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A therapeutic effect of cbd-enriched ointment in inflammatory skin diseases and cutaneous scars

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Abstract

Objective. To investigate the therapeutic effect of CBD-ointment administered on severe skin chronic diseases and/or on their outcome scars.

Methods. A spontaneous, anecdotal, retrospective study of 20 patients with two most frequent skin disorders: psoriasis (n: 5 patients), atopic dermatitis (n: 5) and resulting outcome scars (n: 10). The subjects were instructed to administer topical CBD-enriched ointment to lesioned skin areas twice daily for three months treatment.

Results. Based on skin evaluations (hydration, TEWL, elasticity), clinical questionnaires (SCORAD, ADI, PASI), and supported by photographic data and investigators' clinical assessment, the results showed that topical treatment with CBD-enriched ointment significantly improved the skin parameters, the symptoms and also the PASI index score. No irritant or allergic reactions were documented during the period treatment.

Conclusions. The topical administration of CBD ointment, without any THC, is a safe and effective non-invasive alternative for improve the quality of life in patients with some skin disorders, especially on inflammatory background. ***Clin Ter 2019; 170(2):e?-?. doi: 10.7417/CT.2019.????***

Key words: *CBD, ointment, skin, quality of life*

Introduction

Several chronic inflammatory skin disorders, including atopic dermatitis (or eczema), psoriasis, cutaneous infections, and familial cold autoinflammatory syndrome reduce significantly the patients' quality of life, health outcomes and work productivity **(Kimball et al. 2010, Senra and Wollenberg 2014, Chisari et al. 2018, Fallari et al. 2016)**. Atopic dermatitis (AD) affects 15-30% of children **(Shaw et al. 2011, Bieber 2010)** and 1-8% of adults, it is characterized by recurrent and often excoriated erythematous patches (papules), associated with severe itching **(Guttman-Yassky, Nograles and Krueger 2011, Leung and Guttman-Yassky 2014)**. The pathogenesis of AD is not fully understood: skin barrier defects driven by a combination of genetic and environmental factors (allergen exposure, stress, colonization or infection of the skin with *Staphylococcus aureus* or *herpes simplex virus*), and immune dysregulation (epidermal intercellular edema, increased numbers of IgE-bearing Langerhans cells, inflammatory dendritic epidermal cells, macrophages, eosinophils, and CD4-activated TH2 cells) have been implicated **(Leung and Guttman-Yassky 2014, Wananukul et al. 2015, Nomura et al. 2003, Leung 2000)**. AD is often accompanied by allergic rhinitis (75% of children), asthma (15-50%), and food allergy, as well as conjunctivitis **(Wananukul et al. 2015, Simpson 2012)**. In contrast, the clinical picture of psoriasis presents erythematous, well-demarcated red plaques covered with white scales on the scalp, lower back, and extensor aspects of the elbows and knees, associated with severe pruritus and changes in fingernails and toenails **(Nickoloff 2001, Guttman-Yassky et al. 2011)**. The prevalence of psoriasis, occurred more frequently in women than men, is 0-2% in children and 1-9% in adults. It is characterized by the presence of neutrophil overactivation and overproduction of interleukin (IL)-6 and IL-8 from keratinocytes **(Komine and Tamaki 2000, Iannaccone et al 2016)**. The main triggers for psoriasis exacerbations are 1) environmental factors, including weight gain, smoking, alcohol consumption, stress, withdrawal of corticosteroids, HIV infection, and the use of medications such as lithium, beta-blockers, or antimalarial agents **(Parisi et al. 2013, Roberson and Bowcock 2010)**, 2) microbial factors, (fungi and viruses), e.g. a streptococcal throat infection **(Valdimarsson, Sigmundsdottir and Jonsdottir 1997, Prinz 2001)**, and 3) immune response dysregulation, including epidermal hyperplasia and altered keratinocyte differentiation **(XSun L. 2014, Lowes, Suarez-Farinas and Krueger 2014)**. Both the skin disorders share common mechanisms of disease, including infiltration of circulating immune cells in the skin **(Guttman-Yassky et al. 2007)**, altered expression of proinflammatory cytokines **(Nomura et al. 2003)**, and variable barrier alterations **(Fartasch 1997)**, and can be recognized as systemic rather than localized cutaneous diseases because skin inflammation is often complicated by metabolic, cardiovascular and other comorbidities **(Kim and Krueger 2017, Mansouri and Guttman-Yassky 2015)**. Other chronic inflammatory skin disease is acne vulgaris, resulting from androgen-induced

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increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles on the face, neck, chest, and back by *Propionibacterium acnes*, and it has a prevalence of 90% among adolescents and 10-15% in adults **(Bhate and Williams 2013, Thiboutot et al. 2009)**. These inflammatory acne lesions can result in permanent disfiguring sequelae (acne scars), that can be classified in two basic types: atrophic and hypertrophic scars, depending on whether there is a net loss or gain of collagen **(Fabbrocini et al. 2010)**. Regard the prevalence, minor scarrings occur in up to 95% of the patients, while more severe scarrings occur in up to 22% of patients (mostly aged 25-44 years) **(Layton, Henderson and Cunliffe 1994)**.

The traditional systemic treatments (e.g. methotrexate, cyclosporine for psoriasis) present often some limitations, including cumulative toxicity of target organs and potential drug interactions **(McClure, Valentine and Gordon 2002, Christophers et al. 2006, Ferrandiz, Carrascosa and Boada 2010).** In recent years, several researchers analyzed the use of cannabinoids in the treatment of these dermatologic disorders, including also melanoma and nonmelanoma skin cancer, melasma, and seborrheic dermatitis, and reported its anti-inflammatory properties and inhibitory effect on rapidly proliferating tumorigenic cell lines **(Mounessa et al. 2017, Kogan 2005)**.

The cannabinoids or phytocannabinoids, e.g. cannabidiol (CBD), cannabichromene (CBC), cannabigerol (CBG), cannabinol (CBN) and delta (9)-tetrahydrocannabinol (Δ^9 -THC), are the active constituents of the plant *Cannabis sativa*, and elicit their activity by binding to specific receptors: the CB1 and CB2 cannabinoid receptors [found on neurons and glial cells and in spleen tissue, respectively **(Van Sickle et al. 2005, Munro, Thomas and Abu-Shaar 1993)**] that are part of the G-protein coupled class and their activation results in inhibition of adenylate cyclase activity **(Baker et al. 2003, Iversen 2003, Di Marzo, Bifulco and De Petrocellis 2004)**.

However, the CBD exerts multiple pharmacological actions via no-CB1 and no-CB2 receptors, but by binding transient receptor potential vanilloid type 1 (TRPV1) **(Costa et al. 2004)**, G protein-coupled receptor 55 (GPR55) **(Pertwee et al. 2010, Pertwee 2007)**, and 5-hydroxytryptamine receptor subtype 1A (5-HT1A) **(Russo et al. 2005)**.

Currently, CBD is a widespread ingredient in skin care products formulated as body oils, moisturizers, lotions and lip balms **(Anwar F. 2006)**, but scientific studies on topical safety and efficacy of this extract are lacking.

Therefore, we investigated, in spontaneous, anecdotal, retrospective study, the therapeutic effect of CBD-ointment administered on severe skin chronic diseases and/or on their outcome scars.

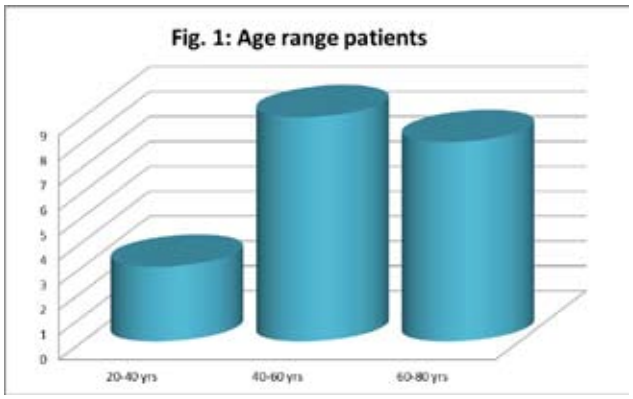
Materials and methods

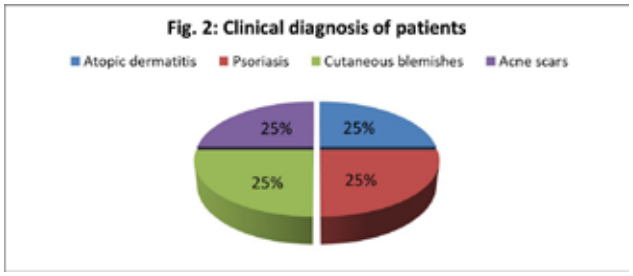
We reviewed medical records (electronic or paper-based) of 20 patients that had appealed to our "Second Opinion Medical Consulting Network", Medical Centre (Modena, Italy), between September 2016 and January 2017, because of inflammatory skin disorders and cutaneous scars/blemishes. The Second Opinion Medical Network is a consultation referral web and Medical Office System recruiting suddenly a wide panel of real-time available specialists, to whom any patient affected by any disease or syndrome and not adequately satisfied by the diagnosis or therapy can apply for an individual clinical audit **(Wunsch A. 2013)**. Due to the doctor-patient communication gap, most of the patients usually wander around the medical websites looking for proper answers to their health problems. However, their search often becomes compulsive and obsessive and often ambiguous and frustrating **(Palmieri B. 2017)**. Palmieri et al. **(Palmieri et al. 2011)** describe this borderline or even pathological behaviour as the "Web Babel Syndrome" – a psychological imbalance affecting young and elderly patients, especially those with multiple synchronous diseases who receive from their caregivers heterogeneous and misleading informations or advices, including confused, contradictory statements and prescriptions **(Palmieri and Iannitti 2011)**. To deal with this problem, the Second Opinion Network aims to be a useful "problem-solving" support revisiting each diagnostic and therapeutic step and properly re-addressing tailored treatments and prognoses, as well as preventing unnecessary investigational procedures and unhelpful and expensive medical and surgical interventions **(Di Cerbo and Palmieri 2012)**.

In this preliminary investigation, we adopted selective inclusion criteria: 1) suffering from moderate/severe skin disorders for at least 6 months and seeking an effective, adequate therapy; and specific exclusion criteria: 1) pregnant or breastfeeding women, 2) topical medication containing steroids for the treatment of skin disease for at least one month, 3) skin intolerance/allergies to the components of product used in the study.

Twenty volunteers (14 females and 6 males) between 20 and 80 years of age **(Fig. 1)**, were visited and informed during a personal interview, gave their permission, and signed an informed consent previously approved by the Local Institutional Review Board, in accordance with the Helsinki Declaration. These patients were complaining of the two most frequent skin disorders: psoriasis (n: 5 patients), atopic dermatitis (n: 5) and resulting scars (n: 10) **(Fig.2)**. The product, hemptouch organic skin care ointment (Hemptouch Ltd, Novo mesto, Slovenia) contained CBD seed oil and natural ingredients, including *Mangifera Indica, Calendula officinalis*, *Lavendula officinalis, Chamomile, Amyris Balsamifera*, and butyrospermum (shea butter) (**Tab.1**) The subjects were instructed to administer topical ointment to lesioned skin areas twice daily, in morning and evening, for three months treatment. During this period, the patients not utilized any skin care product. We performed the following skin evaluations:

a) Hydration and transepidermal water loss (TEWL) assessment at baseline and after three months treatment with a DermaLab® USB instrument (Cortex Technologies, Hadsund, Denmark), this Point of care (POCT) with hydration probe, that is pressed upon the skin, relies upon the conductance principle, which measures the water binding capacity of the stratum corneum **(Laurino, Palmieri and Coacci 2015)**. TEWL is defined, instead, as a measurement of the quantity of water that passes from inside a body through the epidermal layer to the surrounding atmosphere via diffusion





Tab. 1. Components of skin care ointment 50 ml/1.69 floz.

Composition of CBD-ointment	
Component	Concentration mg/ml
Mangifera Indica	N/A
Calendula officinalis	N/A
Lavendula officinalis	N/A
Chamomile	N/A
Amyris Balsamifera	N/A

and evaporation processes, which is physiologically reduced during age **(Elias 2005)**.

b) Elasticity assessment at day 0 and day 90 with ElastiMeter® (Delfin Technologies, Kuopio, Finland), it was measured as stiffness, a physical measure of an object's resistance to change in shape under an external force in N/m. The device consists of a 1 mm length indenter, a reference plate and built-in force sensors. The probe head is quickly pressed against the skin surface with a recommended standard pressure that is displayed on the screen. The indenter induces a constant deformation when the reference plate is in full contact with the skin, and the elasticity is determined by the skin resistance to this deformation **(Iivarinen, Korhonen and Jurvelin 2014)**.

c) Photographic assessment at baseline (day 0), day 30, day 60 and day 90.

d) We also use several questionnaires to evaluate the degree of the symptoms, including Scoring Atopic Dermatitis (SCORAD) index for atopic dermatitis, Acne disability Index (ADI) for acne, and Psoriasis Area Severity Index (PASI), index used to express the severity of psoriasis.

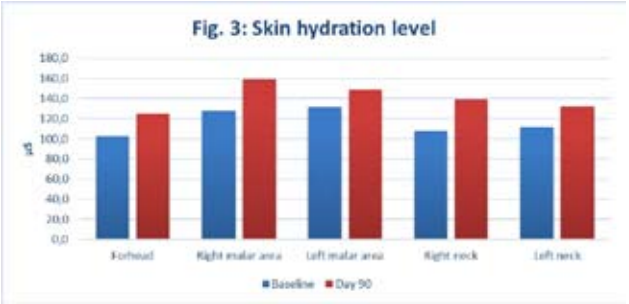
Skin parameters were measured on five selected areas: forehead (F), right and left malar area (RMA and LMA, respectively), and right and left lateral-medial area of the neck (RN and LN, respectively). We assessed also the elasticity of the forearm (FO) as control, according to the manufacturer's instructions, since skin arm elasticity changes less quickly then skin face elasticity. The value of hydration [(expressed in microSiemens units (μS)], TEWL (measured by diffusion gradient in g/m^2/h) and elasticity (expressed in μS) is the arithmetic mean of 3-5 repetitive measures in the same area.

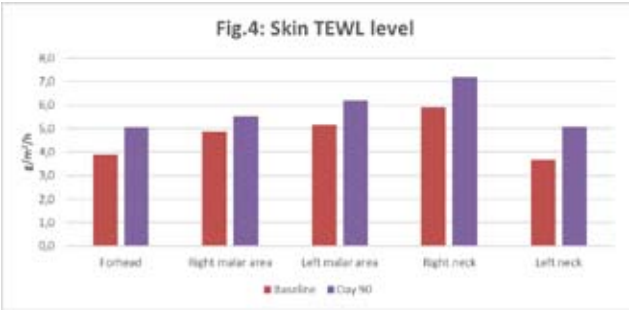
Statistical analysis

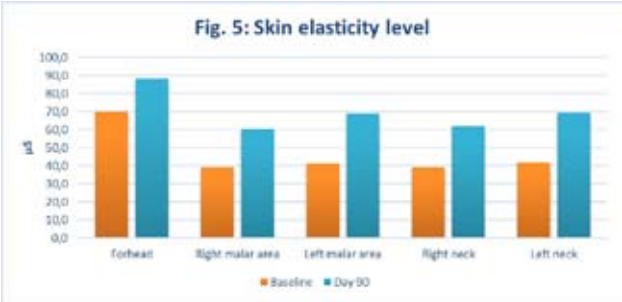
The statistical analysis was performed using the Mann-Whitney test (continuous variables not normally distributed) and the chi-squared test (categorical variables). Statistical significance was set at a P value < 0.05, and all data and graphics were analyzed using the R software, version 3.1.2 (2015, Vienna, Austria) **(RA. 2015)**.

Results

After a treatment period of three months, the evaluated skin parameters significantly improved in all the patients. Specifically, the hydration ($p< 0.01$) increased of 6.9% in F area, 6.1% in RMA, 6.5% in LMA, 6.8% in RN and 5.5% in LN **(Fig.3)**. TEWL also significantly improved ($p < 0.001$) in these selected sites: increase of 28.1% in F area, 20.7% in RMA, 23.7% in LMA, 17.6% in RN and of 24.7% in LN **(Fig.4)**. At last, elasticity ($p < 0.001$) improved of 17.1% in F field, 27.1% in RMA, 23.2% in LMA, 22.9% in RN







and of 26.1% in LN area **(Fig.5)**. Unretouched photos taken before treatment and after 12 weeks of treatment showed a significant reduction of major signs of cutaneous blemishes in a woman (73 aa) and of scar due a cyst removal surgery in the men (78 aa), confirming significant improvement in these symptoms and none experiencing worsening **(Fig. 6-8)**. Additionally, we recorded reductions in the numbers of papules (−20%), pustules (−31%) in dermatological patients. The topical ointment was significantly ($p< 0.001$) efficacious in improving also PASI index score (excluding the head, which was not treated) at day 90.

Fig. 6-8: Photography of cutaneous blemishes (sunspots) on the right leg (Fig.6), and right arm (Fig.7) of the patient (woman, 73 aa), and scar (Fig.8) due a cyst removal surgery (men, 78aa) before and after 3 consecutive months of twice-daily application of the study cream.

Discussion

Several studies evidenced that topical route of CBD administration represents significant therapeutic tool in the treatment of chronic conditions, encephalomyelitis (EAE), multiple sclerosis (MS), with less side effects because due to

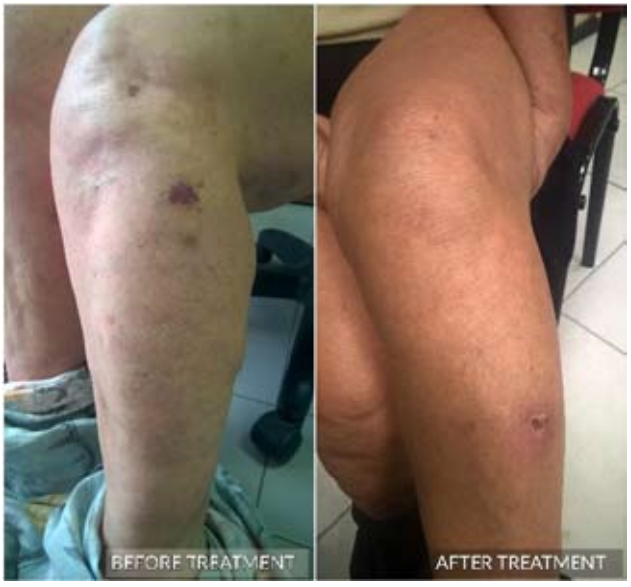


Fig. 6

Fig. 7

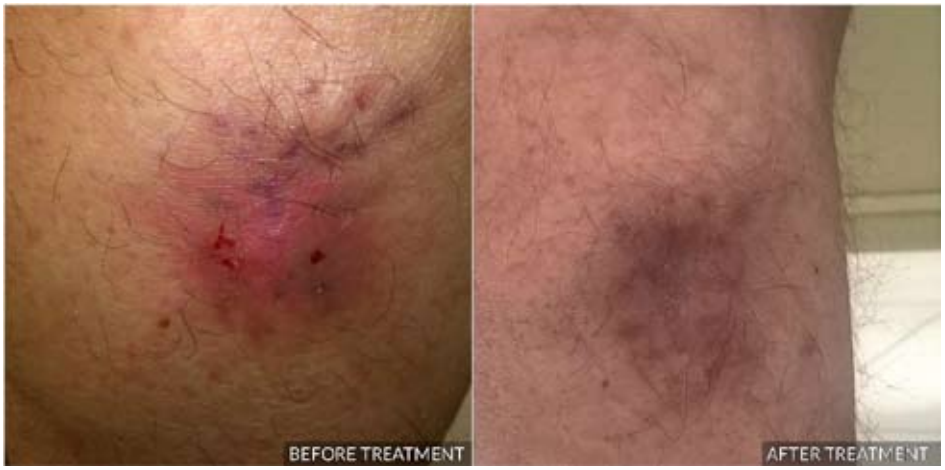


Fig. 8

the lower peak plasma levels **(Lodzki et al. 2003, Touitou E 1988)**. For istance, Giacoppo et al, showed that a preparation of 1% CBD-cream reduces the expression of Nitrotyrosine (iNOS) in tissues from EAE treated C57BL/6 mice, suggesting that plant-derived cannabinoids (CBD, THC, CBN), may be responsible for the reduction of cytokines production, that in turn counteract the rise of iNOS levels and the downstream cascade of events triggered by the inflammatory process, reducing thus oxidative stress **(Giacoppo et al. 2015)**. Indeed, published studies evidenced that THC may inhibite the proliferation of mouse lymphocytes and decrease the production of interleukin-2 (IL-2) and interferon-c (IFNc) **(Klein et al. 2000, Klein, Newton and Friedman 2001, Klein et al. 1985)**; but also may reduce the secretion of pro-inflammatory cytokines like IL-1a, IL-1b and tumor necrosis factor-alpha (TNFa) in microglial cells. In another study, CBD and CBN were shown to exert a suppressive effect on human keratinocyte proliferation. Here, the synthetic CB receptor agonists HU-210, a structural analogue of THC, displayed an inhibitory effect on cell proliferation, clearly confirming the anti-inflammatory activity of the cannabinoids beyond its interaction with specific CB1 and CB2 receptors. This is reminiscent of palmitolylethanolamide (PEA), an endogenous fatty acid with cannabimimetic properties that attenuates skin inflammation, although it does not bind to CB1 or CB2 receptor **(Stander, Reinhardt and Luger 2006, Jordt et al. 2004)**.

Our results showed that topical treatment with CBD-enriched ointment significantly improved the quality of life of patients with several skin diseases.

The mean skin elasticity level on baseline visit was 46 μs, whereas at the end of study, the same value was increased gradually (70 μs). This effect may be due to essential fatty acids, including α- linolenic acid, γ-linolenic acid, linoleic and oleic acids, and phytosterols (β-sitosterol) **(Dobrev 2007, Zaman S 2012)**, present in the used topical cream, that may inhibit the enzyme 5-α-reductase, subsequently inhibiting the excessive skin sebum secretion and improving elasticity and hydration.

No irritant or allergic reactions were documented during the period treatment. A topical product also improved severity of itch and loss of sleep in the AD patients. Gaffal et al, demonstrated that CBD application may attenuate ovalbumin-induced allergic airway inflammation in experimental mouse model of atopic dermatitis (C57Bl/6 mice) as indicated by a reduced number of lung-infiltrating immune cells and of the serum IgE and IgG levels **(Gaffal et al. 2013)**.

We observed also antiproliferative and antinflammatory effects of CBD treatment in patients with acne scars. These effects could be associated to specific sebostatic actions of CBD: a) normalize the pathologically elevated lipogenesis induced by "pro-acne" agents, b) suppresse cell proliferation and c) prevent the actions of toll-like receptor (TLR) activation or "pro-acne" agents to elevate proinflammatory cytokine levels **(Olah et al. 2014)**. This is especially promising, because the currently available,anti-acne agent, isotretinoin (accutane), is known to cause serious side effects, including hypertriglyceridemia, hepatotoxicity, and mood changes, e.g depression and psychosis **(Kurokawa et al. 2009, Ellis and Krach 2001, Rigopoulos, Larios and Katsambas 2010).**

Our results showed clearly that cannabinoids inhibited the proliferation of keratinocytes, thus demonstrating a therapeutic potential as well for the treatment of psoriasis, but further investigation is urgently needed to identify its actions mechanism. To date, the literature on human CBD safety and pharmacokinetics is lacking, however, given the extensively documented accumulation of phytocannabinoids from smoked cannabis in the pilosebaceous unit (e.g hair, sebaceous gland) **(Kintz, Cirimele and Mangin 1995, Skopp et al. 2007)**, it is expected that CBD, due to its high lipophilicity, may reach and accumulate in the sebaceous glands, via the transfollicular route **(Lodzki et al. 2003, Tubaro et al. 2010, Hueber, Wepierre and Schaefer 1992)**. This accumulation is been evidenced for several topically applied lipophilic compounds, including steroid hormones, photosensitizers **(Hueber et al. 1992, Togsverd-Bo K 2012)**.

Main limitations of our study include the uncontrolled and retrospective design study and the small clinically heterogeneous cohort.

Conclusions

The topical administration of CBD ointment, without any THC, is a safe and effective non invasive alternative for improve the quality of life in patients with some skin disorders, especially on inflammatory background.

In a next future, further trials on safety, tolerability and efficacy of topical cannabinoids combining CBD and THC but also cannabis terpenes and other plant extracts, would give us definite informatons about the most effective integrated formula of this sort of panacea in the dermatological setting.

References

Anwar F, Latif S, Ashraf M. Analytical characterization of hemp (Cannabis sativa) seed oil from different agro-ecological zones of Pakistan. Journal of the American Oil Chemists' Society, 2006; 83:323-9

Baker D, Pryce G, Giovannoni G, et al. The therapeutic potential of cannabis. Lancet Neurol. 2003; 2(5):291-8

Bhate K, Williams HC. Epidemiology of acne vulgaris. Br J Dermatol. 2013 Mar;168(3):474-85

Bieber T. Atopic dermatitis. Ann Dermatol. 2010; 22(2):125-37

Chisari G, Chisari EM, Borzì AM, et al. Etiology of chronic skin lesions in subjects with peripheral arterial disease. Clin Ter. 2018; 169(2):e51-e57

Christophers E, Griffiths CE, Gaitanis G, et al. The unmet treatment need for moderate to severe psoriasis: results of a survey and chart review. J Eur Acad Dermatol Venereol. 2006; 20 (8): 921-5.

Costa B, Giagnoni G, Franke C, et al. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br J Pharmacol. 2004;143(2):247-50

Di Cerbo A, Palmieri B. The economic impact of second opinion in pathology. Saudi Med J. 2012; 33(10):1051-2

Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov. 2004; 3(9):771-84

Dobrev H. Clinical and instrumental study of the efficacy of a new sebum control cream. J Cosmet Dermatol 2007; 6(2):113-8

Elias PM. Stratum corneum defensive functions: an integrated view. J Invest Dermatol. 2005; 125(2):183-200

Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. J Am Acad Dermatol. 2001; 45(5):S150-7

Fabbrocini G, Annunziata MC, D'Arco V. Acne scars: pathogenesis, classification and treatment. Dermatol Res Pract. 2010; 2010:893080

Fallahi P, Ruffilli I. Contact dermatitis and interferon-γ dependent chemokines. Clin Ter. 2016;167(5):e112-e116

Fartasch M. Epidermal barrier in disorders of the skin. Microsc Res Tech, 1997; 38:361-72

Ferrándiz C, Carrascosa JM, Boada A. et al. A new era in the management of psoriasis? The biologics: facts and controversies. Clin Dermatol. 2010; 28(1):81-7

Gaffal E, Cron M, Glodde N. et al. Anti-inflammatory activity of topical THC in DNFB-mediated mouse allergic contact dermatitis independent of CB1 and CB2 receptors. Allergy. 2013 Aug;68(8):994-1000

Giacoppo S, Galuppo M, Pollastro F. et al. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. Daru. 2015; 21:23:48

Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, et al. Major differences in inflammatory dendritic cells and their products distinguish atopic dermatitis from psoriasis. J Allergy Clin Immunol. 2007; 119 (5):1210-7

Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis--part II: immune cell subsets and therapeutic concepts. J Allergy Clin Immunol. 2011; 127(6):1420-32

Hueber F, Wepierre J, Schaefer H. Role of transepidermal and transfollicular routes in percutaneous absorption of hydrocortisone and testosterone: in vivo study in the hairless rat. Skin Pharmacol. 1992; 5(2):99-107

Iivarinen JT, Korhonen RK, Jurvelin JS. Experimental and numerical analysis of soft tissue stiffness measurement using manual indentation device--significance of indentation geometry and soft tissue thickness. Skin Res Technol. 2014; 20(3):347-54

Iannaccone AM, Verrusio G, Iurassich S. Discomfort and adaptation in psoriatic patients: an inchoate supportive care trial. Clin Ter. 2016;167(4):105-12.

Iversen L. Cannabis and the brain. Brain, 2003; 126:1252-70

Jordt SE, Bautista DM, Chuang HH et al. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature. 2004; 15;427(6971):260-5

Kim J, Krueger JG. Highly Effective New Treatments for Psoriasis Target the IL-23/Type 17 T Cell Autoimmune Axis. Annu Rev Med, 2017; 68:255-69

Kimball AB, Gieler U, Linder D. Psoriasis: is the impairment to a patient's life cumulative? J Eur Acad Dermatol Venereol. 2010; 24(9):989-1004

Kintz P, Cirimele V, Mangin P. Testing human hair for cannabis. II. Identification of THC-COOH by GC-MS-NCI as a unique proof. J Forensic Sci. 1995; 40(4):619-22

Klein TW, Lane B, Newton CA et al. The cannabinoid system and cytokine network. Proc Soc Exp Biol Med 2000; 225(1): 1-8.

Klein TW, Newton CA, Friedman H. Cannabinoids and the immune system. Pain Res Manag, 2001; 6(2):95-101

Klein TW, Newton CA, Widen R et al. The effect of delta-9-tetrahydrocannabinol and 11-hydroxy-delta-9-tetrahydrocannabinol on T-lymphocyte and B-lymphocyte mitogen responses. J Immunopharmacol. 1985; 7(4):451-66

Kogan NM. Cannabinoids and cancer. Mini Rev Med Chem, 2005; 941-52

Komine M, Tamaki K. An open trial of oral macrolide treatment for psoriasis vulgaris. J Dermatol, 2000; 27:508-12

Kurokawa I, Danby FW, Ju Q, et al. New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol, 2009; 18(10):821-32

Laurino C, Palmieri B, Coacci A. Efficacy, Safety, and Tolerance of a New Injection Technique for High- and Low-Molecular-Weight Hyaluronic Acid Hybrid Complexes. Eplasty, 2015; 15:e46

Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol, 1994; 19(4):303-8

Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol, 2000; 105 (5): 860-76

Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. J Allergy Clin Immunol, 2014; 134(4):769-79

Lodzki M, Godin B, Rakou L, et al. Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model. J Control Release, 2003; 93(3):377-87

Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol, 2014; 32:227-55

Mansouri Y, Guttman-Yassky E. Immune Pathways in Atopic Dermatitis, and Definition of Biomarkers through Broad and Targeted Therapeutics. J Clin Med, 2015; 4(5):858-73

McClure SL, Valentine J, Gordon KB. Comparative tolerability of systemic treatments for plaque-type psoriasis. Drug Saf, 2002; 25(13):913-27

Mounessa JS, Siegel JA, CA. Dunnick CA, et al. The role of cannabinoids in dermatology. J Am Acad Dermatol, 2017; 77:188-90

Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature, 1993; 365 (6441): 61-5

Nickoloff BJ. Creation of psoriatic plaques: the ultimate tumor suppressor pathway. A new model for an ancient T-cell-mediated skin disease. Viewpoint. J Cutan Pathol, 2001; 28:57-64

Nomura I, Goleva E, M.D. Howell MD et al. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. J Immunol, 2003; 15:171(6) 3262-9

Olah A, Toth BI, Borbirò I et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. J Clin Invest, 2014, 124 (9), 3713-24.

Palmieri B, Iannitti T. The Web Babel syndrome. Patient Educ Couns, 2011; 85(2):331-3

Palmieri B, Iannitti T, Capone S et al.[Second opinion clinic: is the Web Babel Syndrome treatable?]. Clin Ter, 2011;162(6): 575-83.

Palmieri B, Laurino C, Vadalà M. The "Second Opinion Medical Network". Int. J. Pathol and Clin Res, 2017; 3:1-7

Parisi R, Symmons DP, Griffiths CE. Identification, P. Management of & t. Associated ComorbidiTy project (2013) Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol, 2013; 133(2):377-85

Pertwee RG. GPR55: a new member of the cannabinoid receptor clan? Br J Pharmacol, 2007; 152(7):984-6

Pertwee RG, Howlett AC, Abood ME et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid

receptors and their ligands: beyond CB(1) and CB(2). Pharmacol Rev, 2010, 62 (4)**,** 588-631.

Prinz JC. Psoriasis vulgaris--a sterile antibacterial skin reaction mediated by cross-reactive T cells? An immunological view of the pathophysiology of psoriasis. Clin Exp Dermatol, 2001; 26: 326-32.

RA C. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, 2015. (Vienna, Austria) URL https://www.R-project.org/.

Rigopoulos D, Larios G, Katsambas AD. The role of isotretinoin in acne therapy: why not as first-line therapy? facts and controversies. Clin Dermatol, 2010; 28(1):24-30

Roberson ED, Bowcock AM. Psoriasis genetics: breaking the barrier. Trends Genet, 2010; 26(9):415-23

Russo EB, Burnett A, Hall B & K. K. Parker. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res, 2005; 30: 1037-43

Senra MS, Wollenberg A. Psychodermatological aspects of atopic dermatitis. Br J Dermatol, 2014; 170 Suppl 1:38-43

Shaw TE, Currie GP, Koudelka CW et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol, 2011; 131(1):67-73

Simpson EL. Comorbidity in Atopic Dermatitis. Curr Dermatol Rep, 2012; 1:29-38

Skopp G, Strohbeck-Kuehner P, Mann K et al. Deposition of cannabinoids in hair after long-term use of cannabis. Forensic Sci Int, 2007; 170(1):46-50

Stander S, Reinhardt HW, Luger TA [Topical cannabinoid agonists. An effective new possibility for treating chronic pruritus]. Hautarzt, 2006; 57(9):801-7

Sun L, Zhang X. The immunological and genetic aspects in psoriasis. Applied Informatics, 2014; 1:3

Thiboutot D, Gollnick H, Bettoli V, et al. Global Alliance to Improve Outcomes in (2009) New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. J Am Acad Dermatol, 2009; 60 (5):S1-50

Togsverd-Bo K, Lerche CM. Porphyrin biodistribution in UV-exposed murine skin after methyl- and hexyl-aminolevulinate incubation. Exp Dermatol, 2012; 21:260-4

Touitou E, Fabin B, Dany S, et al.Transdermal delivery of tetrahydrocannabinol. Int J Pharm, 1988; 43:9-15

Tubaro A, Giangaspero A, Sosa S. Comparative topical anti-inflammatory activity of cannabinoids and cannabivarins. Fitoterapia, 2010; 81:816-9

Valdimarsson H, Sigmundsdottir H, Jonsdottir I. Is psoriasis induced by streptococcal superantigens and maintained by M-protein-specific T cells that cross-react with keratin? Clin Exp Immunol, 1997; 107 Suppl 1:21-4

Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science, 2005; 310(5746):329-32

Wananukul S, Chatproedprai S, Tempark T, et al. The natural course of childhood atopic dermatitis: a retrospective cohort study. Asian Pac J Allergy Immunol, 2015; 33(2):161-8

Wunsch A, Palmieri B. The role of second opinion in oncology: an update. Eur J Oncol, 2013;18:3-10

Zaman S, Akhtar N, Khan BA, et al. A development of a sebum control cream from a local desert plant capparis decidua. J Med Plant Res 2012; 6:744-8