moisture Locking Balm (0.1% CBD and PEA)	Petrolatum, Caprylyl Methicone, Dimethicone, Polysilicone-11, Dimethicone/Vinyl Dimethicone Crosspolymer, Microcrystalline Wax, **Cannabis Sativa (Hemp) Seed Oil**, Cetyl PEG/PPG-10/1 Dimethicone, **Palmitoylethanolamide (PEA)**, **Cannabis Sativa (Hemp) Oil**, Bisabolol
Spot Treatment Gel (1% CBD and PEA)	Dimethicone Polysilicone-11, Caprylyl Methicone, Dimethicone/Vinyl Dimethicone Crosspolymer, Dimethyl Isosorbide, Caprylic/Capric Triglyceride, Persea Gratissima (Avocado) Oil, PPG-12/SMDI Copolymer, Ethoxydiglycol, **Cannabis Sativa (Hemp) Seed Oil, Palmitoylethanolamide (PEA), Cannabis Sativa (Hemp) Oil,** Oleic Acid, Cetyl PEG/PPG-10/1 Dimethicone, Avena Sativa (Oat) Kernel Flour (Colloidal Oatmeal), Bisabolol

CBD, cannabidiol; NS, not significant; PEA, palmitoylethanolamide. [a]Active ingredients studied are highlighted in **bold**.

cream product featuring hemp seed oil, which contains no detectable CBD or PEA. By contrast, 0.1% CBD, PEA and hemp seed oil in the balm did not result in any observed phototoxicity. Greater concentrations of CBD were not tested for phototoxic potential in our studies.

While essential oils have been shown to be phototoxic (e.g. furanocoumarins), literature reporting on the fatty acids that make up hemp seed oil has not demonstrated phototoxic potential in either animal or human participants,[14] perhaps necessitating further analysis of the other ingredients in the formulation.

Several studies have suggested that the antipruritic, lipostatic and anti-inflammatory effects of CBD- and PEA-containing products have therapeutic potential for inflammatory skin disorders such as atopic dermatitis and acne vulgaris.[2, 3, 15–21] However, the findings extrapolated from our study can only support the tolerability of certain cannabinoid products among healthy participants with nondiseased skin.

There were several limitations to our study. The products tested maintain internal validity (from the same batch and manufacturer, with third party-tested potencies); however, other consumer-available products may vary unreliably in CBD potency and composition due to lack of standard federal regulations,[22] thus rendering experimental reproducibility difficult. Experimental bias is another limitation, due to testing of a small number of healthy participants, although prior studies testing products for skin irritation have used comparable sample sizes.[11,23] Consequently, while our findings serve as promising pilot data to prompt future studies and guide downstream commercialization efforts, it is not yet possible to extrapolate these results to those with damaged, inflamed or otherwise diseased skin or side effects over an extended timeframe.

Conclusion

The data in this study provide support for the tolerability of topical cannabinoid products containing CBD, PEA and hemp seed oil in human participants. In this single-centre, randomized, evaluator-blinded, compilation of human clinical studies and one *in vitro* experiment, we demonstrate that CBD and PEA are nonirritating and nonsensitizing when applied to healthy human skin. Mild phototoxic reaction was present at 48 h for the cream formulation containing hemp seed oil; other low-concentration (0.1%) CBD products demonstrated no significant phototoxicity. Further longitudinal testing of CBD-containing topical agents is required in order to fully characterize the safety profile of these products. This study has demonstrated tolerability of topical cannabinoids on normal human skin, thereby laying the groundwork for future studies to assess applications in diseased skin and as potential therapeutics.

What's already known about this topic?

- Topical cannabinoids are recognized for their anti-inflammatory, lipostatic and antipruritic properties in small preclinical human studies and animal models assessing potential use in treatment of inflammatory skin disorders.
- The anti-inflammatory effects of CBD are mediated through direct modulation of the immune system, while PEA enhances endogenous cannabinoids.
- Current consumer-available products containing cannabinoids are unregulated by the US Food and Drug Administration and have not been adequately assessed for tolerability.

What does this study add?

- Topical cannabinoid products with varying concentrations of CBD (0.1% to 10%) have nonirritating and nonsensitizing effects on the skin of healthy human participants.
- Topical products containing hemp seed oil had mild, self-limited phototoxic potential at 48 h on healthy human skin.
- In an *in vitro* assessment of ocular toxicity, topical cannabinoid products performed with comparable effects to those seen with historically nonirritating products.

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Conflict of interest

RPD is a shareholder and former medical consultant to CQ Science (dba CQuell) (relationship ended 1 August 2020). TS serves as a medical advisor to Antedotum Inc. PL is a Board member and Scientific Advisory Committee Member of the National Eczema Association; reports research grants/funding from AOBiome, Regeneron/Sanofi Genzyme and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, Pfizer, LEO, Eli Lilly, Galderma and L'Oreal; reports consulting/advisory boards for Almirall, ASLAN Pharmaceuticals, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos, L'Oreal, Pierre-Fabre, Johnson & Johnson, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, CQ Science (dba CQuell), Galderma, Arbonne, Amyris, Bodewell and Burt's Bees; has a patent pending for a Theraplex product with royalties paid; and is a shareholder of CQ Science (dba CQuell). HY is a former employee of CQ Science (dba CQuell). JF is co-founder and shareholder of CQ Science (dba CQuell). The remaining authors declare that they have no conflicts of interest.

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