Received: 8 February 2021 | Revised: 6 May 2021 | Accepted: 7 May 2021

DOI: 10.1111/exd.14395

REGULAR ARTICLE

Experimental Dermatology WILEY

Topical cannabis-based medicines – A novel adjuvant treatment for venous leg ulcers: An open-label trial

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Abstract

Venous leg ulcers are highly prevalent lower limb integumentary wounds that remain challenging to heal despite the use of evidence-based compression therapies. A multitude of adjuvant treatments has been studied but none have demonstrated enough efficacy to gain adoption into treatment guidelines. Global attention on Cannabis-Based Therapies is increasing and has been driven by quantum scientific advancements in the understanding of the endocannabinoid signalling system. Topical Cannabis-Based Medicines represent a novel treatment paradigm for venous leg ulcers in terms of promoting wound closure. Fourteen complex patients with sixteen recalcitrant leg ulcers were treated with Topical Cannabis-Based Medicines in conjunction with compression bandaging, every second day, to both wound bed and peri-wound tissues. The cohort had a mean age of 75.8 years and was medically complex as reflected by a mean M3 multimorbidity index score of 2.94 and a mean Palliative Performance Scale score of 67.1%. Complete wound closure, defined as being fully epithelialized, was achieved among 11 patients (79%) and 13 wounds (81%) within a median of 34 days. All three remaining patients demonstrated progressive healing trends but were lost to follow-up. The treatments were well tolerated, and no significant adverse reactions were experienced. The rapid wound closure of previously non-healing venous leg ulcers among elderly and highly complex patients suggests that Topical Cannabis-Based Medicines may become effective adjuvants in conjunction with compression therapy. This may also indicate that they may have an even broader role within integumentary and wound management. Therefore, this treatment paradigm warrants being subjected to controlled trials.

KEYWORDS
compression therapy, Endocannabinoid System, integumentary wounds, peri-wound tissues, Topical Cannabis-Based Medicines, venous leg ulcers, wound bed, wound closure

Clinical Trial Registry: ISRCTN registry (Study ID # ISRCTN16488940).

1 | INTRODUCTION

Accounting for up to 90% of all lower limb integumentary ulcerations, venous leg ulcers (VLU) represent a significant global public health concern.[1–3] Although the overall North American prevalence is approximately 1%, it exceeds 3% in those over 65 years of age. Their prevalence in persons under 65 years of age has doubled over the past 2 decades from 0.3% to 0.6%.[4] Globally, VLU prevalence is projected to continue rising.[1–4] A recent systematic review studying VLU in all world regions reported a female-to-male ratio of 1.2:1, average age of 47–65 years, mean wound duration of 13.8–65.5 months, and up to 30% of patients reported feeling depressed.[4] The annual costs to treat VLU in the USA are estimated to approach 14 billion USD.[5,6] Beyond their quantum healthcare financial costs, VLU are also major drivers of disability, disoccupation, personal suffering, chronic pain and reduced quality of life.[1–4] Risk factors associated with non-healing VLU include venous incompetency, arterial insufficiency, decreased ambulatory capacity, reduced ankle mobility, advanced age, obesity and co-morbid medical conditions such as hypertension and diabetes mellitus.[1–4]

The most evidence-based treatment for VLU is compression therapy of affected lower limbs. A Cochrane systematic review concluded that although any form of compression therapy increases healing rates, multilayered compression systems are associated with higher ulcer healing rates than those that are single-layered.[7] Generally speaking, compression bandaging is employed to treat active ulcerations, while compression hosiery and/or customized compression garments are used for both primary and secondary prevention. However, optimized compression, as monotherapy, does not guarantee complete wound closure. A recent Canadian study reported that the proportion of patients with VLU that achieved complete closure at 3 and 6 months, while using compression therapy, was 42.2% and 48.6%, respectively.[8] Data from the USA wound registry report a 3-month healing rate for VLU of 44.1%.[9]

Furthermore, even when best practice guidelines are implemented, only 50% to 75% of VLU achieve complete healing after 6 months of treatment.[10] Sadly, once healed, the likelihood of VLU recurrence is between 40% to 70% within 12 months.[11] Table 1 summarizes the conclusions from systematic reviews that assessed a wide range of adjuvant treatments including topically applied anti-microbials, protease modulating matrix and medical honey, together with negative pressure wound therapy, endoscopic perforator surgery, autologous platelet-rich plasma and bilayered human skin equivalent.[12–29] Among these treatments, only cadexomer iodine and bilayered human skin equivalent both demonstrated improved healing rates, and only the latter was associated with significant reductions in median time to complete wound closure.[12,13,16] Additionally, orally administered medications, Trental® (Pentoxifylline) and Phlebotonics, such as Daflon® (90% diosmin +10% Hesperidin), have been studied as systemic adjuvants in the context of VLU. However, Cochrane systematic reviews report only low-level evidence supporting wound healing, along with cautionary alerts related to systemic side effects, and potential risks from drug interactions.[30,31] Therefore, the quest for novel adjuvant treatments must advance in order to strive for higher wound closure rates that occur within the shortest times possible. Ideally, such adjuvant therapies should be non-invasive, non-systemic, easily accessible in all global healthcare settings, safe, economical and allow for potential self-administration by patients.

The Endocannabinoid System (ECS) is a pivotal chemical signalling system that holds a ubiquitous presence within all organ systems among mammalian species.[32] Moreover, the ECS is expressed throughout all levels, appendages and tissues of the integumentary system, both cutaneous and mucous membranes.[32–36] Our appreciation of the ECS, and its impact on bodily homeostatic mechanisms, is evolving rapidly. It is now acknowledged that ECS signalling goes beyond the classic G protein-coupled cannabinoid receptors, CB(1) and CB(2), and also involves other surface membrane receptors such as other members of the GPR family, TRPV, 5-HT, GlyR, adenosine A2A and α_2R.[32–37] Additionally, ECS signalling involves interactions with nuclear receptors such as the PPAR receptor family and associated cross-talk with the NF-κB transcription factor pathway; such intracellular interactions may allow for epigenetic modulation and associated outcomes.[38–41] Dysregulated ECS signalling has been theorized to be central to the pathophysiology of integumentary and wound conditions.[32–36] Dubbed the "entourage effect," it has been postulated that potentiated and synergistic positive healthcare outcomes, including healing of integumentary wounds, may be promoted through the combined activities of the main molecular families derived from legalized medical grade cannabis.[42,43]

This study introduces a novel and non-invasive therapeutic approach to the management of VLU using Topical Cannabis-Based Medicines (TCBM). The chemical composition of the TCBM used in this trial was derived from a meta-synthesis of all the available preclinical and human evidence related to integumentary wound healing using the main molecular classes expressed by the cannabis plant. Furthermore, the TCBM was created to be compliant with guidelines for Cannabis-Based Medicinal products published by the UK National Institute for Health and Clinical Excellence (NICE).[44] The formulae used in this study, VS-12 and VS-14, are composed of the three main molecular classes found in medical grade cannabis, namely, cannabinoids, terpenes and flavonoids (Table 2). This study was conducted in Toronto, Canada, where medical cannabis was federally legalized in 2001. There is a global trend for legalization, and as of early 2021, medical cannabis has been legalized in more than 40 countries and almost 40 American states.[45]

The conceptual framework that has guided global wound management for over 2 decades is the "Wound Bed Preparation" (WBP) paradigm.[46] Its main limitation is that it does not directly address the health of peri-wound tissues. New scientific insights reflect that both wound beds and peri-wound tissues harbour pathophysiologic features, such as inflammation, ischaemia, acidosis, that predispose to wound chronicity and deterioration.[46–50] This trial involves the topical application of VS-12 to the wound bed and VS-14 to the peri-wound tissues.

TABLE 1 Summary of results from Systematic Reviews on non-systemic adjuvant treatments used together with compression therapy for VLU

Adjuvant treatments (Tx)	Comparator (Comp)	Study duration	Reported healing rates (Tx vs. Comp)	Significant difference in healing rates?	Reported median/mean time to wound closure (Tx vs. Comp)	References
Bilayered human skin equivalent	Standard care	6 months	61% vs. 40%	Yes	61 vs. 181 days	12,13
Autologous platelet-rich plasma	Standard care	4–9 months	68% vs. 70%	No	5 vs. 5 weeks	22–24
Human recombinant epidermal growth factor	Standard care	10 weeks	35% vs. 11%	No	Not reported	25,26
Subfascial endoscopic perforator surgery	Standard care	24 months	90% vs. 76%	Only at 12–24 months	4.2 vs. 5.7 months	27,28
Negative pressure wound therapy	Standard care	12 months	97% vs. 97%	No	29 vs. 45 days	14,29
Foam dressing	Standard care	12–52 weeks	30.6–47.0% vs. 22.9–52.0%	Not available	49.0–73.5 vs. 42.0–66.0 days	15
Cadexomer iodine	Standard care	4–12 weeks	33.0% vs. 15.1%	Yes	Not Available	16
Medical honey	Hydrogel or “clinician's choice”	12 weeks	53.1% vs. 46.0%	No	63.5 vs. 65.3 days	16,17
Silver-impregnated dressings	Non-anti-microbial dressings	4–12 weeks	42.3% vs. 36.0%	No	67.0 vs. 58.0 days	16,18
Alginate dressing	Standard care	6–12 weeks	22.0–87.0% vs. 0.0–80.0%	Not available	56.6 vs.. 41.8 days	19,20
Protease modulating matrix	Other dressings	4–24 weeks	Not reported	No	Not reported	21

2 | METHODS

This prospective open-label cohort trial recruited 14 patients with 16 chronic and non-healing leg ulcers referred to a regional consultative wound management clinic in Toronto, Canada. This cohort was part of an overall prospective open-label trial (Study ID #ISRCTN16488940) involving 33 patients afflicted with various wound classes. All patients manifested VLU, of more than 6 months duration, that failed to close despite being subjected to at least 4 weeks of compression therapy together with all available locally administered best practices in accordance with the Wound Bed Preparation paradigm.[46] All patients demonstrated clinical stigmata for chronic venous leg hypertension and underwent duplex venous Dopplers that confirmed the presence of venous incompetency. Wound biopsies were carried out to rule out neoplasm, vasculitis and rare vasculopathies. All patients provided informed consent for treatment using proprietary Cannabis-Based Medicines, VS-12 and VS-14 (Table 2), composed of mixtures of cannabinoids, terpenes and flavonoids, applied topically to the wound beds and peri-wound tissues. VS-12 and VS-14 are chemically equivalent but compounded in separate vehicles that promote absorption through a wound bed and intact integument, respectively. Treatments were carried out every second day and continued until complete wound closure, defined as the wound bed being 100% epithelialized, was achieved. This research project was approved by the Research Ethics Board at the William Osler Health System in Brampton, Ontario, Canada (Study 18-0038).

On their initial visits, all patients' degrees of global medical complexity were calculated using both the M3 multimorbidity index tool and the Palliative Performance Scale score (PPS).[51–53] Qualitative clinical assessments of their degrees of lipodermatosclerosis, oedema and peripheral arterial disease were also scored and documented. Following gentle cleansing with sterile normal saline, each patient underwent application of evenly applied thin layers of VS-12 to the wound beds, and VS-14 to a 4–6 cm radial cuff of peri-wound integument every second day. Tissues were then covered with one

TABLE 2 Specifications of VS-12 and VS-14

Components	VS-12 Applied to wound bed	VS-14 Applied to peri-wound
Base carrier	Hyaluronic acid + Aloe Vera Gel 1/1 v/v	Liposomal base
CBD[a] (mg/ml)	3.8	3.8
THC[b] (mg/ml)	<1	<1
Quercetin[c] (mg/ml)	31.3	31.3
Diosmin[c] (mg/ml) (mg/ml)	25.3	25.3
Hesperidin[c] (mg/ml)	2.5	2.5
Beta-Caryophyllene[d] (mg/ml)	152.7	152.7

[a]Cannabidiol
[b]Delta-9 Tetrahydrocannabinol
[c]Flavonoid
[d]Terpene

TABLE 3 Patient characteristics

Subject ID	Number of wounds treated	Gender	Age	M3 multimorbidity index	Palliative performance scale score (%)	Lipodermatosclerosis	Oedema	Peripheral arterial disease
1	1	M	73	0.2	90	***	**	No
2	1	M	81	2.7	60	***	*	Yes
3	1	M	89	4.8	30	**	*	Yes
4	2	F	89	4.0	50	**	**	Yes
5	1	M	66	0.9	100	**	*	No
6	1	M	80	3.8	50	**	*	Yes
7	1	F	48	0.4	100	**	*	NO
8	2	F	90	5.7	30	*	**	Yes
9	1	F	70	2.1	70	**	**	No
10	1	F	81	4.4	60	***	***	Yes
11	1	F	69	4.3	90	**	**	No
12	1	F	58	0.9	100	**	**	No
13	1	M	83	2.6	60	**	**	Yes
14	1	F	84	4.3	50	**	***	Yes
N = 14	*N* = 16	F: *N* = 8 M: *N* = 6				*: *N* = 1 **: *N* = 10 ***: *N* = 3	*: *N* = 5 **: *N* = 7 ***: *N* = 2	No: *N* = 6 Yes: *N* = 8
Mean			75.8	2.94	67.1			

Legend: ***: Severe; **: Moderate; *: Mild.

layer each of Jelonet® and Mesorb®. This was followed by the application of inelastic compression bandages, chosen based upon patient preferences, using spiral technique, between the level of the metatarsal phalangeal joints and the infra-popliteal space.

Two-dimensional wound measurements, namely, widest width and longest length, were documented at each visit after debridement was carried out. Given the irregular and eclectic wound bed contours, the wound area calculations were approximated by matching them to various geometric shapes and applying their respective mathematical formulae. Data were also fitted to a linear regression model to report the general trend and the estimated time to complete wound closure. The observed time to complete wound closure, defined as the number of days since treatment onset to observe complete wound closure since start of treatment, was calculated. The wound area data points were also fitted using a least squares linear regression model. The slope was extracted to report both the absolute (cm^2 per 30 days) and relative (% of original wound area per 30 days) rates of wound healing. The estimated time to achieve wound healing, defined as the number of days since treatment onset for the linear fit line to reach zero, was reported. This allowed for evaluation of the 3 wounds that were almost closed but lost due to unforeseen circumstances.

3 | RESULTS

Characteristics of the cohort are summarized in Table 3. Sixteen wounds from 14 patients (six male, eight female) were included in this trial. All wounds were chronic and the median time between wound onset and beginning of the novel treatment was 191.5 days; remarkably, one patient, an 81-year-old man with a surgically fused ankle, was affected by his wound for 12.2 years; photographs of this patient and two other patients are displayed in Figures S1–S3. The mean age of the patients at TCBM treatment onset was 75.8 years (min: 48 years, max: 90 years). The mean M3 index at TCBM treatment onset was 2.94 (min: 0.21, max: 5.71). The mean PPS score was 67.1% (min: 30%, max: 100%). 8 (57%) of the patients demonstrated clinical evidence of peripheral arterial disease. The number of patients whose degree of lipodermatosclerosis was rated as mild, moderate and severe was 1, 10 and 3, respectively. The number of patients whose oedema was rated as mild, moderate and severe was 5, 7 and 2, respectively. All patients had undergone some form of compression therapy before the TCBM treatment onset, which failed to close the wound in all cases despite access to available best practices. 8 patients (10 wounds; 1 patient with 1 wound lost to follow-up) underwent compression bandaging consisting of gauze kling roll, Comprilan® and Easifix®. In five patients (five wounds; two patients with two wounds lost to follow-up), compression bandaging consisted of Coban 2® and one patient (one wound) was bandaged with Viscopaste®, gauze kling roll and Coban® (Table 4).

Wounds in this trial involved various areas of the affected lower limbs including medial ankle (n = 9), lateral ankle (n = 4) and anterior shin (n = 3). A wide range of wound surface areas were observed at the outset of the trial (min: 0.4 cm^2, max: 49.4 cm^2, mean: 12.4 cm^2). 11 of 14 patients (79%) with 13 of 16 wounds (81%) were followed up until complete wound closure, and this occurred within a median of 34 days (Table 5). Three patients, corresponding to three wounds, were unfortunately lost to follow-up; one patient moved out of country, and two others died of reasons unrelated to VLU (motor vehicle accident and complications from dementia). However, those three wounds were on target to wound closure and were almost closed when last seen, at 3.04, 1.8, 6.12 cm^2 on days 94, 97 and 36, respectively. Figure S1 displays a least squares linear regression model that was fitted to all wounds to calculate healing rate and estimated duration for closure. The rate of wound healing and duration to achieve complete wound closure is broken down by wound size in Table 5. The median closure time for 13 wounds that were followed up until observed closure is 34 days. The linear model for all 16 wounds yielded a median time to complete closure of 36.5 days, median rate of surface area changes of −3.3 cm^2 per 30 days and −82% per 30 days. Figure S4 summarizes the wound closure data in graphic format.

TABLE 4 Summary of types of compression used for each patient and time to wound closure

Compression during TCBM Trial	Compression Pre-TCBM	N[a]	Median time to wound closure (days)
Comprilan/Easifix	Tubigrip E stocking	3	21
	Compression stockings 15–20 mmHg	3	14
	Comprilan/Easifix	2	150
	Tubigrip D stocking	1	34
Coban 2	Compression stockings 20–30 mmHg	2	36.5
	Viscopaste/Kling roll/Coban	1	37
Viscopaste/Kling roll/Coban	Compression stockings 20–30 mmHg	1	77
Total		13[a]	34

[a]Counting only the 11 out of 14 (13 out of 16 wounds) patients who completed the full prescribed regimen, and all achieved full wound closure.

TABLE 5 Summary of wound surface area, rate of wound healing and time required to achieve complete wound closure in all patients

Pretreatment wound surface area (cm^2)	*N*	Median time to wound closure (days)	Median rate of wound change[b] (cm^2/30 days)	Median rate of wound change[b] (%/30 days)	Median time b/w wound & treatment onset[b] (days)
0–10	6	38	−1.05	−82%	191.5
>10	10	29[a]	−8.05	−64%	200.5
Total	16	34[a]	−3.3	−82%	191.5

[a]Excluding three wounds that were lost to follow-up.

[b]Including all wounds.

Throughout the entire course of this trial, there were no significant side effects, systemically, regionally or locally, experienced by any of the patients. In addition, staff involved in administering the treatment protocol did not report experience any ill effects from handling the Cannabis-Based Medicines. Furthermore, none of the patients developed hypertrophic scars or keloids.

4 | DISCUSSION

This is the first human clinical trial to report on the use of TCBM, as adjuvants to compression bandaging, to promote complete wound closure of VLU. This trial may be viewed as a compelling test of efficacy given the fact that the 14 patients were significantly older and more medically complex than study populations from the controlled studies on adjuvant therapies posted in Table 1. Notably, their mean M3 index and PPS scores were 2.94% and 67.1%, respectively. This reflects high levels of medical complexity when one realizes that almost two-thirds of typical populations score zero on the M3 index, while entirely healthy persons score 100% on the PPS. In addition, more than half of this trial cohort had moderate to severe lipodermatosclerosis, oedema and peripheral arterial disease, all of which are significant pathophysiologic factors that mitigate against wound closure. Furthermore, this trial cohort had already failed existing evidence-based treatments that included compression therapies. TCBM was associated with healing rates and median times to closure that were better than those associated with most of the adjuvant therapies in Table 1. The rates of wound closure of −3.3 cm^2/month and −82% of wound surface area/month also exceeded what was reported in a Canadian study that reported −0.56 cm^2/month and −33.4% of wound surface area/month in patients with VLU treated with compression therapy alone.[8]

Although the overall body of published data pertaining to the healing of human integumentary wounds using TCBM is sparse, it is nonetheless beginning to accrue. A cohort of children with epidermolysis bullosa experienced a degree of wound healing in an open-label trial involving topical cannabidiol (CBD) preparation.[54] A cohort of patients with chronic non-uremic calciphylaxis leg wounds, treated with VS-12 and VS-14, demonstrated complete wound closure within a mean of 2.5 months.[55] One patient with a severe case of chronic uremic calciphylaxis demonstrated positive healing trends when treated with VS-12 and VS-14.[56] One patient with chronic leg ulcers associated with sickle cell disease achieved complete closure of multiple wounds within a mean of 43 days when treated with topical Cannabis-Based Medicines, VS-21 and VS-22, which are chemically related to VS-12 and VS-14 but augmented with the addition of tetrahydrocannabinolic acid (THCA).[57]

Although it is theorized that the positive results observed were due to local absorption and associated activities within the tissues of the wound bed and peri-wound, it is not known if systemic absorption of the various components of TCBM contributed to the outcomes. Nonetheless, we postulate that the positive outcomes reported are the result of a potentiation and synergy between cannabinoids, terpenes and flavonoids, acting on both wound bed and peri-wound tissues. VS-12, compounded with hyaluronic acid gel and aloe vera gel, promotes absorption of the active agents through lipophilic wound bed tissues, while VS-14, compounded with liposomal base, facilitates their penetration into peri-wound tissues through a relatively impervious stratum corneum.

Chronic non-healing wounds are known to be stagnated in a phase of hyper-inflammation that essentially arrests the normal wound healing cascade.[58] Based upon published preclinical data, it is theorized that VS-12/VS-14 components such as the cannabinoids, tetrahydrocannabinol (THC), CBD, through their intrinsic anti-inflammatory properties, may be able to dampen inflammation to a more physiologic and homeostatic level, thereby allowing wounds to progress towards the subsequent stages of wound healing that include granulation tissue formation, angiogenesis, re-epithelialization, and tissue remodelling.[59,60] The anti-inflammatory properties of cannabinoids may operate through their ability to reduce levels of TNFα, reactive oxygen species and lipoxygenases.[60–64] Furthermore, cannabinoids also possess the capacity to improve tissue perfusion and oxygenation via direct vasodilation.[65] After the state of hyper-inflammation has been modulated, the processes related to proliferation of granulation tissue, angiogenesis and cellular differentiation commence. Cannabinoids direct these complex physiologic processes through numerous cellular signalling pathways, both extracellular and intracellular.[32–38] Through their capacity to interact with nuclear receptors such as the PPAR family, cannabinoids may also potentially promote wound healing through epigenetic mechanisms.[38–41] Stem cells from the basal layer of the epithelium along with the bulge component of hair follicles are largely responsible for re-epithelialization of wounds emanating from wound margins.[64] A recent human in vitro study, using human scalp hair follicles, demonstrated stimulation of epithelial stem cells that was due to CB1 mediated signalling through both MAPK and

Akt pathways.[66] However, in this particular model, CB1 stimulation also led to apoptosis of the differentiated keratinocytes from the differentiated progeny of the aforementioned epithelial stem cells.[66] Another recently published in vitro study demonstrated that both THC and CBD have the capacity to stimulate human adipose-derived stem cells and bone marrow-derived stem cells, thus enhancing their regenerative profiles.[67] This latter finding is significant in the case of integumentary wounds that have penetrated beyond the basement membrane, thereby entering into the subcutaneous adipose space.

In addition to cannabinoids, VS-12 and VS-14 contain the terpene, β-caryophyllene and the flavonoids quercetin, diosmin and hesperidin. β-caryophyllene is a robust CB(2) agonist and thus is associated with analgesic and anti-inflammatory properties.[68] A recently published mouse model in which β-caryophyllene, a known strong agonist of CB(2), promoted wound healing through multiple mechanisms including modulation of inflammation and promotion of re-epithelialization.[69] Flavonoids have long been pivotal components of numerous polyherbal and nutraceutical integumentary and wound treatments. Flavonoids, as a class, possess anti-inflammatory and antioxidant properties.[70] In a preclinical model, quercetin accelerated cutaneous wound healing by increasing levels of Vascular endothelial growth factor (VEGF) and transforming growth factor (TGF-β1).[71] Both VS-12 and VS-14 contain diosmin and hesperidin in the same proportions as found in the oral tablet, Daflon 500mg®. The combination of diosmin and hesperidin has been demonstrated to be venoactive and phlebotonic through their inhibition of expression of vascular cell adhesion molecule (VCAM), endothelial intercellular adhesion molecule 1 (ICAM-1) and other leucocyte adhesion molecules.[72]

This trial has a number of limitations: as a pilot trial, it involved only 14 patients at a single centre; thus, it is difficult to draw strong statistical conclusions. This trial did not measure wound depth and was limited to approximated surface area measurements. Although it lacked the customary elements of a controlled trial, it nonetheless did enrol highly complex and elderly patients that failed evidence-based best practices and were truly intractable in relation to both their healing capacity and their high levels of co-morbid illness. Although the type of compression bandaging was not standardized among the 14 patients, nonetheless, the quality of the bandaging technique was standardized by virtue of being administered by the same expert team of wound experts.

5 | CONCLUSIONS

Topical Cannabis-Based Medicines, applied to both wound beds and peri-wound tissues, represent a promising novel, non-invasive and safe adjuvant treatment option for VLU to be used in tandem with prime evidence-based compression therapy. The ease and simplicity of its application also allows for potential self-application and self-titration by patients. Given that TCBM was associated with rapid wound closure in previously non-healing wounds affecting highly complex patients, they may be poised for an even broader role within overall integumentary and wound management. Therefore, this novel treatment paradigm warrants being trialled in other wound types and classes, and ultimately should be subjected to randomized controlled trials.

ACKNOWLEDGEMENTS

We wish to extend our gratitude to Anna Mann, our hospital librarian, for her guidance and support.

CONFLICT OF INTEREST

VM is the President and CEO of VinSan Therapeutics Inc which holds intellectual property and patents related to the formulae and methodology used in this study. The other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

VM: Study design; data collection; analysis design; manuscript drafting; manuscript review. RS: Analysis design; statistical analysis; manuscript drafting; manuscript review. FF: Analysis design; manuscript drafting; manuscript review. LZ: Study design; Analysis design; manuscript drafting; manuscript review.

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REFERENCES

1. Nelson EA, Adderley U. Venous leg ulcers. *BMJ Clin Evid*. 2016;2016(5):686-694.
2. Graves N, Zheng H. The Prevalence and Incidence of Chronic Wounds: A Literature Review. 2014;(1). https://search.informit.org/doi/10.3316/informit.272162994803134
3. Alavi A, Sibbald RG, Phillips TJ, et al. What's new: Management of venous leg ulcers approach to venous leg ulcers. *J Am Acad Dermatol*. 2016;74(4):627-640. https://doi.org/10.1016/j.jaad.2014.10.048
4. Gethin G, Vellinga A, Tawfick W, et al. The profile of patients with venous leg ulcers: a systematic review and global perspective. *J Tissue Viability*. 2021;30(1):78-88. https://doi.org/10.1016/j.jtv.2020.08.003
5. Rice JB, Desai U, Cummings AKG, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. *J Med Econ*. 2014;17(5):347-356. https://doi.org/10.3111/13696998.2014.903258
6. Ma H, O'Donnell TF, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. *J Vasc Surg Venous Lymphat Disord*. 2014;2(4):355-361. https://doi.org/10.1016/j.jvsv.2014.04.006
7. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev*. 2012;2012(11). https://doi.org/10.1002/14651858.CD000265.pub3
8. Rajhathy EM, Murray HD, Roberge VA, Woo KY. Healing rates of venous leg ulcers managed with compression therapy: a secondary analysis of data. *J Wound Ostomy Cont Nurs*. 2020;47(5):477-483. https://doi.org/10.1097/WON.0000000000000693
9. Fife CE, Eckert KA, Carter MJ. Publicly reported wound healing rates: the fantasy and the reality. *Adv wound care*. 2018;7(3):77-94. https://doi.org/10.1089/wound.2017.0743
10. Moffatt CJ, Franks PJ, Oldroyd M, et al. Community clinics for leg ulcers and impact on healing. *BMJ*. 1992;305(6866):1389-1392. https://doi.org/10.1136/bmj.305.6866.1389

11. Finlayson KJ, Parker CN, Miller C, et al. Predicting the likelihood of venous leg ulcer recurrence: the diagnostic accuracy of a newly developed risk assessment tool. *Int Wound J*. 2018;15(5):686-694. https://doi.org/10.1111/iwj.12911
12. Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. *Cochrane Database Syst Rev*. 2013;2013(1). https://doi.org/10.1002/14651858.CD001737.pub4
13. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. *Arch Dermatol*. 1998;134(3):293.
14. Vuerstaek JDD, Vainas T, Wuite J, Nelemans P, Neumann MHA, Veraart JCJM. State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg*. 2006;44(5):1029-1037. https://doi.org/10.1016/j.jvs.2006.07.030
15. O'Meara S, Martyn-St JM. Foam dressings for venous leg ulcers. *Cochrane Database Syst Rev*. 2013;2013(5):CD009907. https://doi.org/10.1002/14651858.CD009907.pub2
16. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev*. 2014;2014(1). https://doi.org/10.1002/14651858.CD003557.pub5
17. Jull A, Walker N, Parag V, Molan P, Rodgers A. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg*. 2007;95(2):175-182. https://doi.org/10.1002/bjs.6059
18. Michaels JA, Campbell B, King B, Palfreyman SJ, Shackley P, Stevenson M. Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial). *Br J Surg*. 2009;96(10):1147-1156. https://doi.org/10.1002/bjs.6786
19. O'Meara S, Martyn-St James M, Adderley UJ. Alginate dressings for venous leg ulcers. *Cochrane Database Syst Rev*. 2015;2015(8). https://doi.org/10.1002/14651858.CD010182.pub3
20. Harding KG, Price PE, Robinson B, Thomas S, Hofman D. Cost and dressing evaluation of hydrofiber and alginate dressings in the mManagement of community-based patients with chronic leg ulceration. *Wounds*. 2001;13(6):229-236.
21. Westby MJ, Norman G, Dumville JC, Stubbs N, Cullum N. Protease-modulating matrix treatments for healing venous leg ulcers. *Cochrane Database Syst Rev*. 2016;2016(12). https://doi.org/10.1002/14651858.CD011918.pub2
22. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, et al. Autologous platelet-rich plasma for treating chronic wounds. *Cochrane Database Syst Rev*. 2016;2016(5). https://doi.org/10.1002/14651858.CD006899.pub3
23. Stacey M, Mata S, Trengove N, Mather C. Randomised double-blind placebo controlled trial of tropical autologous platelet lysate in venous ulcer healing. *Eur J Vasc Endovasc Surg*. 2000;20(3):296-301. https://doi.org/10.1053/ejvs.2000.1134
24. Senet P, Bon FX, Benbunan M, et al. Randomized trial and local biological effect of autologous platelets used as adjuvant therapy for chronic venous leg ulcers. *J Vasc Surg*. 2003;38(6):1342-1348. https://doi.org/10.1016/S0741-5214(03)00908-X
25. de Carvalho MR, Silveira IA, de Oliveira BGRB. Treatment of venous ulcers with growth factors: systematic review and meta-analysis. *Rev Bras Enferm*. 2019;72(1):200-210. https://doi.org/10.1590/0034-7167-2017-0865
26. Falanga V, Eaglstein WH, Bucalo B, Katz MH, Harris B, Carson P. Topical use of human recombinant epidermal growth factor (h-EGF) in venous ulcers. *J Dermatol Surg Oncol*. 1992;18(7):604-606. https://doi.org/10.1111/j.1524-4725.1992.tb03514.x
27. Lin ZC, Loveland PM, Johnston RV, Bruce M, Weller CD. Subfascial endoscopic perforator surgery (SEPS) for treating venous leg ulcers. *Cochrane Database Syst Rev*. 2019;2019(3). https://doi.org/10.1002/14651858.CD012164.pub2
28. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg*. 2006;44(3):563-571. https://doi.org/10.1016/j.jvs.2006.04.053
29. Dumville JC, Land L, Evans D, Peinemann F. Negative pressure wound therapy for treating leg ulcers. *Cochrane Database Syst Rev*. 2015;2015(7). https://doi.org/10.1002/14651858.CD011354.pub2
30. Jull AB, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev*. 2012. https://doi.org/10.1002/14651858.cd001733.pub3
31. Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, et al. Phlebotonics for venous insufficiency. *Cochrane database Syst Rev*. 2020;11:CD003229. https://doi.org/10.1002/14651858.CD003229.pub4
32. Maccarrone M, Bab I, Bíró T, et al. Endocannabinoid signaling at the periphery: 50 years after THC. *Trends Pharmacol Sci*. 2015;36(5):277-296. https://doi.org/10.1016/j.tips.2015.02.008
33. Tóth KF, Ádám D, Bíró T, Oláh A. Cannabinoid signaling in the skin: Therapeutic potential of the "c(ut)annabinoid" system. *Molecules*. 2019;24(5):918. https://doi.org/10.3390/molecules24050918
34. Bíró T, Tóth BI, Haskó G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. *Trends Pharmacol Sci*. 2009;30(8):411-420. https://doi.org/10.1016/j.tips.2009.05.004
35. Oddi Sergioand Maccarrone M. Endocannabinoids and skin barrier function: molecular pathways and therapeutic opportunities. In: Wondrak GT, ed. *Skin Stress Response Pathways: Environmental Factors and Molecular Opportunities*. Cham: Springer International Publishing; 2016:301-323. https://doi.org/10.1007/978-3-319-43157-4_15
36. del Río C, Millán E, García V, Appendino G, DeMesa J, Muñoz E. The endocannabinoid system of the skin. A potential approach for the treatment of skin disorders. *Biochem Pharmacol*. 2018;157:122-133. https://doi.org/10.1016/j.bcp.2018.08.022
37. Correia-Sá I, Paiva A, Carvalho CM, Vieira-Coelho MA. Cutaneous endocannabinoid system: does it have a role on skin wound healing bearing fibrosis? *Pharmacol Res*. 2020;159:104862. https://doi.org/10.1016/j.phrs.2020.104862
38. O'Sullivan SE. An update on PPAR activation by cannabinoids. *Br J Pharmacol*. 2016;173(12):1899-1910. https://doi.org/10.1111/bph.13497
39. Lewis CJ, Mardaryev AN, Sharov AA, Fessing MY, Botchkarev VA. The epigenetic regulation of wound healing. *Adv Wound Care*. 2014;3(7):468-475. https://doi.org/10.1089/wound.2014.0522
40. Pucci M, Rapino C, Di Francesco A, Dainese E, D'Addario C, Maccarrone M. Epigenetic control of skin differentiation genes by phytocannabinoids. *Br J Pharmacol*. 2013;170(3):581-591. https://doi.org/10.1111/bph.12309
41. D'Addario C, Di Francesco A, Pucci M, Finazzi Agrò A, MacCarrone M. Epigenetic mechanisms and endocannabinoid signalling. *FEBS J*. 2013;280(9):1905-1917. https://doi.org/10.1111/febs.12125
42. Russo EB. The case for the entourage effect and conventional breeding of clinical cannabis: No "Strain", no gain. *Front Plant Sci*. 2019;9:1969. https://doi.org/10.3389/fpls.2018.01969
43. Mansouri K, Norooznezhad AH. Cannabinoids: a possible treatment for chronic cutaneous wounds. *J Dermatolog Treat*. 2021;32(1):128-129. https://doi.org/10.1080/09546634.2019.1690620
44. Chang-Douglass S, Mulvihill C, Pilling S. Cannabis-based medicinal products: summary of NICE guidance. *BMJ*. 2020;369:m1108. https://doi.org/10.1136/bmj.m1108
45. PwC Canada. PwC Canada's Cannabis Series: Chapter 9 — Cannabis in the Pharmaceutical Industry. 2019. https://www.pwc.com/ca/en/industries/cannabis/pwc-cannabis-series-chapt

er-9-cannabis-in-the-pharmaceutical-industry.html. Accessed 8 February, 2021.
46. Harries RL, Bosanquet DC, Harding KG. Wound bed preparation: TIME for an update. *Int Wound J*. 2016;13:8-14. https://doi.org/10.1111/iwj.12662
47. Polak A, Kucio C, Kloth LC, et al. A randomized, controlled clinical study to assess the effect of anodal and cathodal electrical stimulation on periwound skin blood flow and pressure ulcer size reduction in persons with neurological injuries. *Ostomy Wound Manag*. 2018;64(2):10-29. https://doi.org/10.25270/owm.2018.2.1029
48. Dowsett C, Gronemann MN, Harding K, et al. Taking wound assessment beyond the edge. *Wounds Int*. 2015;6(1):19-23.
49. Onesti MG, Fioramonti P, Carella S, Maruccia M. The importance of periwound skin in the treatment of "difficult wound". *G Chir*. 2011;32(1–2):83-88.
50. Dini V, Janowska A, Oranges T, De Pascalis A, Iannone M, Romanelli M. Surrounding skin management in venous leg ulcers: a systematic review. *J Tissue Viability*. 2020;29(3):169-175. https://doi.org/10.1016/j.jtv.2020.02.004
51. Stanley J, Sarfati D. The new measuring multimorbidity index predicted mortality better than Charlson and Elixhauser indices among the general population. *J Clin Epidemiol*. 2017;92:99-110. https://doi.org/10.1016/j.jclinepi.2017.08.005
52. Gurney JK, Stanley J, Sarfati D. The M3 multimorbidity index outperformed both Charlson and Elixhauser indices when predicting adverse outcomes in people with diabetes. *J Clin Epidemiol*. 2018;99:144-152. https://doi.org/10.1016/j.jclinepi.2018.04.002
53. Lau F, Maida V, Downing M, Lesperance M, Karlson N, Kuziemsky C. Use of the Palliative Performance Scale (PPS) for end-of-life prognostication in a palliative medicine consultation service. *J Pain Symptom Manage*. 2009;37(6):965-972. https://doi.org/10.1016/j.jpainsymman.2008.08.003
54. Chelliah MP, Zinn Z, Khuu P, Teng JMC. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. *Pediatr Dermatol*. 2018;35(4):e224-e227. https://doi.org/10.1111/pde.13545
55. Maida V, Shi RB, Fazzari FGT, Zomparelli L. Topical cannabis-based medicines - A novel paradigm and treatment for non-uremic calciphylaxis leg ulcers: An open label trial. *Int Wound J*. 2020;17(5):1508-1516. https://doi.org/10.1111/iwj.13484
56. Maida V, Shi RB, Fazzari FGT, Zomparelli L. Promoting wound healing of uremic calciphylaxis leg ulcers using topical cannabis-based medicines. *Dermatol Ther*. 2020;33(6):e14419. https://doi.org/10.1111/dth.14419
57. Maida V, Shi RB, Fazzari FGT, Zomparelli L. A new treatment paradigm for sickle cell disease leg ulcers: Topical cannabis-based medicines. *Exp Dermatol*. 2021;30(2):291-293. https://doi.org/10.1111/exd.14256
58. Zhao R, Liang H, Clarke E, Jackson C, Xue M. Inflammation in chronic wounds. *Int J Mol Sci*. 2016;17(12): https://doi.org/10.3390/ijms17122085
59. Zurier RB, Burstein SH. Cannabinoids, inflammation, and fibrosis. *FASEB J*. 2016;30(11):3682-3689. https://doi.org/10.1096/fj.201600646R
60. Sangiovanni E, Fumagalli M, Pacchetti B, et al. *Cannabis sativa* L. extract and cannabidiol inhibit in vitro mediators of skin inflammation and wound injury. *Phyther Res*. 2019;33(8):2083-2093. https://doi.org/10.1002/ptr.6400
61. Han KH, Lim S, Ryu J, et al. CB1 and CB2 cannabinoid receptors differentially regulate the production of reactive oxygen species by macrophages. *Cardiovasc Res*. 2009;84(3):378-386. https://doi.org/10.1093/cvr/cvp240
62. Takeda S, Jiang R, Aramaki H, et al. Δ9-tetrahydrocannabinol and its major metabolite Δ9-tetrahydrocannabinol-11-oic acid as 15-lipoxygenase inhibitors. *J Pharm Sci*. 2011;100(3):1206-1211. https://doi.org/10.1002/jps.22354
63. Takeda S, Usami N, Yamamoto I, Watanabe K. Cannabidiol-2′,6′-dimethyl ether, a cannabidiol derivative, is a highly potent and selective 15-lipoxygenase inhibitor. *Drug Metab Dispos*. 2009;37(8):1733-1737. https://doi.org/10.1124/dmd.109.026930
64. Weigelt MA, Sivamani R, Lev-Tov H. The therapeutic potential of cannabinoids for integumentary wound management. *Exp. Dermatol*. 2020;00:1-11. https://doi.org/10.1111/exd.14241
65. Richter JS, Quenardelle V, Rouyer O, et al. A systematic review of the complex effects of cannabinoids on cerebral and peripheral circulation in animal models. *Front Physiol*. 2018;9(622). https://doi.org/10.3389/fphys.2018.00622
66. Sugawara K, Zakany N, Tiede S, et al. Human epithelial stem cell survival within their niche requires "tonic" cannabinoid receptor 1-signalling-Lessons from the hair follicle. *Exp. Dermatol*. 2021;30(4):479-493. https://doi.org/10.1111/exd.14294
67. Miller H, De Leo N, Badach J, et al. Role of marijuana components on the regenerative ability of stem cells. *Cell Biochem Funct*. 2021;39(3):432-441. https://doi.org/10.1002/cbf.3609
68. Guimarães AG, Serafini MR, Quintans-Júnior LJ. Terpenes and derivatives as a new perspective for pain treatment: A patent review. *Expert Opin Ther Pat*. 2014;24(3):243-265. https://doi.org/10.1517/13543776.2014.870154
69. Koyama S, Purk A, Kaur M, et al. Beta-caryophyllene enhances wound healing through multiple routes. *PLoS One*. 2019;14(12):e0216104. https://doi.org/10.1371/journal.pone.0216104
70. Serra R, Grande R, Butrico L, et al. Effects of a new nutraceutical substance on clinical and molecular parameters in patients with chronic venous ulceration. *Int Wound J*. 2016;13(1):88-96. https://doi.org/10.1111/iwj.12240
71. Gopalakrishnan A, Ram M, Kumawat S, Tandan SK, Kumar D. Quercetin accelerated cutaneous wound healing in rats by increasing levels of VEGF and TGF-B1. *Indian J Exp Biol*. 2016;54(3):187-195.
72. Coleridge-Smith P, Lok C, Ramelet AA. Venous leg ulcer: A meta-analysis of adjunctive therapy with micronized purified flavonoid fraction. *Eur J Vasc Endovasc Surg*. 2005;30(2):198-208. https://doi.org/10.1016/j.ejvs.2005.04.017

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Figure S1. Wound area data for all $N = 16$ wounds over their treatment period. (a) $N = 6$ wounds up to original wound area of 8.1 cm^2 and (b) $N = 7$ wounds larger than 11.0 cm^2 up to 49.4 cm^2. All wounds shown in (a) and (b) were treated in the TCBM trial until complete closure. (c) $N = 3$ wounds that were lost to follow-up during the trial period, and linear fit to their closure trajectories. The goodness-of-fit R^2 of the three trendlines were (from smallest original wound to largest): 0.59, 0.77, 0.74. (d) Kaplan-Meier plot of all wound closure times.
Figure S2. 73-year-old man with right medial leg ulcer of 18.2 months duration. Previous right leg deep venous thrombosus. Fully closed on day 96 (48 applications).

Figure S3. 83-year-old man with left anterior shin ulcer of 6.3 months duration. He had a left common iliac artery stenosis. Two areas of exposed tendon sheath are noted within the wound bed. Fully closed on day 127 (63 applications).

Figure S4. 81-year-old man with left lateral leg ulcer of 12.2 years duration. His left ankle was surgically fused following a skiing accident. He was lost to follow-up after day 97 (48 applications) as he died in a motor vehicle accident. Linear model projected full closure on day 139.

How to cite this article: Maida V, Shi RB, Fazzari FGT, Zomparelli L. Topical cannabis-based medicines – A novel adjuvant treatment for venous leg ulcers: An open-label trial. *Exp Dermatol*. 2021;00:1–10. https://doi.org/10.1111/exd.14395