Scientific evidence of the therapeutic benefits of several selected ingredients

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1. Introduction

1.1. About DEMAND Hub

The Data-Enabled Medical Technologies And Devices (DEMAND) Hub project is funded by the European Regional Development Fund as part of the European Structural and Investment Funds Programme 2014-2020 – Priority Axis1: Promoting Research and Development. The project is delivered by the University of Birmingham in strategic partnership with University Hospitals Birmingham NHS Foundation Trust. The DEMAND Hub programme will run until June 2023 and will support SME businesses in, or looking to enter, the healthcare market by delivering scientific services and commercial pathway support. In addition, there will be a strong focus on the utility of patient reported outcomes and healthcare data in guiding product design, testing and development, removing barriers for innovative businesses and stratifying product development.

The distinctive offering of the DEMAND Hub is characterised by the creation of new academic-clinical-innovation pathways between our existing Birmingham Health Partners expertise in medical technologies, health data and clinical trials, working with established medical technology companies as well as innovative digital SME companies, to enable them to access the opportunities within the regional medical and healthcare sector so as to facilitate development of new technologies across systems software, devices, algorithms, AI solutions and beyond.

1.2. Product description

Earth Beauty have received some customer feedback that their skin conditions such as eczema or psoriasis have improved or have significantly reduced irritation or inflammation. Earth Beauty would like to find some scientific evidence for the therapeutic benefits of several selected ingredients used in its products, containing shea butter, hemp seed oil, magnesium flakes, pink Himalayan salt and essential oils bergamot.

1.3 Reviewer's biography

Dr. Cong Sui is a research fellow in the Healthcare Technologies Institute and has been a PhD student in School of Chemical Engineering at the University of Birmingham since 2013. He was also awarded a PhD in Biomaterial in Hefei National Laboratory for Physical Sciences at the Microscale in University of Science and Technology of China in 2017. His dual PhD research areas cover biomaterial, tissue engineering, multifunctional micro/nano material, imaging, terahertz, MRI contrast agent, encapsulation and controlled release. Dr. Sui has published 7 full peer reviewed papers and has filed 2 patents. He also worked with many international companies, including Unilever, Philips and Firmenich global companies. He is currently a part-time MBA health student in the Global Business School for Health in the UCL.

This literature review was performed by Dr. Cong Sui based on his extensive academic and industrial research experience as well as his business and global health knowledge.

2. Scientific evidence of the therapeutic benefits of the selected ingredients

2.1 Shea butter

The exact mechanism of therapeutic effects of shea butter in a variety of dermatoses has been considered as limited scientific investigation. The therapeutic benefits to skin and hair are listed below.

Anti-inflammation

Shea butter is reported to mixed with other ingredients for wound healing due to its anti-inflammatory properties[1,2]. It is used with *boa constrictor* oil to generate positive outcomes in the treatment of keloids in zootherapy[3]. Buruli ulcer scars and leprosy scars are reported to be cured by applying shea butter only[4]. It is also recorded to be used in wound care, burns, keloids, ulcers, scars, bruises[5]. Furthermore, shea butter is served as a type of anti-inflammatory

scarring product in curing smallpox, which is attributed to the primary nonglyceride constituents of shea. Its high triterpene alcohol and tocopherol content offers the anti-inflammatory and anti-oxidant properties[6,7]. Shea butter is also used in the treatment of measles[8], herpes[9] and skin irritations[10]. At the molecular level, the triterpene (α-amyrin) in shea butter topicaly shows anti-inflammatory effects that inhibits skin inflammatory responses such as an increase in tissue IL-1β levels, edema formation, and even the migration of polymorphonuclear leukocyte[11].

Fungal and bacterial infections, scabies, acne vulgaris

Shea butter is widely applied as a kind of antimicrobial agent in commercial products in ethnomedicine[12]. It is effective in superficial dermatophytoses (tinea cruris, corporis, pubis, and capitis), pityriasis versicolor, folliculitis, and scabies[5]. The average treatment time for complete recovery is: 5.8 weeks (fungal), 11.6 weeks (bacterial), 6.1 weeks (scabies) and 3.8 weeks (acne vulgaris)[13]. However, the sample size of the above study is too small to reach a conclusive determination. Besides, shea butter is reported to be more efficacious in nasal congestion than conventional nasal drops[14-16].

Hair loss, hair strengthening, dandruff

As a treatment for hair loss, shea is reported to be applied alone or associated with aloe vera, or palm oil and *Carapa Procera* to strengthen the hair[9]. In one clinical trial, shea butter in the form of a soap and ointment was proved to be particularly efficacious in the treatment of dandruff. The treatment was conducted twice per day for an average of 3.8 weeks to recover[13].

Emollient and skin moisturizer

Shea butter contains vitamins A and E, which makes it a good moisturiser for hair. Its semi-solid characteristics and buttery consistency makes it an excellent emollient and moisturiser

for the scalp and skin[17]. It serves as an emollient for the treatment of eczema[18,19] and hair moisturiser[20,21]. A double-blind, randomised, controlled clinical trial conducted in Mali proved that Psorospermine is more effective than shea butter for the different symptoms of eczema including pruritus, erythema, vesicles, exudation, and lichenification[22]. It was more effective for acute than for chronic eczema (12% and 33% of treatment failures, respectively). Figure 1 shows the efficacy of shea butter as adjuvant treatment in skin conditions by health practitioners.

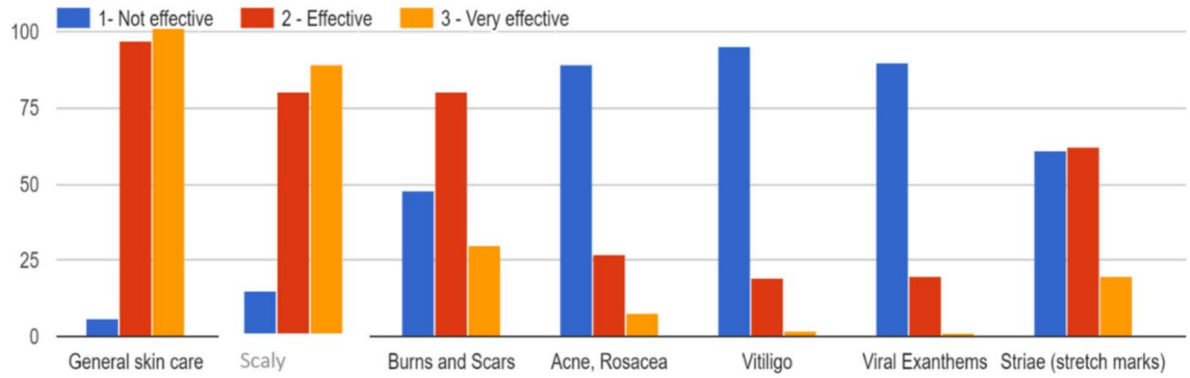

Figure 1. Rating of efficacy of shea butter as adjuvant treatment in skin conditions by health practitioners[20].

Anti-aging Properties

Shea butter has been proved to exhibit the anti-photo-aging property and UV anti-erythemic activity, which helps to soften the skin and stimulates cell regeneration for anti-aging process[23]. It also can help enhance the collagen production[24]. The unsaponifiable components in shea butter are reported to contribute to anti-aging and collagen-boosting activities[25].

Cancer

There is only one case reported using shea butter and palm oil to cure hyperpigmented lesions that were subsequently diagnosed as malignant melanoma[26].

2.2 Hemp Seed oil

Hemp Seed oil contains non-psychoactive cannabinoid cannabidiol, which exhibits high therapeutic value in numerous diseases. The scientific and clinical studies on the use of cannabinoids to treat dermatological disorders have been summarised in a review paper (table 1)[27].

Table 1. Summary of research and clinical studies on the use of cannabinoids to treat dermatological disorders[27].

Disease	Type of Study	Short Description	Results
Acne and seborrhea	In vitro lab research	Production and effects of ECBs in cultured human SZ95 sebocytes.	Cells produced AEA and 2-AG and expressed CB2R but not CB1R. Lipid synthesis and apoptosis-driven cell death via CB2R were upregulated by AEA and 2-AG.
	In vitro lab research	Effect of CBD in cultured human SZ95 sebocytes and human skin organ culture.	CBD inhibited the lipogenic actions of several compounds, suppressed sebocyte proliferation and had anti-inflammatory action, inhibiting the NF-κB signaling pathway.
	Single-blind comparative study (11 participants)	Effect of *C. sativa* seed extract cream (3%) on acne symptoms.	Decreased sebum and erythema levels.
	In vitro lab research	Effect of cannabinoids in cultured human SZ95 sebocytes.	CBC, CBDV suppressed AA-induced seborrhea lipogenesis. THCV inhibited sebocyte proliferation and AA-induced seborrhea lipogenesis. CBG, CBGV had pro-lipogenic and pro-acne actions.
	In vitro lab research	Effect of hemp seed extracts on human HaCaT keratinocytes and primary human sebocytes.	Hemp seed hexane extracts (HSHE) had antimicrobial activity against C. acnes, anti-inflammatory, anti-lipogenic, and collagen-promoting properties.
	Clinical trial (368 participants)	Effect of BTX 1503 (topical solution with 5% CBD).	After 12 weeks of treatment there was a 40% reduction in acne lesions.
Allergic contact dermatitis (ACD)	In vivo lab research	Effect of CB2R antagonists/reverse agonists in a mice ear ACD model.	Mice ears showed swelling within 1 day after being treated with a 2-AG analogue and within 1-8 days after treatment with a CB2R agonist. Oral administration of a CB2R antagonist or reverse agonist decreased the swelling in these ACD models and also in an DNFB-induced ACD model.

AA, arachidonic acid; ACD, allergic contact dermatitis; AD, atopic dermatitis; AEA, anandamide; 2-AG, 2-arachidoynyl-glycerol; CBC, cannabichromene; CBD, cannabidiol; CBDV, cannabidivarin; CBG, cannabigerol; CBGV, cannabigerovarin; CBN, cannabinol; CB1R/CB2R, G protein-coupled CNB (main) receptors; DMS, Derma Membrane Structure; DNFB, 2,4-dinitrofluorbenzene; ECB, endocannabinoid; FAAH, fatty acid amide hydrolase; FTIC, fluorescein isothiocyanate; HSHE, hemp seed hexane extracts; IFN-, interferon; IL, interleukin; MCP-2, monocyte chemotactic protein-2; PCL, polycaprolactone; PEA, N-palmitoylethanolamine; PPAR-, peroxisome proliferator-activated receptor; TEWL, transepidermal water loss; THC, trans-D-9-tetrahydrocannabinol; THCV, tetrahydrocannabivarin; TNF-, tumor necrosis factor; TRPV1, transient potential channel receptor 1; TSLP, thymic stromal lymphopoietin; WT, wild type.

Table 1. *Cont.*

Disease	Type of Study	Short Description	Results
Allergic contact dermatitis (ACD)	In vivo lab research	Effect of CB1R/CB2R antagonists on oxazolone-induced ACD in mice ears.	Oxazolone-challenged mice ears had increased concentrations of 2-AG. Treatment with a CB2R antagonist (but not CB1R antagonist) suppressed the inflammatory response.
	In vivo lab research	Response of WT and CB1R/CB2R knockout mutant mice to DNFB-induced ACD.	Mice knocked-out for CB1R/CB2R showed exacerbated allergic inflammation to DNFB-induced ACD. Antagonists of CBRs led to exacerbated allergic inflammation in WT mice, while agonists attenuated the inflammatory response. Mice deficient in FAAH had increased concentrations of AEA and reduced allergic responses.
	In vitro and in vivo lab research	Production and effect of PEA in an DNFB-induced ACD mice model and HaCaT keratinocytes.	Endogenous production and exogenous application of PEA decreased symptoms of DNFB-induced ACD. Keratinocytes induced with poly-(I:C) had higher levels of PEA, and exogenous PEA treatment inhibited the secretion of pro-inflammatory mediators, an effect reversed by TRPV1 antagonists, but not PPAR-α or CB2R antagonists.
	In vitro and in vivo lab research	Effect of THC in a DNFB-induced mice model of ACD	Topical application of THC decreased ear swelling independently of CB1R/CB2R by decreasing the secretion of IFN-γ by T cells and myeloid immune cell infiltration. In vitro, THC inhibited the IFN-γ-dependent production of chemokines by mice primary epidermal keratinocytes.
	In vitro lab research	Effect of CBD in poly-(I:C)-stimulated human HaCaT keratinocytes.	Treatment with CBD increased AEA levels and inhibited the production of MCP-2, IL-6, IL-8 and TNF-α. This was reversed by treatment with CB2R and TRPV1 antagonists.
Asteatotic eczema	Randomized double-blind controlled study (60 participants)	Compare PEA/AEA (0.3%/0.21%) emollient cream with a traditional emollient.	Improved scaling, dryness, and itching at day 28. Increased skin hydration (measured by change in capacitance of the skin surface), back to normal levels in 7 days. No difference in TEWL between PEA/AEA and control creams.
Atopic dermatitis (AD)	In vivo lab research	Research the role of CB1R in fluorescein isothiocyanate (FTIC)-induced AD in mice ears.	Mice knocked out for CB1R globally or in keratinocytes had enhanced responses to FTIC and delayed epidermal barrier repair. Inflamed ear tissue had higher pro-inflammatory cytokines and chemokines mRNA level, and higher eosinophil activity. CB1R-deficient epidermal keratinocytes secreted higher levels of TSLP and CCL8, inducing a Th2-type skin inflammation.

Table 1. *Cont.*

Disease	Type of Study	Short Description	Results
Atopic dermatitis (AD)	In vivo lab research	Effects of CB1R agonists on skin inflammation in acute and chronic oxazolone-induced AD animal models.	The topical application of the agonists accelerated the recovery of the epidermal barrier function and had anti-inflammatory effects, confirmed by histological studies.
	In vivo lab research	Effects of CB1R agonists (AEA derived) on mast cell activation.	CB1R agonists suppressed mast cell proliferation in a dose-dependent manner, suggesting an important role for CB1R plays in the modulation of antigen-dependent IgE-mediated mast cell activation.
	Single-blind crossover (20 participants)	Effect of dietary hempseed oil.	Improvement of skin dryness and itchiness. Decrease in dermal medication usage.
	Investigator-blinded comparative study (43 participants)	Effect of PEA-containing non-steroidal cream.	Increased the mean time to the next flare by an average of 28 days, compared to moisturizer cream (both combined with a topical corticosteroid cream).
	Cohort (2546 participants)	Effect of emollient cream containing PEA.	Decreased severity, flare-ups and use of topical steroids. Improved symptoms, disease tolerance and sleep.
	In vitro (skin model); in vivo (3 human volunteers)	Effect of PCL patch with hemp seed oil.	Long-term release of hemp seed oil from the patches (55% over 6 h) and 20–25% increase in skin hydration.
Chronic pruritus	Double-blinded comparative study (12+6 participants)	Effect of cannabinoid receptor agonist HU210 (skin patch or microdialysis).	Reduced experimentally-induced itch and attenuated increase in blood flow.
	Clinical trial (21 participants)	Effect of AEA/PEA cream with Derma Membrane Structure (DMS) in uremic pruritus.	After a 3 week therapy, there was a complete elimination of pruritis in 38% patients and reduction in xerosis in 81% patients. The product was well tolerated by all patients.
	Cohort (22 participants)	Effect of emollient cream containing PEA.	Reduced subjective severity of itch (average reduction of 86%). Antipruritic effect observed in 64% of the cases.
	Single-blind comparative study (100 participants)	DMS-based dermatocosmetic lotion containing PEA.	No significant differences between DMS-based PEA lotion group and control group concerning itch, quality of life, or cosmetic acceptance.
Psoriasis	In vitro lab research	Effect of THC, CBD, CBN, CBG on keratinocyte proliferation.	Inhibition of cell proliferation, concentration-dependent and independent of CB1R/CB2R.
	In vitro and in situ lab research	Effect of CB1R agonist in the levels of keratins K6 and K16.	Downregulation of keratins expression in situ (organ-cultured human skin) and in vitro (HaCaT keratinocytes), suggesting the involvement of CB1R in the process.
	Hypothesis	Use of JWH-133 (synthetic cannabinoid) as a therapy for psoriasis.	Study of JWH-133, a potent antiangiogenic and anti-inflammatory agent, for the treatment of psoriasis.
	Patent	Effects of CBD/CBG oil in 2 psoriatic patients.	16–33% reduction in lesions observed after 6 weeks.
	Case study	Effect of products with THC distillate in a 33-year-old psoriasis patient.	Treatment with cream, soap and oil improved psoriasis symptoms as early as 2 days after beginning. Flare-ups could be controlled by reinitiating the treatment.

2.3 Pink Himalayan salt

Himalayan salt mainly consists of 95-98% sodium chloride and some mineral impurities. Baths containing fairly large amounts of sodium chloride are very useful to moisturise skin, add lipids to the damaged skin and aid its desquamation, which can help the symptomatic treatment of ichthyoses[28,29]. However, one study shows that it exhibits no effect in the treatment of psoriatic[30].

2.4 Magnesium flakes

Enhance skin barrier

The ingredient of the magnesium flakes is magnesium chloride ($MgCl_2$), which is believed to exert a therapeutical effect on various skin diseases. For example, the Dead Sea salt significantly improved the skin barrier function and reduced the skin roughness and redness, which is seen as the marker for inflammation, compared to the tap water-treated control group. This is attributed to the high magnesium salt contents, which are known to bind water, enhance stratum corneum hydration, affect epidermal proliferation and differentiation, and promote permeability barrier repair[31]. The improvement of skin barrier can prevent aeroallergens grass pollen, birch pollen, cat dander, and house dust mite from penetrating into the skin, thereby perpetuating eczematous lesions and inducing inflammation[31]. In addition, the penetration of magnesium through human stratum corneum depends on its concentration and time of exposure[32]. The effectiveness of magnesium ions can be facilitated not only by calcium ions to influence epidermal proliferation and differentiation[33,34], but also by hair follicles exerting a significant contribution to the magnesium penetration process[32].

Alleviate psoriasis

Magnesium ions such as magnesium bromide and magnesium chloride are proved to inhibit the well-known excessive proliferation of psoriatic keratinocytes based on the *in vitro* studies[35]. Magnesium regulates adhesion molecules E-catherin and $\alpha_2\alpha_1$-integrin-mediated migration of keratinocytes[36]. Higher levels of magnesium and calcium ions play important roles in cell proliferation and differentiation, which have been described in psoriatic keratinocytes and after sodium laurylsulfate-induced irritation[37,38]. The concentrations of magnesium ions in wound fluid from porcine and rat skin are increased based on *in vivo* studies[39-41].

A prospective, double blind, controlled study evaluated the therapeutic effect of Dead Sea salts in patients with psoriasis, showing a mild improvement after 3 weeks of treatment compared to the control group[42]. Another study using saline spa water alone (sodium concentration, 250 g/l; magnesium, 980 mg/l) was reported to have a minor therapeutic effect on psoriasis compared with UVB exposure in an randomised clinical trial (RCT) on 90 patients[43].

Inflammatory skin diseases

Magnesium ion-containing ointment significantly inhibited the croton-oil-induced inflammation of the skin[44]. Topically application of magnesium ions exerts a beneficial effect on the skin of dermatitis patients[45]. This should be attributed to the magnesium ions which inhibit the antigen-presenting capacity of Langerhans' cells, most important for sensitisation and elicitation of allergic reactions[46].

Another 2 studies demonstrate the therapeutic effects of using Dead Sea spa to cure atopic dermatitis[29,47]. The complete clearance of lesions was recorded in 90% of 1408 patients after 4 to 6 weeks therapy at the Dead Sea area. A reduction in itching was also recorded during the first week of stay at the Dead Sea area[48].

Allergy

Topical application of magnesium salt in patients exhibits a beneficial effect for skin allergy based on clinical observation[49].

Concern about the transdermal permeation

Regarding the concern about the transdermal permeation of magnesium ions into the body, a study was conducted on isolated human cadaver skin, demonstrating no obvious sign of skin penetration of magnesium by topically using $MgCl_2$ solution.

Other balneotherapy ingredients

Table 2 summarise the balneotherapy in patients with dermatologic disorders, using different kinds of bath ingredients.

Table 2. Balneotherapy in patients with dermatologic disorders[48].

Disease	Authors	Mode of therapy	n	Treatment duration	Efficacy	*Evidence (Design and journal type)
Atopic dermatitis	Kubota et al. (8)	Acidic hot-spring bath pH: 2.0 plus Mn 1.4 mg/l, I 0.3 mg/l	70	Median of 2 months	Significant clearing of skin lesions and reduction in itch	B (B)
	Shani et al. (9)	Balneotherapy in the Dead Sea	1408	4 to 6 weeks	Complete clearance of lesions in 90% of patients	A (B)
Psoriasis	Halvey et al. (11)	Dead Sea balneotherapy	25	3 weeks	Mild improvement comparing to those treated with common salts bath	B (A)
	Leaute-labreze et al. (12)	Saline water balneotherapy (sodium concentration, 250 g/l; magnesium, 980 mg/l)	71	3 weeks	Minor therapeutic effects with saline spa water alone, and no beneficial effect of bathing to enhance phototherapy	C (A)
	Pinton et al. (18)	Immersion and drinking selenium rich spa (70 µg/l)	92	3 weeks	Improvement in psoriatic plaques	A (B)
Cutaneous microcirculation	Hartmann et al. (15)	Balneotherapy with CO_2 (1200 mg/kg water) water	18	20 minutes	Cutaneous vasodilation and increased oxygen utilization	A (A)

* Evidence. A: effective, B: probably effective, C: may not be effective.
Design and journal type: A: Randomized clinical trial (RCT) in a major journal, a: RCT in a non-major journal, B: non-randomized clinical study in a major journal, b: non-randomized clinical study in a non-major journal.

2.5 Bergamot essential oil (BEO)

Bergamot oil contains two types of actives: volatile (93%-96%) and non-volatile (4%-7%).[50] The first one includes monoterpene limonene (25%-53%) and high quantities of oxygenated compounds, such as linalool (2%-20%), linalyl acetate (15%-40%), γ-terpinene and β-pinene[51].

Limonene serves as an effective transdermal delivery enhancer to increase human skin permeability and decreased lag time[52]. It also exhibits effectiveness in antimicrobial, anti-inflammatory, antiproliferative, analgesic activity and skin metabolism. Therefore, it should be used with caution when topically applied (usually associated with vegetable oils and directly on the skin)[53].

BEO could improve acne vulgaris by reducing the growth rate of sebaceous gland spots, inhibiting triglyceride accumulation, decreasing the release of inflammatory cytokines (notably reducing IL-1α levels), promoting apoptosis in the sebaceous gland, and decreasing the ratio of T(testosterone)/E2(estrogen2)[54,55]. Bergamot and orange essential oil may have better effects (dose dependent) on alleviating acne vulgaris than the other types of juice. BEO also showed a significant anti-inflammatory activity[56]. This may be attributed to the presence of citropten and bergapten, which are strong inhibitors of interleukin-8 (IL-8) expression and could be used as potential anti-inflammatory molecules for reducing lung inflammation in patients with cystic fibrosis[57]. It appears to be a potential source of natural antioxidant/anti-inflammatory products to be used as nutraceuticals[57].

According to the animal *in vivo* studies, the topical application of bergamot extract for 42 days increased the activity of superoxide dismutase and the collagen content and decreased the content of malondialdehyde in the skin of mice. It also significantly promoted hair growth[58]. BEO has been reported to be served as hair tonic to control and eliminate seborrhea and alopecia on the scalp[59].

The clinical study on subjects with psoriasis that received a treatment with UVB + BEO applied on the psoriatic plaques 30 min before the procedures, thrice weekly, showed a significant reduction of Psoriasis Area and Severity Index[60].

Citrus bergamia extracts were found active against several types of bacteria, fungi and yeasts, due to the existence of coumarins and furocoumarins[61-63]. Bergamot oil was found active *in vitro* against clinical isolates of dermatophytes[64].

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