(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
08 April 2021 (08.04.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/062555 A1

(51) International Patent Classification:

A61K 31/352 (2006.01)	*A61P 17/02* (2006.01)
A61K 31/015 (2006.01)	*C07C 13/32* (2006.01)
A61K 31/7048 (2006.01)	*C07D 311/74* (2006.01)
A61K 31/728 (2006.01)	*C07D 311/80* (2006.01)
A61K 36/185 (2006.01)	*C07H 17/07* (2006.01)
A61K 36/886 (2006.01)	*C08J 3/075* (2006.01)
A61K 9/10 (2006.01)	*C08L 5/08* (2006.01)

(21) International Application Number:
PCT/CA2020/051326

(22) International Filing Date:
02 October 2020 (02.10.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3057647 03 October 2019 (03.10.2019) CA

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: TOPICAL FORMULATIONS AND INSTILLATES, KITS, AND METHODS FOR TREATING INTEGUMENTARY WOUNDS, AND USES THEREOF

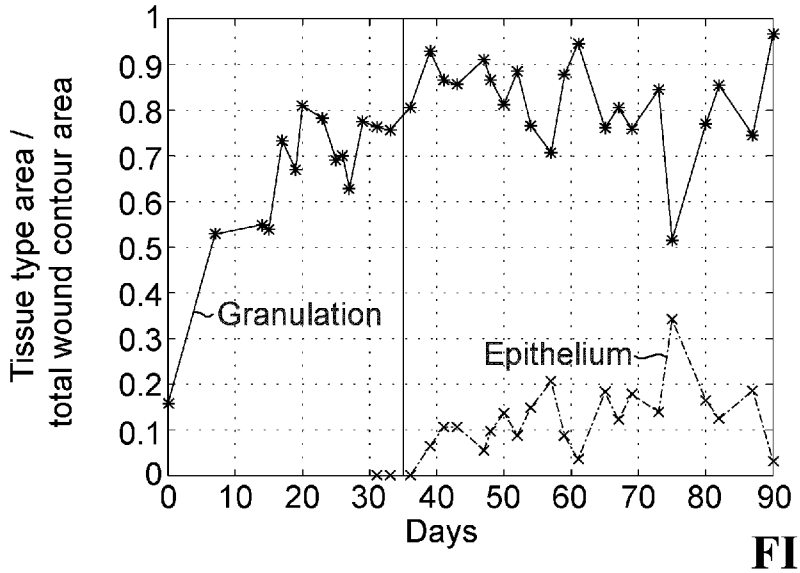


FIG. 4

(57) Abstract: Topical formulations comprising one or more cannabinoids, one or more terpenes, and one or more flavonoids; and methods and uses thereof for the treatment of an integumentary wound, wherein the one or more cannabinoids comprise tetrahydrocannabinolic acid.

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TOPICAL FORMULATIONS AND INSTILLATES, KITS, AND METHODS FOR TREATING INTEGUMENTARY WOUNDS, AND USES THEREOF

FIELD

[0001] The present application relates generally to treatment of integumentary wounds (including chronic and acute wounds involving both cutaneous and mucous membranes), and in particular to topical formulations and instillates, kits, and methods for treating integumentary wounds, and uses thereof.

BACKGROUND

[0002] Wound healing normally progresses through highly organized and regulated sequence of events that are mediated by multiple cell lines and associated growth factors. Tissue damage, caused by either disease process or trauma, is followed by hemostasis. Thereafter, wound healing may be generally described to occur as three overlapping phases: the inflammatory, proliferative, and remodeling phases (Bielefeld et al. *Cell. Mol. Life Sci.* (2013) 70:2059-2081; and de Oliveira Gonzalez et al. *An Bras Dermatol.* 2016;91(5):614-20).

[0003] The inflammatory phase prepares the wound site for healing by immobilizing the wound and causing it to swell and become painful. The inflammatory phase also results in vasodilation and phagocytosis, which lead to release of histamines and serotonins.

[0004] The proliferative phase is characterized by the proliferation of epidermal cells at the wound edge, and by repair of the underlying dermal or mesenchymal layer. This is accompanied by neovascularization. This process usually occurs 2 days to 3 weeks following injury and results in granulation tissue at the wound site.

[0005] Granulation tissue formation occurs during the proliferative phase and involves the following mechanisms: an increase in fibroblastic proliferation; collagenous and elastic biosynthesis, which creates a three-dimensional extracellular network of connective tissue; and the production of chemotactic factors and IFN-beta by fibroblasts. (de Oliveira Gonzalez et al.) Healthy granulation tissue is granular and uneven in texture; it does not bleed easily and is pink / red in colour.

[0006] In the final remodeling phase, remodeling of dermal tissue to produce greater tensile strength whereby new collagen is formed is the main aim of this phase. The principal cell type involved is the fibroblast. Collagen molecules begin to form whereby they undergo further modification and molecules begin to form in a characteristic triple helical structure. Together, these changes result in the contraction of the wound and the formation of acellular scar tissue.

[0007] FIG. 1 illustrates an exemplary normal wound healing sequence: upon tissue injury, hemostasis 101 occurs which may involve epinephrine, platelets, and transforming growth factor beta (TGF-β); inflammation 102 may follow hemostasis 101 and involve neutrophils, macrophages, reactive oxygen species, matrix metalloproteinases (MMPs), interleukins (IL), tumor necrosis factors (TNF), vascular endothelial growth factor (VEGF), TGF-β, and platelet-derived growth factor (PDGF); inflammation 102 may become prolonged inflammation 103 that may lead to a chronic wound; granulation and angiogenesis 104 may follow inflammation 102 and involve fibroblasts, macrophages, endothelial cells, MMPs, IL, TNF, VEGF, TGF-β, PDGF, and keratinocyte growth factor (KGF); re-epithelialization 105 may follow granulation and angiogenesis 104 and involve keratinocytes, endothelial cells, epidermal growth factor, KGF, and MMPs; and tissue remodeling 106 may follow re-epithelialization 105 and involve fibroblasts, collagen fiber cross-linking, TGF-β, and MMPs, which may lead to a healed wound.

[0008] With numerous disease processes, the cascade of events involved in wound healing can be affected, resulting in chronic, non-healing wounds. This could be due to a complex combination of local and systemic factors. The pathophysiology of the "stalled" or "arrested" healing process may be characterized by a state of heightened and prolonged inflammation.

[0009] In an exemplary chronic wound cycle, prolonged inflammation stimulates macrophages and neutrophils to wound where pro-inflammatory cytokines such as TNFα and IL-1β are released; release of these cytokines lead to increased expression of MMPs and decreased expression of tissue inhibitor of metalloproteinase, which contribute to degradation of extracellular matrix (resulting in impaired cell migration and connective tissue deposition) and growth factors, thereby reinforcing prolonged inflammation. Effects of this exemplary chronic wound cycle may include delayed healing, repeated trauma, local tissue ischemia, necrotic tissue, heavy bacterial burden and tissue breakdown.

[0010] Chronic wounds, wounds that fail to heal in an orderly and timely fashion, can generate untold suffering, reduced quality of life, lost productivity, loss of limbs, and reduced life expectancy, while consuming ever increasing proportions of global healthcare budgets. The United States of America spends in excess of 90 billion dollars annually on overall wound management and this is growing faster than any other area within healthcare, approaching 8% per annum.

[0011] While there are topical wound therapies and dressings available based on anecdotal experience, few have published or prospective data to support their effectiveness in promoting wound healing. There are also a number of advanced therapies, such as negative

pressure wound therapy and hyperbaric oxygen therapy, but these advanced therapies often require special equipment/devices or surgical procedures. For example, negative pressure wound therapy requires a regulated vacuum dressing and hyperbaric oxygen therapy requires a hyperbaric oxygen chamber.

[0012] The overall treatment of wounds is recognized as one of the most dismally managed domains within global healthcare. Therefore, there exists a need for the development of wound therapies, dressings, and protocols that are effective in promoting wound healing and easy to be administered to patients.

SUMMARY

[0013] In one aspect, there is provided a topical formulation comprising:

(a) 0.1 mg/ml to 40 mg/ml of one or more cannabinoids;

(b) 25 mg/ml to 1000 mg/ml of one or more terpenes;

(c) 10 mg/ml to 500 mg/ml of one or more flavonoids; and

(d) a liquid carrier,

wherein the one or more cannabinoids comprise at least 0.1 mg/ml tetrahydrocannabinolic acid.

[0014] In an embodiment of the topical formulation as described herein, the one or more cannabinoids further comprise cannabidiol or cannabidiolic acid.

[0015] In an embodiment of the topical formulation as described herein, the one or more terpenes comprise beta-caryophyllene, and the concentration of beta-caryophyllene is 50 mg/ml to 500 mg/ml.

[0016] In an embodiment of the topical formulation as described herein, the one or more terpenes further comprise linalool, and the concentration of linalool is 25 mg/ml to 500 mg/ml.

[0017] In an embodiment of the topical formulation as described herein, the one or more flavonoids comprise at least one of diosmin, quercetin, and hesperidin.

[0018] In an embodiment of the topical formulation as described herein, the one or more flavonoids comprise diosmin, quercetin, and hesperidin.

[0019] In another aspect, there is provided a topical formulation for direct application to an integumentary wound, comprising:

(a) 0.1 mg/ml to 40 mg/ml of one or more cannabinoids;

(b) 25 mg/ml to 1000 mg/ml of one or more terpenes; and

(c) 10 mg/ml to 500 mg/ml of one or more flavonoids,

wherein the one or more cannabinoids comprise at least 0.1 mg/ml tetrahydrocannabinolic acid.

[0020] In an embodiment of the topical formulation as described herein, the one or more cannabinoids further comprise cannabidiol or cannabidiolic acid.

[0021] In an embodiment of the topical formulation as described herein, the one or more terpenes comprise beta-caryophyllene, and the concentration of beta-caryophyllene is 50 mg/ml to 500 mg/ml.

[0022] In an embodiment of the topical formulation as described herein, the one or more terpenes further comprise linalool, and the concentration of linalool is 25 mg/ml to 500 mg/ml.

[0023] In an embodiment of the topical formulation as described herein, the one or more flavonoids comprise at least one of diosmin, quercetin, and hesperidin.

[0024] In an embodiment of the topical formulation as described herein, the one or more flavonoids comprise diosmin, quercetin, and hesperidin.

[0025] In an embodiment of the topical formulation as described herein, the topical formulation further comprises a liquid carrier selected for instillation of the topical formulation onto an integumentary wound.

[0026] In another aspect, there is provided use of a first topical formulation for the treatment of an integumentary wound of a subject, wherein the first topical formulation comprises one or more cannabinoids; one or more terpenes; and one or more flavonoids, and is for application onto the integumentary wound, and wherein the one or more cannabinoids comprise at least 0.1 mg/ml tetrahydrocannabinolic acid.

[0027] In an embodiment of the use as described herein, the use further comprises use of a second topical formulation comprising one or more cannabinoids; one or more terpenes; and one or more flavonoids, wherein the second topical formulation is for application onto a periwound area around the integumentary wound.

[0028] In an embodiment of the use as described herein, the first topical formulation comprises an aloe vera gel and a hyaluronic acid gel, and the second topical formulation comprises pluronic lecithin organogel or a transdermal base comprising a liposomal component.

[0029] In an embodiment of the use as described herein, the first topical formulation and/or the second topical formulation is a topical formulation as described herein.

[0030] In an embodiment of the use as described herein, the use further comprises use of an oral formulation comprising one or more cannabinoids; one or more terpenes; and one or more flavonoids.

[0031] In an embodiment of the use as described herein, the integumentary wound is caused by a skin disease or condition, wherein the skin disease or condition is Skin Cancer (e.g., Primary Neoplasms, Metastatic Neoplasms, or Bowen's Disease), Vasculopathic Ulcers and

Erosions (e.g., Sickle Cell Disease, Martorell's Ulcer, Uremic Calciphylaxis, Non-Uremic Calciphylaxis, Venous Leg Ulcers, or Arterial Ulcers), Integumentary Ulcers and Erosions caused by microbes (e.g., a bacterium, fungus, virus, or mycobacterium), Ulcers and Erosions related to diabetes (e.g., Diabetic Foot Ulcers, Necrobiosis Lipoidica Diabeticorum, or Diabetic Dermopathy), Blistering Skin Conditions (e.g., Epidermolysis Bullosa, Pemphigus, or Bullous Pemphigoid), Ulcers and Erosions caused by autoimmune diseases (e.g., Pyoderma Gangrenosum, Rheumatoid arthritis, Systemic Lupus Erythematosis, Scleroderma, or Morphea), Vasculitic Ulcers and Erosions (e.g., Cutaneous vasculitis, Leukocytoclastic Vasculitis, Cutaneous polyarteritis nodosa, or Microscopic polyangiitis), or Ulcers and Erosions caused by other complex diseases (e.g., Hidradenitis Suppurativa, Lichen Simplex Chronicus, Lichen Sclerosus, Lichen Planus, Wegener's Granulomatosis, Cryoglobulinemia, Behcet's Disease, Cryofibrinogenemia, Antiphospholipid Syndrome, Allergic Dermatitis, Psoriasis, or Porokeratosis).

[0032] Other aspects, features, and embodiments of the present disclosure will become apparent to those of ordinary skill in the art upon review of the following description of specific embodiments in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE FIGURES

[0033] FIG. 1 is a diagram showing an exemplary normal wound healing sequence.

[0034] FIG. 2a is a schematic section view of a portion of normal tissues with intact skin.

[0035] FIG. 2b is a schematic section view of wounded tissues with an exposed wound bed.

[0036] FIGS. 2c-2g are schematic section views of the wound of FIG. 2b during treatment illustrating a treatment process according embodiments disclosed herein.

[0037] FIG. 3a shows representative analysis performed on day 15 in Example 2.

[0038] FIG. 3b shows representative analysis performed on day 41 in Example 2.

[0039] FIG. 3c shows representative analysis performed on day 87 in Example 2.

[0040] FIG. 4 shows the trend of wound healing as represented by the granulation and epithelial tissue density inside a wound area. Accounting of epithelial tissue started on approximately day 30 when significant epithelium growth started.

[0041] FIG. 5a shows wound size as measured by longest length.

[0042] FIG. 5b shows wound size as measured by widest width.

[0043] FIG. 5c shows wound size as measured by product of longest length and widest width as an upper-bound estimate of total wound area.

[0044] FIG. 6 is a schematic block diagram illustrating an exemplary kit according to an embodiment of the present disclosure.

[0045] FIG. 7 shows images of the right (column A) and left (column B) lateral ankle wounds at Day 97 (i.e., Day 0 of the second treatment; top images) and Day 150 (Day 53 of the second treatment; bottom images) of the treatment of the sickle cell disease patient as described in the case report of Example 4.

[0046] FIGS. 8A-8C relate to the treatment of NUC Patient A as described in the case report of Example 4. FIG.8A shows representative images of the wound region of Patient A on day 0, 27, 54 and 74. FIG. 8B shows the results of tracking of wound area through duration of treatment. The wound was completely closed on day 74. When fitted to a linear regression model, the expected wound closure date is 77.0 days. FIG. 8C shows the result of wound composition analysis showing the relative area of granulated tissue vs. reepithelialized tissue.

[0047] FIGS. 9A-9E relate to the treatment of NUC Patient B as described in the case report of Example 4. It shows representative images of the wound region of Patient A's left leg (FIG. 9A) on day 0, 27, 55, and 81 (2 days after closure), and Patient A's right leg (FIG. 9B) on day 0, 27, 55, and 76. FIG. 9C shows the result of tracking of wound area through duration of treatment for both legs. The wound was seen completely closed on day 79 and 76, respectively. When fitted to a linear regression model, the expected wound closure dates are 100 and 77 days, respectively. FIG. 9D and 9E show the result of wound composition analysis showing the relative area of granulated tissue vs. reepithelialized tissue for the left and right legs respectively.

[0048] FIG. 10 relates to the treatment of an arterial-venous ulcer with superimposed porokeratosis as described in the case report of Example 4. The decrease in size of the wound in cm^2 over the treatment period is depicted and the line of best fit (dotted) is plotted.

DETAILED DESCRIPTION

[0049] Selected combinations of a cannabinoid, a terpene and a flavonoid have been shown to provide healing effects upon direct application onto the wound bed of an integumentary wound. It has been surprisingly discovered by the present inventor that tetrahydrocannabinolic acid (THCa), which is non-psychoactive, produces better wound healing effects than decarboxylated tetrahydrocannabinol (THC), which is psychoactive. Thus, topical formulations disclosed herein may be substantially void of any psychoactive effects. Without being limited by any particular theory, it is expected that THCa contributes to downregulation of inflammation as well as improvement of angiogenesis, granulation tissue formation, and epithelial differentiation, via activation of PPAR family, NF-κB and other nuclear receptors.

[0050] As used herein, "integument" refers to the outer protective layer(s), both cutaneous membrane and mucous membrane, of a living being and the term "integumentary wound" refers to a breakdown and loss of at least a portion of the integument including the outermost sub-layer(s) of the integument, namely the epidermis, and optionally destruction of deeper tissues such as the dermis, fat, fascial connective tissues, and often muscle and bone. An integumentary wound may include a wound commonly referred to as an open wound (also known as wound bed), where an injured body area exposes the dermal layer of skin or tissue(s) and structure(s) beneath the dermal layer (such as fat, muscle, fascia, and bone) of skin to air. As can be appreciated by those skilled in the art, the integument has two main layers: (i) the outer layer, referred to as the epidermis, which functions as a barrier to the external environment, and (ii) the inner layer, referred to as the dermis, which is composed of connective tissue and provides the skin with some of its mechanical properties.

[0051] In an embodiment, treatment of an integumentary wound includes topically delivering the selected cannabinoid(s), terpene(s) and flavonoid(s) to the integumentary wound, and optionally a periwound area around the integumentary wound, as instillates.

[0052] An embodiment of the present disclosure thus provides a topical formulation comprising a selected composition of cannabinoids, terpenes and flavonoids, at concentrations within specific respective ranges, formulated for direct application onto an integumentary wound, and optionally a periwound area around the integumentary wound.

[0053] For example, in a particular embodiment, the formulation may include a topical instillate, which includes: (a) 5 mg/ml to 30 mg/ml of cannabidiol or cannabidiolic acid, and 2 mg/ml to 10 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid; (b) 30 mg/ml to 60 mg/ml of beta-caryophyllene and 10 mg/ml to 30 mg/ml of linalool; (c) 10 mg/ml to 30 mg/ml of diosmin and 10 mg/ml to 30 mg/ml of quercetin; and (d) aloe vera gel and optionally hyaluronic acid gel.

[0054] In another particular embodiment, the formulation may include a topical instillate, which includes: (a) 0.1 mg/ml to 20 mg/ml of cannabidiol or cannabidiolic acid, and 0 mg/ml to 5 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid; (b) 50 mg/ml to 500 mg/ml of beta-caryophyllene and 10 mg/ml to 150 mg/ml of linalool; (c) 0 mg/ml to 50 mg/ml of diosmin and 10 mg/ml to 50 mg/ml of quercetin; and (d) aloe vera gel and optionally hyaluronic acid gel.

[0055] In another particular embodiment, the formulation may include a topical instillate, which includes: (a) 2.3 mg/ml of cannabidiol or cannabidiolic acid, and 1.0 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid; (b) 81.5 mg/ml of beta-caryophyllene and

28.4 mg/ml of linalool; (c) 16.7 mg/ml of micronized diosmin and 16.7 mg/ml of micronized quercetin; and (d) aloe vera gel and hyaluronic acid gel.

[0056] In another particular embodiment, the formulation may include a topical instillate, which includes: (a) 2.6 mg/ml of cannabidiol or cannabidiolic acid; (b) 118 mg/ml of beta-caryophyllene; (c) 19.6 mg/ml of micronized diosmin, 21.7 mg/ml of micronized quercetin, and 2.2 mg/ml of hesperidin; and (d) aloe vera gel and hyaluronic acid gel.

[0057] Unless indicated otherwise, the stated concentrations in the present disclosure are based on the total volume of the formulation and the dry weights of respective active agents.

[0058] The formulation may include a solution or a colloid, and is formulated for direct application to the wound bed of an integumentary wound via instillation, such as by dropping, spraying, diffusing, dispersing, squirting, or spreading the formulation onto the integumentary wound bed, to promote wound healing.

[0059] Further embodiments of the present disclosure relate to methods of treating integumentary wounds. In a particular method, the method includes directly applying a topical formulation comprising a cannabinoid, a terpene, and a flavonoid onto an integumentary wound, and optionally a periwound area around the integumentary wound.

[0060] Still further embodiments of the present disclosure relate to uses of selected topical formulations disclosed herein for the treatment of an integumentary wound.

[0061] Selected topical formulations disclosed herein may also have one or more other beneficial effects such as management of pain (e.g., baseline pain and breakthrough pain), analgesic effects, anti-inflammatory effects, anti-pruritic effects, opioid-sparing effects, anti-microbial activity or the like.

Topical Formulations

[0062] The term "topical formulation" is generally understood to mean a mixture of substances that is suitable for application to a particular place on or in the body. A topical formulation may be a solution in which one or more solutes are uniformly distributed within a solvent, or a colloid in which one substance is not dissolved in, but suspended throughout, another substance. A topical formulation may exist in any phase or a combination of phases. Within the context of the present disclosure, suitable forms of a topical formulation for application to a cutaneous wound may include solution, lotion, cream, ointment, gel, emulsion, liposome, foam, powder, impregnated gauze sheet, tulle, vapor and paste, and suitable forms of a topical formulation for application to a mucous wound may include aerosolized spray for nasal and oral applications and suppository for rectal and vaginal applications.

[0063] In an embodiment, a topical formulation may include one or more cannabinoids, one or more terpenes, one or more flavonoids, and a liquid carrier selected for instillation of the topical formulation onto an integumentary wound.

[0064] The term "cannabinoid" is generally understood to include any chemical compound that acts upon a cannabinoid receptor. Examples of cannabinoids include cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), tetrahydrocannabivarin (THCV), cannabichromanon (CBCN), cannabielsoin (CBE), cannbifuran (CBF), tetrahydrocannabinol (THC), cannabinodiol (CBDL), cannabicyclol (CBL), cannabitriol (CBT), cannabivarin (CBV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), cannabigerol monomethyl ether (CBGM), cannabinerolic acid, cannabidiolic acid (CBDa), cannabinodiol (CBND), cannabinol propyl variant (CBNV), cannabitriol (CBO), tetrahydrocannabinolic acid (THCa), tetrahydrocannabivarinic acid (THCVa), and derivatives thereof. Further examples of cannabinoids are discussed in PCT Patent Application Pub. No. WO2017/190249 and US Patent Application Pub. No. US2014/0271940.

[0065] A cannabinoid may be in an acid form or a non-acid form, the latter also being referred to as the decarboxylated form since the non-acid form can be generated by decarboxylating the acid form. Within the context of the present disclosure, where reference is made to a particular cannabinoid, the cannabinoid can be in its acid or non-acid form, or be a mixture of both acid and non-acid forms.

[0066] In some embodiments, a topical formulation provided herein may include cannabidiol (CBD). CBD is not psychoactive, and is expected to relieve convulsion, inflammation, anxiety, and nausea. In some embodiments, CBD may be substituted entirely by CBDa.

[0067] The terms "cannabidiol," "CBD," or "cannabidiols" are generally understood to refer to one or more of the following compounds, and, unless a particular other stereoisomer or stereoisomers are specified, include the compound "Δ^2-cannabidiol." These compounds are: (1) Δ^5- cannabidiol (2-(6-isopropenyl-3-methyl-5-cyclohexen-l-yl)-5-pentyl-l,3-benzenediol); (2) Δ^4- cannabidiol (2-(6-isopropenyl-3-methyl-4-cyclohexen-l-yl)-5-pentyl-l,3-benzenediol); (3) Δ^3- cannabidiol (2-(6-isopropenyl-3-methyl-3-cyclohexen-l-yl)-5-pentyl-l,3-benzenediol); (4) $\Delta^{3,7}$- cannabidiol (2-(6-isopropenyl-3-methylenecyclohex-l-yl)-5-pentyl-l,3-benzenediol); (5) Δ^2-cannabidiol (2-(6-isopropenyl-3-methyl-2-cyclohexen-l-yl)-5-pentyl-l,3-benzenediol); (6) Δ^1-cannabidiol (2-(6-isopropenyl-3-methyl-l-cyclohexen-l-yl)-5-pentyl-l,3-benzenediol); and (7) Δ^6-cannabidiol (2-(6-isopropenyl-3-methyl-6-cyclohexen-l-yl)-5-pentyl-l,3-benzenediol).

[0068] These compounds have one or more chiral centers and two or more stereoisomers as stated below: (1) Δ^5-cannabidiol has 2 chiral centers and 4 stereoisomers; (2) Δ^4-cannabidiol has 3 chiral centers and 8 stereoisomers; (3) Δ^3-cannabidiol has 2 chiral centers and 4 stereoisomers; (4) $\Delta^{3,7}$- cannabidiol has 2 chiral centers and 4 isomers; (5) Δ^2-cannabidiol has 2 chiral centers and 4 stereoisomers; (6) Δ^1- cannabidiol has 2 chiral centers and 4 stereoisomers; and (7) Δ^6-cannabidiol has 1 chiral center and 2 stereoisomers.

[0069] In some embodiments, a topical formulation provided herein may include Δ^2-cannabidiol.

[0070] Unless specifically stated, a reference to "cannabidiol," "CBD," or "cannabidiols" or to any of specific cannabidiol compounds (l)-(7) as referred to above includes all possible stereoisomers of all compounds included by the reference. For example, "Δ^2-cannabidiol" may be a mixture of the Δ^2-cannabidiol stereoisomers that are present in a plant, or an extract thereof, such as Cannabis sativa, Cannabis indica, or another plant of the Cannabis genus;"Δ^2-cannabidiol" may be a mixture of the Δ^2-cannabidiol stereoisomers that are present in a plant, or an extract thereof, such as Cannabis sativa, Cannabis indica, or another plant of the Cannabis genus, wherein said mixture of stereoisomers is at, or at about, the naturally occurring ratio of isomers; and "Δ^2-cannabidiol" may be a single stereoisomer.

[0071] In some embodiments, a topical formulation provided herein may comprise one or more cannabinoids, such as cannabinol, cannabigerol, cannabichromene, and tetrahydrocannabivarin, in addition to CBD. The combination of CBD and CBN may be particularly useful for managing burn pain.

[0072] In some embodiments, a topical formulation provided herein may also include THC. In other embodiments, a topical formulation provided herein may not contain THC. THC is only psychoactive in its decarboxylated state. Delta-9-tetrahydrocannabinol (Δ9-THC) and delta-8-tetrahydrocannabinol (Δ8-THC) produce the effects associated with cannabis by binding to the CB1 cannabinoid receptors in the brain. THC is expected to ease moderate pain (analgesic) and to be neuroprotective, while also offering the potential to reduce neuroinflammation and to stimulate neurogenesis. In some embodiments, THC may be substituted entirely by THCV. The carboxylic acid form (THCa) is non-psychoactive.

[0073] In some embodiments, a topical formulation provided herein may contain both THC and THCa. In some embodiments, a topical formulation provided herein may contain THCa, but not THC.

[0074] In some embodiments, a topical formulation provided herein may include 0.1 mg/ml to 40 mg/ml of cannabinoid(s). For example, a topical formulation provided herein may

comprise 0.1 mg/ml to 30 mg/ml, 0.5 mg/ml to 30 mg/ml, 1 mg/ml to 30 mg/ml, 0.1 mg/ml to 25 mg/ml, 0.5 mg/ml to 25 mg/ml, 1 mg/ml to 25 mg/ml, 0.1 mg/ml to 20 mg/ml, 0.5 mg/ml to 20 mg/ml, 1 mg/ml to 20 mg/ml, 0.1 mg/ml to 15 mg/ml, 0.5 mg/ml to 15 mg/ml, 1 mg/ml to 15 mg/ml, 0.1 mg/ml to 10 mg/ml, 0.5 mg/ml to 10 mg/ml, 1 mg/ml to 10 mg/ml, 0.1 mg/ml to 5 mg/ml, 0.5 mg/ml to 5 mg/ml, 1 mg/ml to 5 mg/ml, 0.1 mg/ml to 2 mg/ml, 0.5 mg/ml to 2 mg/ml, 1 mg/ml to 2 mg/ml, 2 mg/ml to 40 mg/ml, 2 mg/ml to 30 mg/ml, 2 mg/ml to 25 mg/ml, 2 mg/ml to 20 mg/ml, 2 mg/ml to 15 mg/ml, 2 mg/ml to 10 mg/ml, 2 mg/ml to 5 mg/ml, 5 mg/ml to 40 mg/ml, 5 mg/ml to 30 mg/ml, 5 mg/ml to 25 mg/ml, 5 mg/ml to 20 mg/ml, 5 mg/ml to 15 mg/ml, 5 mg/ml to 10 mg/ml, 10 mg/ml to 40 mg/ml, 10 mg/ml to 30 mg/ml, 10 mg/ml to 25 mg/ml, 10 mg/ml to 20 mg/ml, 10 mg/ml to 15 mg/ml, 15 mg/ml to 40 mg/ml, 15 mg/ml to 30 mg/ml, 15 mg/ml to 25 mg/ml, 15 mg/ml to 20 mg/ml, 20 mg/ml to 40 mg/ml, 20 mg/ml to 30 mg/ml, 20 mg/ml to 25 mg/ml, 25 mg/ml to 40 mg/ml, 25 mg/ml to 30 mg/ml, or 30 mg/ml to 40 mg/ml of cannabinoid(s).

[0075] In some embodiments, a topical formulation provided herein may include 0.1 mg/ml to 10 mg/ml of THCa. For example, a topical formulation provided herein may comprise 0.1 mg/ml to 5 mg/ml, 0.5 mg/ml to 5 mg/ml, 1 mg/ml to 5 mg/ml, 2 mg/ml to 5 mg/ml, 0.1 mg/ml to 4 mg/ml, 0.5 mg/ml to 4 mg/ml, 1 mg/ml to 4 mg/ml, 2 mg/ml to 4 mg/ml, 0.1 mg/ml to 3 mg/ml, 0.5 mg/ml to 3 mg/ml, 1 mg/ml to 3 mg/ml, 2 mg/ml to 3 mg/ml, 0.1 mg/ml to 2 mg/ml, 0.5 mg/ml to 2 mg/ml, 1 mg/ml to 2 mg/ml, 0.1 mg/ml to 1 mg/ml, or 0.5 mg/ml to 1 mg/ml of THCa.

[0076] In some embodiments, a topical formulation provided herein may comprise at least 0.1 mg/ml, 0.5 mg/ml, 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml, 5 mg/ml, 6 mg/ml, 7 mg/ml, 8 mg/ml, 9 mg/ml, 10 mg/ml, 11 mg/ml, 12 mg/ml, 13 mg/ml, 14 mg/ml, 15 mg/ml, 16 mg/ml, 17 mg/ml, 18 mg/ml, 19 mg/ml, 20 mg/ml, 21 mg/ml, 22 mg/ml, 23 mg/ml, 24 mg/ml, 25 mg/ml, 26 mg/ml, 27 mg/ml, 28 mg/ml, 29 mg/ml, 30 mg/ml, 31 mg/ml, 32 mg/ml, 33 mg/ml, 34 mg/ml, 35 mg/ml, 36 mg/ml, 37 mg/ml, 38 mg/ml, or 39 mg/ml of cannabinoid(s).

[0077] In some embodiments, a topical formulation provided herein may comprise 0.1 mg/ml, 0.5 mg/ml, 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml, 5 mg/ml, 6 mg/ml, 7 mg/ml, 8 mg/ml, 9 mg/ml, 10 mg/ml, 11 mg/ml, 12 mg/ml, 13 mg/ml, 14 mg/ml, 15 mg/ml, 16 mg/ml, 17 mg/ml, 18 mg/ml, 19 mg/ml, 20 mg/ml, 21 mg/ml, 22 mg/ml, 23 mg/ml, 24 mg/ml, 25 mg/ml, 26 mg/ml, 27 mg/ml, 28 mg/ml, 29 mg/ml, 30 mg/ml, 31 mg/ml, 32 mg/ml, 33 mg/ml, 34 mg/ml, 35 mg/ml, 36 mg/ml, 37 mg/ml, 38 mg/ml, 39 mg/ml or 40 mg/ml of cannabinoid(s).

[0078] In some embodiments, the concentrations of cannabinoids in a topical formulation provided herein may be adjusted depending on the phase of wound healing. For example, during

the inflammatory phase, a higher level of a mixture of THC and CBD (e.g., 5 mg/ml to 20 mg/ml of cannabidiol and 2 mg/ml to 10 mg/ml of tetrahydrocannabinol) can be beneficial since wound pain is most intense during this phase and higher levels of THC and CBD can help to manage the pain. In comparison, during the re-epithelial and remodeling phases, a reduced concentration of THC (e.g., 0 mg/ml to 5 mg/ml) may be desirable since preclinical studies suggest that THC may inhibit keratinocyte differentiation, while the CBD concentration may remain relatively high (e.g., 0.1 mg/ml to 20 mg/ml).

[0079] The term "terpene" is generally understood to include any organic compound derived biosynthetically from units of isoprene, and the term "terpenoid" generally refers to a chemically modified terpene (e.g., by oxidation). As used herein, terpenes include terpenoids. Terpenes may be classified in various ways, such as by their sizes. For example, suitable terpenes may include monoterpenes, sesquiterpenes, or triterpenes. At least some terpenes are expected to interact with, and potentiate the activity of, cannabinoids.

[0080] Examples of terpenes known to be extractable from cannabis include aromadendrene, bergamottin, bergamotol, bisabolene, borneol, 4-3-carene, beta-caryophyllene, cineole/eucalyptol, p-cymene, dihydrojasmone, elemene, farnesene, fenchol, geranylacetate, guaiol, humulene, isopulegol, limonene, linalool, menthone, menthol, menthofuran, myrcene, nerylacetate, neomenthylacetate, ocimene, perillylalcohol, phellandrene, pinene, pulegone, sabinene, terpinene, terpineol, terpinen-4-ol, terpinolene, and derivatives thereof.

[0081] Additional examples of terpenes include nerolidol, phytol, geraniol, alpha-bisabolol, thymol, genipin, astragaloside, asiaticoside, camphene, beta-amyrin, thujone, citronellol, 1,8-cineole, cycloartenol, and derivatives thereof. Further examples of terpenes are discussed in US Patent Application Pub. No. US2016/0250270.

[0082] In some embodiments, a topical formulation provided herein may include at least one of beta-caryophyllene, linalool, thymol, alpha-bisabolol, myrcene, limonene, and pinene. In some embodiments, a topical formulation provided herein may comprise beta-caryophyllene and a monoterpene such as linalool, thymol, alpha-bisabolol, alpha-terpineol and genipin or a triterpene such as astragaloside and asiaticoside. In some embodiments, a topical formulation provided herein may comprise beta-caryophyllene, linalool, or both.

[0083] Cannabinoid oils available on the market often contain trace amounts of various terpenes. In some embodiments, a topical formulation provided herein may have a total concentration of terpene(s) that is higher than the total concentration of terpenes found in commercially available cannabinoid oils.

[0084] For example, in some embodiments, a topical formulation provided herein may include 10 mg/ml to 1000 mg/ml of terpene(s). More particularly, the total terpene concentration in a topical formulation provided herein may be 10 mg/ml to 1000 mg/ml, 10 mg/ml to 500 mg/ml, 10 mg/ml to 400 mg/ml, 10 mg/ml to 300 mg/ml, 10 mg/ml to 250 mg/ml, 10 mg/ml to 200 mg/ml, 10 mg/ml to 180 mg/ml, 10 mg/ml to 160 mg/ml, 10 mg/ml to 140 mg/ml, 10 mg/ml to 120 mg/ml, 10 mg/ml to 100 mg/ml, 10 mg/ml to 80 mg/ml, 10 mg/ml to 60 mg/ml, 10 mg/ml to 40 mg/ml, 10 mg/ml to 25 mg/ml, 10 mg/ml to 20 mg/ml, 10 mg/ml to 15 mg/ml, 15 mg/ml to 1000 mg/ml, 15 mg/ml to 500 mg/ml, 15 mg/ml to 400 mg/ml, 15 mg/ml to 300 mg/ml, 15 mg/ml to 250 mg/ml, 15 mg/ml to 200 mg/ml, 15 mg/ml to 180 mg/ml, 15 mg/ml to 160 mg/ml, 15 mg/ml to 140 mg/ml, 15 mg/ml to 120 mg/ml, 15 mg/ml to 100 mg/ml, 15 mg/ml to 80 mg/ml, 15 mg/ml to 60 mg/ml, 15 mg/ml to 40 mg/ml, 15 mg/ml to 25 mg/ml, 15 mg/ml to 20 mg/ml, 20 mg/ml to 1000 mg/ml, 20 mg/ml to 500 mg/ml, 20 mg/ml to 400 mg/ml, 20 mg/ml to 300 mg/ml, 20 mg/ml to 250 mg/ml, 20 mg/ml to 200 mg/ml, 20 mg/ml to 180 mg/ml, 20 mg/ml to 160 mg/ml, 20 mg/ml to 140 mg/ml, 20 mg/ml to 120 mg/ml, 20 mg/ml to 100 mg/ml, 20 mg/ml to 80 mg/ml, 20 mg/ml to 60 mg/ml, 20 mg/ml to 40 mg/ml, 20 mg/ml to 25 mg/ml, 25 mg/ml to 1000 mg/ml, 25 mg/ml to 500 mg/ml, 25 mg/ml to 400 mg/ml, 25 mg/ml to 300 mg/ml, 25 mg/ml to 250 mg/ml, 25 mg/ml to 200 mg/ml, 25 mg/ml to 180 mg/ml, 25 mg/ml to 160 mg/ml, 25 mg/ml to 140 mg/ml, 25 mg/ml to 120 mg/ml, 25 mg/ml to 100 mg/ml, 25 mg/ml to 80 mg/ml, 25 mg/ml to 60 mg/ml, 25 mg/ml to 40 mg/ml, 40 mg/ml to 1000 mg/ml, 40 mg/ml to 500 mg/ml, 40 mg/ml to 400 mg/ml, 40 mg/ml to 300 mg/ml, 40 mg/ml to 250 mg/ml, 40 mg/ml to 200 mg/ml, 40 mg/ml to 180 mg/ml, 40 mg/ml to 160 mg/ml, 40 mg/ml to 140 mg/ml, 40 mg/ml to 120 mg/ml, 40 mg/ml to 100 mg/ml, 40 mg/ml to 90 mg/ml, 40 mg/ml to 80 mg/ml, 40 mg/ml to 60 mg/ml, 60 mg/ml to 1000 mg/ml, 60 mg/ml to 500 mg/ml, 60 mg/ml to 400 mg/ml, 60 mg/ml to 300 mg/ml, 60 mg/ml to 250 mg/ml, 60 mg/ml to 200 mg/ml, 60 mg/ml to 180 mg/ml, 60 mg/ml to 160 mg/ml, 60 mg/ml to 140 mg/ml, 60 mg/ml to 120 mg/ml, 60 mg/ml to 100 mg/ml, 60 mg/ml to 80 mg/ml, 80 mg/ml to 1000 mg/ml, 80 mg/ml to 500 mg/ml, 80 mg/ml to 400 mg/ml, 80 mg/ml to 300 mg/ml, 80 mg/ml to 250 mg/ml, 80 mg/ml to 200 mg/ml, 80 mg/ml to 180 mg/ml, 80 mg/ml to 160 mg/ml, 80 mg/ml to 140 mg/ml, 80 mg/ml to 120 mg/ml, 80 mg/ml to 100 mg/ml, 100 mg/ml to 1000 mg/ml, 100 mg/ml to 500 mg/ml, 100 mg/ml to 400 mg/ml, 100 mg/ml to 300 mg/ml, 100 mg/ml to 250 mg/ml, 100 mg/ml to 200 mg/ml, 100 mg/ml to 180 mg/ml, 100 mg/ml to 160 mg/ml, 100 mg/ml to 140 mg/ml, 100 mg/ml to 120 mg/ml, 120 mg/ml to 1000 mg/ml, 120 mg/ml to 500 mg/ml, 120 mg/ml to 400 mg/ml, 120 mg/ml to 300 mg/ml, 120 mg/ml to 250 mg/ml, 120 mg/ml to 200 mg/ml, 120 mg/ml to 180 mg/ml, 120 mg/ml to 160 mg/ml, 120 mg/ml to 140 mg/ml, 140 mg/ml to 1000

mg/ml, 140 mg/ml to 500 mg/ml, 140 mg/ml to 400 mg/ml, 140 mg/ml to 300 mg/ml, 140 mg/ml to 250 mg/ml, 140 mg/ml to 200 mg/ml, 140 mg/ml to 180 mg/ml, 140 mg/ml to 160 mg/ml, 160 mg/ml to 1000 mg/ml, 160 mg/ml to 500 mg/ml, 160 mg/ml to 400 mg/ml, 160 mg/ml to 300 mg/ml, 160 mg/ml to 250 mg/ml, 160 mg/ml to 200 mg/ml, 160 mg/ml to 180 mg/ml, 180 mg/ml to 1000 mg/ml, 180 mg/ml to 500 mg/ml, 180 mg/ml to 400 mg/ml, 180 mg/ml to 300 mg/ml, 180 mg/ml to 250 mg/ml, 180 mg/ml to 200 mg/ml, 200 mg/ml to 1000 mg/ml, 200 mg/ml to 500 mg/ml, 200 mg/ml to 400 mg/ml, 200 mg/ml to 300 mg/ml, or 200 mg/ml to 250 mg/ml.

[0085] In some embodiments, the total terpene concentration in a topical formulation provided herein may be at least 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, 50 mg/ml, 55 mg/ml, 60 mg/ml, 65 mg/ml, 70 mg/ml, 75 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml, 110 mg/ml, 120 mg/ml, 130 mg/ml, 140 mg/ml, 150 mg/ml, 160 mg/ml, 170 mg/ml, 180 mg/ml, 190 mg/ml, 200 mg/ml, 210 mg/ml, 220 mg/ml, 230 mg/ml, 240 mg/ml, 250 mg/ml, 300 mg/ml, 400 mg/ml, 500 mg/ml, 600 mg/ml, 700 mg/ml, 800 mg/ml, or 900 mg/ml.

[0086] In some embodiments, the total terpene concentration in a topical formulation provided herein may be 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, 50 mg/ml, 55 mg/ml, 60 mg/ml, 65 mg/ml, 70 mg/ml, 75 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml, 110 mg/ml, 120 mg/ml, 130 mg/ml, 140 mg/ml, 150 mg/ml, 160 mg/ml, 170 mg/ml, 180 mg/ml, 190 mg/ml, 200 mg/ml, 210 mg/ml, 220 mg/ml, 230 mg/ml, 240 mg/ml, 250 mg/ml, 300 mg/ml, 400 mg/ml, 500 mg/ml, 600 mg/ml, 700 mg/ml, 800 mg/ml, or 900 mg/ml.

[0087] In some embodiments, the concentrations of terpenes in a topical formulation provided herein may be adjusted depending on the phase of wound healing. For example, it has been discovered that a high level of beta-caryophyllene (e.g., 50 mg/ml to 500 mg/ml) may be desirable during the re-epithelialization and remodeling phases as beta-caryophyllene is a strong agonist for CB2 receptors of the endocannabinoid system.

[0088] The term “flavonoid” is generally understood to include any secondary plant metabolite that has a general 15-carbon skeleton structure which consists of two phenyl rings and a heterocyclic ring. Flavonoids are generally classified into subclasses by the state of oxidation and the substitution pattern at the C2-C3 unit, including flavanones, flavonols, flavones, anthocyanidins, chalcones, dihydrochalcones, aurones, flavanols, dihydroflavanols, proanthocyanidins (flavan-3,4-diols), isoflavones and neoflavones. Specific examples of

flavonoids include cannaflavins, kaempferol (3,4',5,7-tetrahydroxyflavone), apigenin (4',5,7-trihydroxyflavone), chrysin, diosmin, hesperidin, luteolin, rutin, and quercetin.

[0089] In some embodiments, a topical formulation provided herein may include quercetin. In some embodiments, a topical formulation provided herein may include diosmin, quercetin, hesperidin, or a combination thereof. In some embodiments, a topical formulation provided herein may include diosmin and hesperidin at a ratio of about 9:1. In some embodiments, a topical formulation provided herein may include quercetin, kaempferol, apigenin, or a combination thereof. Each or both of diosmin and quercetin may be micronized, and optionally in the form of dry powders.

[0090] Cannabinoid oils available on the market often contain trace amounts of various flavonoids. In some embodiments, a topical formulation provided herein may have a total flavonoid concentration that is higher than the total concentration of flavonoids found in commercially available cannabinoid oils.

[0091] In some embodiments, the total flavonoid concentration in a topical formulation provided herein may be 10 mg/ml to 500 mg/ml. For example, the total flavonoid concentration may be 10 mg/ml to 400 mg/ml, 10 mg/ml to 300 mg/ml, 10 mg/ml to 200 mg/ml, 10 mg/ml to 150 mg/ml, 10 mg/ml to 100 mg/ml, 10 mg/ml to 90 mg/ml, 10 mg/ml to 80 mg/ml, 10 mg/ml to 70 mg/ml, 10 mg/ml to 60 mg/ml, 10 mg/ml to 50 mg/ml, 10 mg/ml to 40 mg/ml, 10 mg/ml to 30 mg/ml, 10 mg/ml to 25 mg/ml, 10 mg/ml to 20 mg/ml, 10 mg/ml to 15 mg/ml, 15 mg/ml to 500 mg/ml, 15 mg/ml to 400 mg/ml, 15 mg/ml to 300 mg/ml, 15 mg/ml to 200 mg/ml, 15 mg/ml to 150 mg/ml, 15 mg/ml to 100 mg/ml, 15 mg/ml to 90 mg/ml, 15 mg/ml to 80 mg/ml, 15 mg/ml to 70 mg/ml, 15 mg/ml to 60 mg/ml, 15 mg/ml to 50 mg/ml, 15 mg/ml to 40 mg/ml, 15 mg/ml to 30 mg/ml, 15 mg/ml to 25 mg/ml, 15 mg/ml to 20 mg/ml, 20 mg/ml to 500 mg/ml, 20 mg/ml to 400 mg/ml, 20 mg/ml to 300 mg/ml, 20 mg/ml to 200 mg/ml, 20 mg/ml to 150 mg/ml, 20 mg/ml to 100 mg/ml, 20 mg/ml to 90 mg/ml, 20 mg/ml to 80 mg/ml, 20 mg/ml to 70 mg/ml, 20 mg/ml to 60 mg/ml, 20 mg/ml to 50 mg/ml, 20 mg/ml to 40 mg/ml, 20 mg/ml to 30 mg/ml, 40 mg/ml to 500 mg/ml, 40 mg/ml to 400 mg/ml, 40 mg/ml to 300 mg/ml, 40 mg/ml to 200 mg/ml, 40 mg/ml to 150 mg/ml, 40 mg/ml to 100 mg/ml, 40 mg/ml to 90 mg/ml, 40 mg/ml to 80 mg/ml, 40 mg/ml to 70 mg/ml, 40 mg/ml to 60 mg/ml, 40 mg/ml to 50 mg/ml, 50 mg/ml to 500 mg/ml, 50 mg/ml to 400 mg/ml, 50 mg/ml to 300 mg/ml, 50 mg/ml to 200 mg/ml, 50 mg/ml to 150 mg/ml, 50 mg/ml to 100 mg/ml, 50 mg/ml to 90 mg/ml, 50 mg/ml to 80 mg/ml, 50 mg/ml to 70 mg/ml, 50 mg/ml to 60 mg/ml, 60 mg/ml to 500 mg/ml, 60 mg/ml to 400 mg/ml, 60 mg/ml to 300 mg/ml, 60 mg/ml to 200 mg/ml, 60 mg/ml to 150 mg/ml, 60 mg/ml to 100 mg/ml, 60 mg/ml to 90 mg/ml, 60 mg/ml to 80 mg/ml, 60 mg/ml to 70 mg/ml, 80 mg/ml to 500 mg/ml, 80 mg/ml to 400

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[0092] In some embodiments, the total flavonoid concentration in a topical formulation provided herein may be at least 10 mg/ml, 11 mg/ml, 12 mg/ml, 13 mg/ml, 14 mg/ml, 15 mg/ml, 16 mg/ml, 17 mg/ml, 18 mg/ml, 19 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml, 110 mg/ml, 120 mg/ml, 130 mg/ml, 140 mg/ml, 150 mg/ml, 160 mg/ml, 170 mg/ml, 180 mg/ml, 190 mg/ml, 200 mg/ml, 250 mg/ml, 300 mg/ml, 350 mg/ml, 400 mg/ml, or 450 mg/ml.

[0093] In some embodiments, the total flavonoid concentration in a topical formulation provided herein may be 10 mg/ml, 11 mg/ml, 12 mg/ml, 13 mg/ml, 14 mg/ml, 15 mg/ml, 16 mg/ml, 17 mg/ml, 18 mg/ml, 19 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml, 110 mg/ml, 120 mg/ml, 130 mg/ml, 140 mg/ml, 150 mg/ml, 160 mg/ml, 170 mg/ml, 180 mg/ml, 190 mg/ml, 200 mg/ml, 250 mg/ml, 300 mg/ml, 350 mg/ml, 400 mg/ml, 450 mg/ml, or 500 mg/ml.

[0094] In some embodiments, the concentrations of flavonoids in a topical formulation provided herein may be adjusted depending on the phase of wound healing. For example, it has been discovered that a high level of quercetin (e.g., 10 mg/ml to 50 mg/ml) may be desirable during the granulation phase due to its effects on VEGF and TGF-beta. In comparison, the levels of diosmin may remain high (e.g., 10 mg/ml to 50 mg/ml) throughout all phases of the healing cascade.

[0095] The cannabinoid(s), terpene(s), and flavonoid(s) used in a topical formulation provided herein may be extracted from natural plants or genetically modified host cells (e.g., yeast cells), or may be synthesized. Terpenes or flavonoids may be extracted from non-cannabis plants such as fruits and vegetables. When the cannabinoid(s), terpene(s), or flavonoid(s) is extracted from a source, the amount of solvent(s) in the extract or the concentration of the cannabinoid, terpene or flavonoid in the extract may vary. For example, an extract may comprise one or more solvents (e.g., an oil or a medium-chain triglyceride), or may be substantially free of any solvent (i.e, containing no detectable level of a solvent). In another

example, an extract may be substantially pure (e.g., the concentration of the cannabinoid, terpene or flavonoid in the extract is more than 99% wt).

[0096] In some embodiments, a topical formulation provided herein may include a liquid carrier selected for instillation of the topical formulation onto an integumentary wound, a periwound area around an integumentary wound, or both. The term "liquid carrier" is generally understood to include any carrier that is liquid at ambient temperatures and in which one or more active agents are carried in, dispersed in, or dissolved in. A liquid carrier may be in a form of a viscous liquid, paste, an emulsion or a gel. As can be understood by those skilled in the art, the liquid carrier should be safe for direct application to the integumentary wound, and should avoid or limit irritation or inflammation, or increasing pain level. For example, an alcohol-based carrier would not be suitable for instilling a topical formulation provided herein to the wound bed as it would cause necrosis, pain and irritation at the wound site.

[0097] Within the context of the present disclosure, the term "instillation" refers to gradual application or administration of a topical formulation onto a wound bed of a subject. Instillation of a topical formulation provided herein may be carried out by modes of application that include, but are not limited to, dropping, spraying, diffusing, dispersing, squirting, and spreading.

[0098] In some embodiments, a suitable liquid carrier may include an aloe vera gel, ointment, or cream; a hyaluronic acid gel, ointment, or cream; a vegetable oil (such as olive oil or sunflower oil); a medium-chain triglyceride; pluronic lecithin organogel (PLO); a transdermal base comprising liposomal components; normal saline; or a mixture or combination thereof. In some embodiments, the liquid carrier may be an aloe vera gel. In some embodiments, the liquid carrier may include a mixture or combination of an aloe vera gel and a hyaluronic acid gel, for example, at a 1:1 ratio. In some embodiments, the liquid carrier may be sunflower oil.

[0099] In some embodiments, the liquid carrier may be a transdermal base comprising a liposomal component. Examples of transdermal bases comprising liposomal components are LIPODERM™, a family of transdermal bases that are available exclusively from Professional Compounding Centers of America (PCCA). LIPODERM™ is an elegant alternative to traditional pluronic lecithin organogel (PLO) and contains a proprietary liposomal component to increase the permeation of a variety of active pharmaceutical ingredients (APIs).

[0100] Medium-chain triglycerides are triglycerides which include a glycerol backbone and a number of fatty acids, where two or three of the fatty acids have an aliphatic tail of 6 to 12 carbon atoms.

[0101] Other than cannabinoids, terpenes and flavonoids, which may be considered active agents, a topical formulation provided herein may include one or more additional active agents in some embodiments. The term "active agent" is generally understood to mean an active pharmaceutical ingredient.

[0102] Examples of active agents include active herbal extracts, analgesics, local anesthetics, antiepileptics, antiallergic agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antimicrobials, antimycotics, antiproliferative agents, antioxidants, antipruritics, antipsoriatic agents, antirosacea agents, antiseborrheic agents, antiseptics, antiswelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, vasoconstrictors, vasodilators, vitamins (e.g., vitamin C) and associated derivatives, minerals, wound healing agents and wart removers.

[0103] In some embodiments, topical formulations provided herein may further comprise one or more of an anti-inflammatory agent, a wound healing agent, an anti-oxidizing agent, and an anti-microbial agent.

[0104] Topical formulations provided herein may further comprise at least one excipient that does not interfere with the effectiveness or the biological activities of active agents and is not toxic to the subject to which topical formulations provided herein are applied.

[0105] Suitable excipients may include preservatives; thickening agents; buffers; isotonic agents; wetting, solubilizing, and emulsifying agents; acidifying agents; alkalinizing agents; carrying agents; chelating agents; complexing agents; solvents; suspending or viscosity-increasing agents; oils; penetration enhancers; polymers; stiffening agents; proteins; carbohydrates; and bulking agents.

Methods of Preparation

[0106] An exemplary method of preparing topical formulations provided herein comprises decanting a liquid carrier described herein into a vessel such as a container; adding one or more flavonoids, one or more cannabinoids, and one or more terpenes sequentially to the liquid carrier; and mixing the one or more flavonoids, one or more cannabinoids, and one or more terpenes in the liquid carrier, for example, by shaking the vessel. The method may be

carried out in a sterile environment using sterile technique and equipment. The method may also be carried out in a dark environment (e.g., the vessel being covered with dark tape) in order to protect topical formulations from light.

[0107] A topical formulation provided herein may also be prepared from a kit provided herein by mixing the materials of the kit following the instructions contained within the kit. For example, one or more flavonoids may be pre-mixed with a liquid carrier and contained in one container in a kit, and one or more cannabinoids and one or more terpenes may be added separately to constitute the topical formulation following the instructions.

Wound Dressings

[0108] There are many known topical wound dressings for use in the treatment of wounds or other openings at a physiological target site on a human or animal body which is exuding blood or other bodily fluids. For example, a wound dressing may be selected from wound dressings described in Dhivya S. et al. *Biomedicine (Taipei)* 2015 Dec; 5(4):24-28.

[0109] In an embodiment disclosed herein, a wound dressing or a selected sequence of wound dressings may be used for or after application of a topical formulation to the integumentary wound. A suitable wound dressing may include a wound contact layer. The wound dressing may take the form of a gauze, a bandage, a pad, a foam dressing, a film dressing, a patch, or the like. In some embodiments, the wound contact layer may include a material or layer sold under the trademark JELONET™ or PROFORE WCL™. JELONET™ is a sterile paraffin tulle gras dressing made from open weave gauze and has interlocking threads which minimise fraying when the dressing is cut to shape. PROFORE WCL™ is a 14cm x 20cm (5 1/2" x 8") dressing made of knitted viscose rayon.

[0110] In some embodiments, a wound dressing described above may be used separately from a formulation described herein. For example, the formulation and the wound dressing may be applied to an integumentary wound sequentially. In some embodiments, a wound dressing described above may be used concurrently with a formulation described herein. For example, the formulation may be integrated with the contact layer in the wound dressing before use such that the formulation is releasable from the contact layer at a suitable rate after the wound dressing is applied onto an integumentary wound.

Methods and Uses

[0111] Topical formulations and wound dressings provided herein may be useful for the treatment of an integumentary wound of a subject. Without being limited by any particular theory, it is expected that a topical formulation as described herein may promote wound healing

by synergistically stimulating granulation tissue growth and promoting epithelialization, through one or more epigenetic mechanisms including interaction with the endocannabinoid system.

[0112] The endocannabinoid system (ECS) is ubiquitous throughout the human body and has recently been found to have a significant representation throughout the integumentary system, both cutaneous membranes and mucous membranes. The ECS is principally composed of cannabinoid receptors (CB1 and CB2), endogenous ligands (AEA and 2-AG), biosynthetic pathways (NAPE and DAGL), and degradation pathways (FAAH and MAGL). The ECS signaling pathway also involves other G protein-coupled cannabinoid receptors, ionotropic receptors (TRPV, TRPA, TRPM), nuclear receptors (PPARγ, PPARα, PPARδ, NF-κB), and non-cannabinoid targets (5-HT, GlyR, A2A, α2R). Both cannabinoids and non-cannabinoids, such as terpenes and flavonoids, are capable of complex direct and indirect interactions with the ECS of the integumentary system.

[0113] The terms “treat,” “treating,” or “treatment of” are used herein in their broad senses unless otherwise specifically indicated in the particular context, and results of a treatment may generally include reversing, alleviating, or inhibiting the progress of an indicated disorder or condition, or one or more symptoms of the disorder or condition.

[0114] As used herein, the term “individual” or "subject" means an animal; for example, a mammal such as a human. Mammals also include farm animals, sport animals, companion animals, primates, horses, dogs, cats, mice and rats.

[0115] In some embodiments, a method of treating an integumentary wound may include instilling a topical formulation provided herein, for example, a solution or colloid, onto an integumentary wound of a subject. Instillation may be carried out by dropping, spraying, diffusing, dispersing, squirting, or spreading the topical formulation. An applicator may be used for instillation. Examples of applicators include a dropper, a nebulizer, an impregnated gauze sheet, a syringe, and a cotton swap. Post instillation, the topical formulation may cover one or more areas within the integumentary wound, or may cover the entire integumentary wound (including the wound edge), or may cover the entire integumentary wound as well as an area adjacent to an edge the integumentary wound (e.g., the periwound area).

[0116] In some embodiments, a method of treating an integumentary wound may include applying a topical formulation provided herein, for example, a solution or colloid, onto both an integumentary wound of a subject and a periwound area around the integumentary wound. The periwound area is typically limited to the integument surrounding an open wound within about 4 cm of the wound edge, but may extend beyond the 4 cm limit depending on the extent of the damages present. For example, as can be appreciated by those skilled in the art, the periwound

area may be proportionate to the size of the open wound, and may cover any skin area that is at risk of further breakdown. It is recognized that tissues within the periwound area may exhibit pathophysiologic features such as inflammation, edema, vasoconstriction, lymphatic obstruction, reduced oxygen tensions, and acidosis from reduced cellular chemotaxis ("leukocyte entrapment").

[0117] In some embodiments, topical formulations suitable for application to a periwound area around an integumentary wound of a subject may comprise a liquid carrier that has the ability to penetrate intact skin, such as pluronic lecithin organogel and transdermal bases comprising liposomal components. Such topical formulations are also suitable for instillation onto an integumentary wound. Therefore, a method of treating an integumentary wound may include applying the same topical formulation, for example, one compounded in either PLO or liposomes, to both an integumentary wound of a subject and a periwound area around the integumentary wound.

[0118] In some embodiments, topical formulations suitable for instillation onto an integumentary wound may comprise a different liquid carrier from topical formulations suitable for application to a periwound area around an integumentary wound, in order to achieve better localization of active agents at the integumentary wound. For example, for instillation onto an integumentary wound of a subject, topical formulations provided herein may be compounded in petrolatum, paraffin, an aloe vera gel, a hyaluronic acid gel, or a mixture thereof; and for application to a periwound area around the integumentary wound, topical formulations provided herein may be compounded in PLO or liposomes.

[0119] Treatment according to the method of instilling a topical formulation provided herein onto both an integumentary wound of a subject and a periwound area around the integumentary wound may promote vasodilation and/or oxygenation. Furthermore, treatment of the periwound area is expected to promote wound closure and healing, as well as prevent tissues within the periwound area from deteriorating and enlarging.

[0120] In some embodiments, a wound dressing or a selected sequence of wound dressings may be applied onto the integumentary wound after instilling a topical formulation provided herein. The wound dressing may comprise a wound contact layer that includes a material or layer sold under the trademark JELONET™ or PROFORE WCL™. The wound dressing may be a foam dressing or a film dressing.

[0121] In some embodiments, a topical formulation disclosed herein may be first applied to a wound dressing and the wound dressing is then applied onto an integumentary wound of a subject.

[0122] In some embodiments, topical formulations provided herein are used for the treatment of an integumentary wound of a subject. Topical formulations provided herein may be instilled onto the integumentary wound, and optionally a periwound area around the integumentary wound. Instillation may be carried out by dropping, spraying, diffusing, dispersing, squirting, or spreading the formulation. In some embodiments, the use of topical formulations provided herein further comprises use of an oral formulation comprising one or more cannabinoids; one or more terpenes; and one or more flavonoids.

[0123] In some embodiments, a wound dressing or a selected sequence of wound dressings is used for application onto the integumentary wound after a topical formulation provided herein has been first applied to the integumentary wound. The wound dressing may comprise a wound contact layer that includes a material or layer sold under the trademark JELONET™ or PROFORE WCL™. The wound dressing may be a foam dressing or a film dressing.

[0124] In some embodiments, topical formulations provided herein are used in combination with existing therapies for wound healing. For example, topical formulations provided herein may be instilled onto an integumentary wound of a subject during Negative Pressure Wound Therapy (NPWT). In some embodiments, a topical formulation provided herein comprising normal saline as the liquid carrier is delivered to an integumentary wound through NPWT foam dressing. The formulation may be removed together with exudate from the integumentary wound. Using a NPWT canister, fresh formulation may be instilled onto the integumentary wound and subsequently removed together with exudate in a cyclic manner.

[0125] It has been surprisingly discovered by the present inventor that certain combination therapies can exhibit synergistic effects. For example, it has been found out that combining topical formulations provided herein with Electrical Stimulation Therapy (EST) resulted in better healing efficacy. Without being limited by any particular theory, it is expected that while cannabinoids and non-cannabinoids comprised in topical formulations provided herein bind to extracellular receptors on the membrane of intact cells at an integumentary wound, EST promotes the process of "electroporation" (i.e., creating openings within cell membranes), thereby allowing cannabinoids and non-cannabinoids to enter cells and interact with the intra-cellular binding sites of cannabinoid receptors (both extracellular and intracellular binding are expected to continue after electroporation is reversed). In some embodiments, there is provided a combination therapy comprising applying a topical formulation provided herein to an integumentary wound, and then applying an electric pulse generated by an electrical stimulation

generator to the integumentary wound (for example, via electrodes attached to skin surrounding the wound).

[0126] In some embodiments, topical formulations provided herein may be used in combination with existing intravenous treatments of non-uremic calciphylaxis, including intravenous pamidronate, zoledronate, and STS.

[0127] The integumentary wound to be treated may be acute, such as skin tear, laceration, abrasion, post-operative wounds, and burns. Alternatively, the integumentary wound to be treated may be chronic, stalled, recalcitrant, or a combination thereof. For example, the integumentary wound may be caused by a skin ulcer, a burn (a radiation therapy burn, a chemical burn, a thermal burn, or a sun burn), or a traumatic abrasion or skin tear. Possible skin ulcers include diabetic ulcers (e.g., neuroischemic diabetic foot ulcer or diabetic dermopathies such as Necrobiosis Lipoidica Diabeticorum), pressure injury ulcer, arterial leg ulcer, venous leg ulcer, or arterial ulcer (e.g., arterial ulcer with critical ischemia).

[0128] The integumentary wound may be iatrogenic (drug induced) or caused by a skin disease or systemic condition. For example, the skin disease or condition may be Skin Cancer (e.g., Primary Neoplasms, Metastatic Neoplasms, or Bowen's Disease), Vasculopathic Ulcers and Erosions (e.g., Sickle Cell Disease, Martorell's Ulcer, Uremic Calciphylaxis, Non-Uremic Calciphylaxis, Venous Leg Ulcers, or Arterial Ulcers), Integumentary Ulcers and Erosions caused by microbes (e.g., a bacterium, fungus, virus, and mycobacterium), Ulcers and Erosions related to diabetes (e.g., Diabetic Foot Ulcers, Necrobiosis Lipoidica Diabeticorum, or Diabetic Dermopathy), Blistering Skin Conditions (e.g., Epidermolysis Bullosa, Pemphigus, or Bullous Pemphigoid), Ulcers and Erosions caused by autoimmune diseases (e.g., Pyoderma Gangrenosum, Rheumatoid arthritis, Systemic Lupus Erythematosis, Scleroderma, or Morphea), Vasculitic Ulcers and Erosions (e.g., Cutaneous vasculitis, Leukocytoclastic Vasculitis, Cutaneous polyarteritis nodosa, or Microscopic polyangiitis), or Ulcers and Erosions caused by other complex diseases (e.g., Hidradenitis Suppurativa, Lichen Simplex Chronicus, Lichen Sclerosus, Lichen Planus, Wegener's Granulomatosis, Cryoglobulinemia, Behcet's Disease, Cryofibrinogenemia, Antiphospholipid Syndrome, Allergic Dermatitis, Psoriasis, or Porokeratosis).

[0129] The subject under treatment may be a human, or an animal.

[0130] In some embodiments, treatment of an integumentary wound may provide concurrent or separate analgesia, opioid-sparing effect, antimicrobial activity, and scar tissue mitigation.

[0131] In some embodiments, treatment of an integumentary wound may stimulate granulation tissue growth. For example, tests have shown that at least 33% of an integumentary wound may be granulated within 7 days after instillation of a topical formulation provided herein, or at least 66% of an integumentary wound may be granulated within 14 days after instillation of a topical formulation as disclosed herein.

[0132] In some embodiments, treatment of an integumentary wound may prevent scar (e.g., keloid) formation and/or completely close the wound.

[0133] In a particular embodiment, an integumentary wound may be treated as follows, with reference to FIG. 2.

[0134] FIG. 2a illustrates an intact skin, comprising epidermis 201, dermis 202, subcutaneous tissue 203 and superficial fascia 204.

[0135] As illustrated in FIG. 2b, at stage 1 of the treatment, the integumentary wound 205 is assessed for treatment. An initial formulation is prepared or obtained based on the assessment. The initial formulation may be a formulation as described herein with one or more adjustments based on the assessment. For example, if the wound to be treated is in the inflammatory phase, the concentrations of cannabinoids, using a combination of THC and CBD as an example, may be adjusted as follows: 2 mg/ml to 10 mg/ml of THC, and 5 mg/ml to 20 mg/ml of CBD.

[0136] At stage 1, the wound bed and optionally its periwound area of the integumentary wound 205 are also prepared for treatment. The wound bed may be prepared in any suitable manner or using any suitable technique. For example, the wound bed may be prepared by gentle cleansing with sterile normal saline. Other example wound preparation techniques are provided in Sibbald RG. et al. *Journal of Cutaneous Medicine and Surgery,* 2013, volume 17, issue 4, suppl. pages S12-S22.

[0137] At stage 2, the initial formulation 206 is instilled directly onto the wound bed and optionally its periwound area of the integumentary wound 205. As depicted in FIG. 2c, a layer of the formulation 206 is applied on the top surface of subcutaneous tissue of the open wound, which forms the wound bed, as well as the periwound area. The application of the formulation may be carried out depending on the form of the formulation. For example, if the initial formulation is oil-based, the formulation may be dropped or sprayed over the wound bed. If the initial formulation is a gel, the formulation may be spread onto the wound bed such as with sterile cotton tipped applicator.

[0138] In an alternative embodiment, the initial formulation 206 may be replaced by a first formulation formulated and a second formulation. The first formulation is applied to the

wound bed and the second formulation is applied to the periwound area. The second formulation can be applied to a 4 to 6 cm radial cuff of the periwound area. The first formulation and second formulation may be the same or different.

[0139] At stage 3 depicted in FIG. 2d, a wound dressing including a wound contact layer 207 is applied on top of the formulation layer 206. As can be appreciated, in some cases, a selected sequence of wound dressings may be applied over the wound bed covering the applied formulation. The wound contact layer may be JELONET or PROFORE WCL. The contact layer 207 may optionally include a selected formulation as described herein, which is integrated with the contact layer in a manner such that the formulation is releasable onto the wound bed of the integumentary wound 205 when the contact layer 207 is in contact with the wound bed.

[0140] At optional stage 4 depicted in FIG. 2e, a wound cavity filler 208, such as calcium alginate or hydrofibers, may be used to fill the space above the wound dressing if needed.

[0141] At optional stage 5 depicted in FIG. 2f, an absorptive layer 209, which may include MESORB™ or foam, or the like, may be applied on top of the wound dressing and optionally the cavity filler.

[0142] At optional stage 6 depicted in FIG. 2g, a compression therapy 210 may be optionally conducted. The compression therapy may be elastic or inelastic compression therapy. The compression therapy may be spiral bandaging. The compression therapy may include gauze kling roll, Comprilan™, or Easifix™, or a combination thereof.

[0143] The formulation or formulations may be applied one to four times daily over a period of several days to a number of weeks or months, or until wound healing is complete.

[0144] The wound is re-assessed from time to time over the period of treatment, and depending on the development of the wound healing process, the formulation or formulations to be subsequently applied to the wound may be adjusted.

[0145] For example, when the treated wound has progressed to the proliferative phase and continues into the remodeling phase, a subsequent formulation or formulations may be prepared or obtained, which may have a reduced concentration of cannabinoids, and an increased concentration of terpenes, especially terpenes that are agonists for CB2 receptors. In some embodiments, a topical formulation provided herein comprises beta-caryophyllene, and the concentration of beta-caryophyllene may be 30 mg/ml to 60 mg/ml when the formulation is used during the inflammatory phase, and may be subsequently increased to 50 mg/ml to 500 mg/ml when the inflammatory phase of wound healing is completed. The subsequent formulation or formulations may be applied directly to the wound bed one to four times daily over a period, such as few days to a number of weeks or months, or until wound healing is complete. The

subsequent formulation or formulations may be used through the proliferative and remodeling phases until the wound is completely healed.

[0146] In a different embodiment, treatment with a topical formulation described herein may be applied in one or two phases of the wound healing process. For example, a treatment may start in the proliferative phase, instead of the inflammatory phase.

[0147] In general, the adjustment to the contents of the topical formulation, or the selected wound dressing, may be selected depending on the nature of the integumentary wound, or as the integumentary wound progresses through different phases of wound healing. For example, a higher concentration of THC and/or THCa in the initial formulation may be beneficial for pain management in the inflammatory phase and/or may be desirable for wounds having a low oxygen level. However, after the inflammatory phase, the concentration of the psychoactive THC may be reduced to avoid inhibition of keratinocyte differentiation. In another example, a terpene that is an agonist for CB2 receptors may be beneficially included in the formulation(s) applied to the wound after the inflammatory phase has completed, or the concentration of such a terpene in the formulation(s) may be increased during the proliferative and remodeling phases, as such a terpene may promote re-epithelialization and remodeling.

[0148] The formulations may also be adjusted depending on the natures of the wound and one or more conditions of the treated subject.

[0149] In a specific example, a base topical formulation may include:

(a) 2.3 mg/ml of cannabidiol (CBD), 1.0 mg/ml of tetrahydrocannabinol (THC), and at least 0.1 mg/ml tetrahydrocannabinolic acid (THCa);

(b) 81.5 mg/ml of beta-caryophyllene and 28.4 mg/ml of linalool; and

(c) 16.7 mg/ml of micronized diosmin and 16.7 mg/ml of micronized quercetin.

[0150] The formulations to be used at different phases of treatment and would healing for different subjects under treatment may be adjusted from this base formulation as follows.

[0151] If the subject under treatment has significant levels of venous lymphedema in the lower limbs, the concentration of diosmin is increased to 10 mg/ml to 50 mg/ml.

[0152] During the inflammatory phase of wound healing, the concentration of THC is increased to 2 mg/ml to 10 mg/ml, and the concentration of CBD is increased to 5 mg/ml to 20 mg/ml, since wound pain is expected to be most intense during this phase and increased CBD and THC may help reducing pain.

[0153] During the re-epithelial and remodeling phases, the concentration of THC is maintained within the range of 0 mg/ml to 5 mg/ml, the concentration of CBD is maintained within the range of 0.1 mg/ml to 20 mg/ml, and the concentration of beta-caryophyllene is

maintained within the range of 50 mg/ml to 500 mg/ml, which is expected to avoid inhibition of keratinocyte differentiation and to promote re-epithelialization and remodeling. During the granulation phase, the concentration of quercetin is increased to 10 mg/ml to 50 mg/ml, which is expected to have effects on both VEGF and TGF-beta.

[0154] The base formulation may be further adjusted in some embodiments. For example, linalool may be substituted with another monoterpene such as alpha-bisabolol, thymol, alpha-terpineol, and genipin, or a triterpene such as astragaloside and asiaticoside. THC may be substituted entirely by THCV. The THC, CBD, and THCV may be decarboxylated, or may be substituted by their respective noncarboxylated natural acid forms.

Kits

[0155] In some embodiments, a kit may be provided, which include a container containing a topical formulation as disclosed herein, or a number of containers containing materials for preparing the topical formulation. The kit may also include instructions for treating an integumentary wound using the topical formation including dosage and how the formulation may be applied or instilled onto the wound bed. When separate containers are provided in the kit, and depending on the contents in these containers, the kit may also include instructions for preparing a topical formulation, or formulations with different concentrations of active ingredients, from the materials included in the kit and optionally other materials such as a liquid carrier or other additives. The kit may also include a liquid carrier as described elsewhere herein. The kit may further include an applicator for applying the topical formulation to the wound bed, and may include specific instructions on how to use the applicator.

[0156] In an embodiment, a topical formulation may be prepared or obtained from a kit comprising (a) one or more cannabinoids; (b) one or more terpenes; (c) one or more flavonoids; (d) a liquid carrier selected for instillation of the topical formulation onto an integumentary wound; and (e) instructions, wherein at least one of (a), (b) and (c) is not mixed with (d) in the kit, and wherein the instructions comprise information allowing all of (a), (b) and (c) be mixed with (d) at selected concentrations disclosed herein. The kit may include separate containers (see, e.g., the kit 601 depicted in FIG. 6 comprising a first container 602 comprising (a), a second container 603 comprising (b), a third container 604 comprising (c), a fourth container 605 comprising (d), and a fifth container 606 comprising (e)) or instructions for providing or preparing more than one formulation with different concentrations for one or more of (a), (b) and (c).

[0157] In some embodiments, a kit may include a container containing an instillate or a formulation provided herein. The formulation may be in form of oil, gel, paste or the like as

described above. The container may be, for example, a liquid bottle or a paste tube depending on the physical form of the formulation. In other embodiments, a kit may include a plurality of containers containing materials for forming an instillate or a formulation provided herein. The kit may further comprise at least one of instructions for applying the instillate or formulation directly to a wound bed and optionally a periwound area around the integumentary wound; instructions for using the instillate or formulation to treat an integumentary wound according to the methods or uses provided herein; and instructions for using the materials in the plurality of containers to prepare the instillate or formulation according to the methods of preparation provided herein. Optional components of a kit may include one or more applicators (such as droppers, sprayers, gauze sheets, and cotton tipped applicators) for applying the instillate or formulation onto an open wound bed and a periwound area around the integumentary wound, and one or more wound dressings as described herein. The one or more applicators may be sterilized and contained in a sealed sterile packaging.

Embodiments

[0158] Particular embodiments of the invention include, without limitation, the following:

1. A topical formulation comprising:
   (a) 0.1 mg/ml to 40 mg/ml of one or more cannabinoids;
   (b) 25 mg/ml to 1000 mg/ml of one or more terpenes; and
   (c) 10 mg/ml to 500 mg/ml of one or more flavonoids.
2. The topical formulation of paragraph 1, wherein the one or more cannabinoids comprise cannabidiol or cannabidiolic acid.
3. The topical formulation of paragraph 2, wherein the one or more cannabinoids further comprise at least one of cannabinol, cannabigerol, cannabichromene, and tetrahydrocannabivarin.
4. The topical formulation of paragraph 2 or 3, wherein the one or more cannabinoids further comprise at least 0.1 mg/ml tetrahydrocannabinolic acid (for example, between 1 mg/ml to 5 mg/ml), and optionally tetrahydrocannabinol.
5. The topical formulation of paragraph 2 or 3, wherein the one or more cannabinoids do not comprise tetrahydrocannabinol.
6. The topical formulation of paragraph 1, wherein the one or more cannabinoids do not comprise tetrahydrocannabinol.
7. The topical formulation of any one of paragraphs 1 to 6, wherein the one or more terpenes comprise beta-caryophyllene.

8. The topical formulation of any one of paragraphs 1 to 7, wherein the one or more terpenes further comprise linalool.

9. The topical formulation of any one of paragraphs 1 to 8, wherein the one or more terpenes comprise beta-caryophyllene and a monoterpene such as linalool, thymol, alpha-bisabolol, alpha-terpineol and genipin or a triterpene such as astragaloside and asiaticoside.

10. The topical formulation of any one of paragraphs 1 to 9, wherein the one or more flavonoids comprise quercetin.

11. The topical formulation of any one of paragraphs 1 to 9, wherein the one or more flavonoids comprise at least one of diosmin, quercetin, and hesperidin, or comprise at least one of kaempferol, apigenin, and quercetin, or comprise kaempferol, apigenin, diosmin, hesperidin, and quercetin.

12. The topical formulation of any one of paragraphs 1 to 9, wherein the one or more flavonoids comprise diosmin, quercetin, and hesperidin.

13. The topical formulation of any one of paragraphs 1 to 12, wherein the one or more cannabinoids, terpenes, or flavonoids are extracted from plants or genetically modified host cells, or are synthetic.

14. The topical formulation of any one of paragraphs 1 to 13, which comprises 0.1 mg/ml to 20 mg/ml of cannabidiol or cannabidiolic acid, and 0 mg/ml to 5 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid.

15. The topical formulation of any one of paragraphs 1 to 13, which comprises 5 mg/ml to 20 mg/ml of cannabidiol or cannabidiolic acid, and 2 mg/ml to 10 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid.

16. The topical formulation of paragraph 14 or 15, wherein tetrahydrocannabinol is replaced with tetrahydrocannabivarin.

17. The topical formulation of any one of paragraphs 1 to 16, which comprises 50 mg/ml to 500 mg/ml of the one or more terpenes.

18. The topical formulation of any one of paragraphs 1 to 16, wherein the concentration of beta-caryophyllene is 50 mg/ml to 500 mg/ml.

19. The topical formulation of any one of paragraphs 1 to 16, wherein the concentration of linalool is 25 mg/ml to 500 mg/ml.

20. The topical formulation of any one of paragraphs 1 to 19, which comprises 20 mg/ml to 200 mg/ml of the one or more flavonoids.

21. The topical formulation of any one of paragraphs 1 to 20, which comprises 30 mg/ml to 60 mg/ml of beta-caryophyllene and 10 mg/ml to 30 mg/ml of linalool.

22. The topical formulation of any one of paragraphs 1 to 20, which comprises 50 mg/ml to 500 mg/ml of beta-caryophyllene and 10 mg/ml to 150 mg/ml of linalool.

23. The topical formulation of paragraph 21 or 22, wherein linalool is replaced with a monoterpene such as linalool, thymol, alpha-bisabolol, alpha-terpineol and genipin or a triterpene such as astragaloside and asiaticoside.

24. The topical formulation of any one of paragraphs 1 to 23, which comprises 10 mg/ml to 50 mg/ml of diosmin and 10 mg/ml to 50 mg/ml of quercetin.

25. The topical formulation of any one of paragraphs 1 to 24, wherein the one or more flavonoids are micronized.

26. The topical formulation of any one of paragraphs 1 to 25, wherein the one or more flavonoids are in the form of dry powders.

27. The topical formulation of paragraph 1, comprising (a) 10 mg/ml to 20 mg/ml of cannabidiol or cannabidiolic acid, and at least one of cannabinol, cannabigerol, cannabichromene, and tetrahydrocannabivarin; (b) 0.1 mg/ml to 0.2 mg/ml of at least one of linalool, thymol, alpha-bisabolol, and myrcene; and (c) 100 mg/ml to 200 mg/ml of at least one of kaempferol, apigenin, diosmin, hesperidin, and quercetin.

28. The topical formulation of paragraph 1, comprising (a) 5 mg/ml to 30 mg/ml of cannabidiol or cannabidiolic acid, and 2 mg/ml to 10 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid; (b) 30 mg/ml to 60 mg/ml of beta-caryophyllene and 10 mg/ml to 30 mg/ml of linalool; and (c) 10 mg/ml to 30 mg/ml of diosmin and 10 mg/ml to 30 mg/ml of quercetin.

29. The topical formulation of paragraph 1, comprising (a) 0.1 mg/ml to 20 mg/ml of cannabidiol or cannabidiolic acid, and 0 mg/ml to 5 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid; (b) 50 mg/ml to 500 mg/ml of beta-caryophyllene and 10 mg/ml to 150 mg/ml of linalool; and (c) 0 mg/ml to 50 mg/ml of diosmin and 10 mg/ml to 50 mg/ml of quercetin.

30. The topical formulation of paragraph 1, comprising (a) 2.3 mg/ml of cannabidiol or cannabidiolic acid, and 1.0 mg/ml of tetrahydrocannabinol or tetrahydrocannabinolic acid; (b) 81.5 mg/ml of beta-caryophyllene and 28.4 mg/ml of linalool; and (c) 16.7 mg/ml of micronized diosmin and 16.7 mg/ml of micronized quercetin.

31. The topical formulation of paragraph 1, comprising (a) 2.6 mg/ml of cannabidiol or cannabidiolic acid; (b) 118 mg/ml of beta-caryophyllene; (c) 19.6 mg/ml of micronized

diosmin, 21.7 mg/ml of micronized quercetin, and 2.2 mg/ml of hesperidin; and (d) aloe vera gel and hyaluronic acid gel.

32. The topical formulation of any one of paragraphs 1 to 31, which is for direct application to an integumentary wound.

33. The topical formulation of any one of paragraphs 1 to 32, which is in the form of solution, lotion, cream, ointment, gel, emulsion, liposome, foam, powder, impregnated gauze sheet, tulle, vapor or paste for application to a cutaneous wound; or in the form of aerosolized spray for nasal or oral application to a cutaneous wound; or in the form of suppository for rectal or vaginal application to a cutaneous wound.

34. The topical formulation of any one of paragraphs 1 to 32, which is a solution or colloid.

35. The topical formulation of paragraph 34, which further comprises a liquid carrier selected for instillation of the solution or colloid onto an integumentary wound.

36. The topical formulation of paragraph 35, wherein the liquid carrier comprises an aloe vera gel, a hyaluronic acid gel, a vegetable oil, a medium-chain triglyceride, pluronic lecithin organogel, a transdermal base comprising a liposomal component, or normal saline.

37. The topical formulation of paragraph 36, wherein the vegetable oil is olive oil or sunflower oil.

38. The topical formulation of paragraph 35, wherein the liquid carrier is sunflower oil.

39. The topical formulation of paragraph 35, wherein the liquid carrier is pluronic lecithin organogel or a transdermal base comprising a liposomal component.

40. The topical formulation of paragraph 39, which is in the form of cream.

41. The topical formulation of paragraph 35, wherein the liquid carrier comprises an aloe vera gel.

42. The topical formulation of paragraph 35, wherein the liquid carrier comprises an aloe vera gel and a hyaluronic acid gel.

43. The topical formulation of any one of paragraphs 1 to 42, which further comprises one or more additional active agents.

44. The topical formulation of paragraph 43, wherein the one or more active agents comprise at least one of an anti-inflammatory agent, a wound healing agent, an anti-oxidizing agent, and an anti-microbial agent.

45. The topical formulation of any one of paragraphs 1 to 44, which further comprises an excipient.

46. A wound dressing comprising a wound contact layer and the topical formulation of any one of paragraphs 1 to 41 integrated with the contact layer.

47. The wound dressing of paragraph 46, wherein the wound contact layer comprises a paraffin gauze dressing or a dressing made of knitted viscose rayon.

48. The wound dressing of paragraph 46 or 47, which is a foam dressing.

49. The wound dressing of paragraph 46 or 47, which is a film dressing.

50. A method comprising instilling the topical formulation of any one of paragraphs 1 to 45 onto an integumentary wound of a subject.

51. The method of paragraph 50, wherein the step of instilling covers a portion of the integumentary wound.

52. The method of paragraph 50, wherein the step of instilling covers the entire integumentary wound.

53. The method of paragraph 50, wherein the step of instilling covers the entire integumentary wound and an area adjacent to an edge the integumentary wound.

54. The method of paragraph 53, wherein the area adjacent to the edge of the integumentary wound is a periwound area around the integumentary wound.

55. A method comprising instilling the topical formulation of any one of paragraphs 1 to 45 onto an integumentary wound of a subject and a periwound area around the integumentary wound.

56. A method comprising instilling the topical formulation of paragraph 41 or 42 onto an integumentary wound of a subject, and instilling the topical formulation of paragraph 39 onto a periwound area around the integumentary wound.

57. The method of any one of paragraphs 50 to 56, wherein the instilling comprises dropping, spraying, diffusing, dispersing, squirting, or spreading the formulation.

58. The method of any one of paragraphs 50 to 57, further comprising providing a formulation comprising one or more cannabinoids; one or more terpenes; and one or more flavonoids for oral administration.

59. The method of any one of paragraphs 50 to 58, further comprising applying a wound dressing comprising a wound contact layer onto the integumentary wound after instillation of the topical formulation.

60. The method of paragraph 59, wherein the wound contact layer comprises a paraffin gauze dressing or a dressing made of knitted viscose rayon.

61. The method of paragraph 59 or 60, wherein the wound dressing is a foam dressing.

62. The method of paragraph 59 or 60, wherein the wound dressing is a film dressing.

63. A method comprising applying the wound dressing of any one of paragraphs 46 to 49 onto an integumentary wound, and optionally a periwound area around the integumentary wound, of a subject.

64. The method of any one of paragraphs 50 to 63, wherein the integumentary wound is acute, or is chronic, stalled, recalcitrant, or a combination thereof.

65. The method of any one of paragraphs 50 to 64, wherein the integumentary wound is caused by a skin ulcer, a burn, or a traumatic abrasion or skin tear.

66. The method of paragraph 65, wherein the skin ulcer is a diabetic ulcer, a pressure ulcer, an arterial leg ulcer, a venous leg ulcer, or an arterial ulcer.

67. The method of any one of paragraphs 50 to 66, wherein the integumentary wound is caused by a skin disease or condition.

68. The method of paragraph 67, wherein the skin disease or condition is Skin Cancer (e.g., Primary Neoplasms, Metastatic Neoplasms, or Bowen's Disease), Vasculopathic Ulcers and Erosions (e.g., Sickle Cell Disease, Martorell's Ulcer, Uremic Calciphylaxis, Non-Uremic Calciphylaxis, Venous Leg Ulcers, or Arterial Ulcers), Integumentary Ulcers and Erosions caused by microbes (e.g., a bacterium, fungus, virus, or mycobacterium), Ulcers and Erosions related to diabetes (e.g., Diabetic Foot Ulcers, Necrobiosis Lipoidica Diabeticorum, or Diabetic Dermopathy), Blistering Skin Conditions (e.g., Epidermolysis Bullosa, Pemphigus, or Bullous Pemphigoid), Ulcers and Erosions caused by autoimmune diseases (e.g., Pyoderma Gangrenosum, Rheumatoid arthritis, Systemic Lupus Erythematosis, Scleroderma, or Morphea), Vasculitic Ulcers and Erosions (e.g., Cutaneous vasculitis, Leukocytoclastic Vasculitis, Cutaneous polyarteritis nodosa, or Microscopic polyangiitis), or Ulcers and Erosions caused by other complex diseases (e.g., Hidradenitis Suppurativa, Lichen Simplex Chronicus, Lichen Sclerosus, Lichen Planus, Wegener's Granulomatosis, Cryoglobulinemia, Behcet's Disease, Cryofibrinogenemia, Antiphospholipid Syndrome, Allergic Dermatitis, Psoriasis, or Porokeratosis).

69. The method of any one of paragraphs 50 to 68, wherein the subject is a human.

70. The method of any one of paragraphs 50 to 68, wherein the subject is an animal.

71. The method of any one of paragraphs 50 to 70, which has an analgesic, anti-inflammatory, anti-microbial, or anti-pruritic effect.

72. The method of any one of paragraphs 50 to 71, which has an opioid-sparing effect.

73. The method of any one of paragraphs 50 to 72, which stimulates granulation tissue growth.

74. The method of paragraph 73, wherein at least 33% of the integumentary wound is granulated within 7 days.

75. The method of paragraph 73, wherein at least 66% of the integumentary wound is granulated within 14 days.

76. The method of any one of paragraphs 50 to 75, wherein the topical formulation is effective for reducing scar formation.

77. The method of any one of paragraphs 50 to 76, further comprising adjusting the topical formulation depending on the nature of the integumentary wound, or as the integumentary wound progresses through different phases of wound healing.

78. The method of paragraph 77, wherein adjusting the topical formulation comprises reducing the concentrations of the one or more cannabinoids in the topical formulation, when the inflammatory phase of wound healing is completed.

79. The method of paragraph 78, wherein when the topical formulation comprises cannabidiol and tetrahydrocannabinol, the concentration of cannabidiol is 5 mg/ml to 20 mg/ml before adjustment and is reduced to 0.1 mg/ml to 20 mg/ml when the inflammatory phase of wound healing is completed, and the concentration of tetrahydrocannabinol is 2 mg/ml to 10 mg/ml before adjustment and is reduced to 0 mg/ml to 5 mg/ml when the inflammatory phase of wound healing is completed.

80. The method of paragraph 77, wherein adjusting the topical formulation comprises increasing the concentrations of the one or more terpenes in the topical formulation, when the inflammatory phase of wound healing is completed.

81. The method of paragraph 80, wherein when the topical formulation comprises beta-caryophyllene, the concentration of beta-caryophyllene is 30 mg/ml to 60 mg/ml before adjustment and is increased to 50 mg/ml to 500 mg/ml when the inflammatory phase of wound healing is completed.

82. The method of paragraph 77, wherein adjusting the topical formulation comprises increasing the concentrations of the one or more flavonoids in the topical formulation, when the wound healing is in the granulation phase.

83. The method of paragraph 82, wherein the topical formulation comprises 10 mg/ml to 50 mg/ml quercetin when the wound healing is in the granulation phase.

84. The method of any one of paragraphs 50 to 83, further comprising treating the integumentary wound with an additional therapy for wound healing.

85. The method of paragraph 84, wherein the additional therapy is negative pressure wound therapy.

86. The method of paragraph 84, wherein the additional therapy is electrical stimulation therapy.

87. Use of the topical formulation of any one of paragraphs 1 to 45 for the treatment of an integumentary wound of a subject.

88. The use of paragraph 87, wherein the topical formulation is for instillation onto the integumentary wound and optionally a periwound area around the integumentary wound.

89. Use of the topical formulation of paragraph 41 or 42 in combination with the topical formulation of paragraph 39 for the treatment of an integumentary wound of a subject, wherein the topical formulation of paragraph 41 or 42 is for instillation onto the integumentary wound and the topical formulation of paragraph 39 is for instillation onto a periwound area around the integumentary wound.

90. The use of paragraph 88 or 89, wherein the instillation comprises dropping, spraying, diffusing, dispersing, squirting, or spreading the topical formulation.

91. The use of any one of paragraphs 87 to 90, further comprising use of an oral formulation comprising one or more cannabinoids; one or more terpenes; and one or more flavonoids.

92. The use of paragraph 91, wherein the oral formulation is taken once or twice daily.

93. The use of any one of paragraphs 87 to 92, further comprising use of a wound dressing comprising a wound contact layer, wherein the wound dressing is for application onto the integumentary wound after the topical formulation.

94. The use of paragraph 93, wherein the wound contact layer comprises a paraffin gauze dressing or a dressing made of knitted viscose rayon.

95. The use of paragraph 93 or 94, wherein the wound dressing material is a foam dressing.

96. The use of paragraph 93 or 94, wherein the wound dressing material is a film dressing.

97. Use of the wound dressing of any one of paragraphs 46 to 49 for the treatment of an integumentary wound of a subject.

98. The use of any one of paragraphs 87 to 97, wherein the integumentary wound is acute, or is chronic, stalled, recalcitrant or a combination thereof.

99. The use of paragraph 98, wherein the integumentary wound is caused by a skin ulcer, a burn, or a traumatic abrasion or skin tear.

100. The use of paragraph 99, wherein the skin ulcer is a diabetic ulcer, a pressure injury ulcer, an arterial leg ulcer, a venous leg ulcer, or an arterial ulcer.

101. The use of any one of paragraphs 87 to 98, wherein the integumentary wound is caused by a skin disease or condition.

102. The use of paragraph 101, wherein the skin disease or condition is Skin Cancer (e.g., Primary Neoplasms, Metastatic Neoplasms, or Bowen's Disease), Vasculopathic Ulcers and Erosions (e.g., Sickle Cell Disease, Martorell's Ulcer, Uremic Calciphylaxis, Non-Uremic Calciphylaxis, Venous Leg Ulcers, or Arterial Ulcers), Integumentary Ulcers and Erosions caused by microbes (e.g., a bacterium, fungus, virus, and mycobacterium), Ulcers and Erosions related to diabetes (e.g., Diabetic Foot Ulcers, Necrobiosis Lipoidica Diabeticorum, or Diabetic Dermopathy), Blistering Skin Conditions (e.g., Epidermolysis Bullosa, Pemphigus, or Bullous Pemphigoid), Ulcers and Erosions caused by autoimmune diseases (e.g., Pyoderma Gangrenosum, Rheumatoid arthritis, Systemic Lupus Erythematosis, Scleroderma, or Morphea), Vasculitic Ulcers and Erosions (e.g., Cutaneous vasculitis, Leukocytoclastic Vasculitis, Cutaneous polyarteritis nodosa, or Microscopic polyangiitis), or Ulcers and Erosions caused by other complex diseases (e.g., Hidradenitis Suppurativa, Lichen Simplex Chronicus, Lichen Sclerosus, Lichen Planus, Wegener's Granulomatosis, Cryoglobulinemia, Behcet's Disease, Cryofibrinogenemia, Antiphospholipid Syndrome, Allergic Dermatitis, Psoriasis, or Porokeratosis).

103. The use of any one of paragraphs 87 to 102, wherein the subject is a human.

104. The use of any one of paragraphs 87 to 103, wherein the subject is an animal.

105. The use of any one of paragraphs 87 to 104, which has an analgesic, anti-inflammatory, anti-microbial, or anti-pruritic effect.

106. The use of any one of paragraphs 87 to 105, which has an opioid-sparing effect.

107. The use of any one of paragraphs 87 to 106, which stimulates granulation tissue growth.

108. The use of paragraph 107 wherein at least 33% of the integumentary wound is granulated within 7 days.

109. The use of paragraph 107, wherein at least 66% of the integumentary wound is granulated within 14 days.

110. The use of any one of paragraphs 87 to 109, which prevents scar formation.

111. The use of any one of paragraphs 87 to 110, which promotes vasodilation and/or oxygenation.

112. The use of any one of paragraphs 87 to 111, comprising adjusting the topical formulation depending on the nature of the integumentary wound, or as the integumentary wound progresses through different phases of wound healing.

113. The use of paragraph 112, wherein adjusting the topical formulation comprises reducing the concentrations of the one or more cannabinoids in the topical formulation, when the inflammatory phase of wound healing is completed.

114. The use of paragraph 113, wherein when the topical formulation comprises cannabidiol and tetrahydrocannabinol, the concentration of cannabidiol is 5 mg/ml to 20 mg/ml before adjustment and is reduced to 0.1 mg/ml to 20 mg/ml when the inflammatory phase of wound healing is completed, and the concentration of tetrahydrocannabinol is 2 mg/ml to 10 mg/ml before adjustment and is reduced to 0 mg/ml to 5 mg/ml when the inflammatory phase of wound healing is completed.

115. The use of paragraph 112, wherein adjusting the topical formulation comprises increasing the concentrations of the one or more terpenes in the topical formulation, when the inflammatory phase of wound healing is completed.

116. The use of paragraph 115, wherein when the topical formulation comprises beta-caryophyllene, the concentration of beta-caryophyllene is 30 mg/ml to 60 mg/ml before adjustment and is increased to 50 mg/ml to 500 mg/ml when the inflammatory phase of wound healing is completed.

117. The use of paragraph 112, wherein adjusting the formulation comprises increasing the concentrations of the one or more flavonoids in the topical formulation, when the wound healing is in the granulation phase.

118. The use of paragraph 117, wherein the topical formulation comprises 10 mg/ml to 50 mg/ml quercetin when the wound healing is in the granulation phase.

119. The use of any one of paragraphs 87 to 118, further comprising an additional therapy for wound healing.

120. The use of paragraph 119, wherein the additional therapy is negative pressure wound therapy.

121. The use of paragraph 119, wherein the additional therapy is electrical stimulation therapy.

122. A kit comprising: a container containing the topical formulation of any one of paragraphs 1 to 45, or a plurality of containers containing materials for forming the topical formulation of any one of paragraphs 1 to 45.

123. The kit of paragraph 122, further comprising instructions for applying the topical formulation directly to an integumentary wound and optionally a periwound area around the integumentary wound.

124. The kit of paragraph 122 or 123, further comprising instructions for using the topical formulation to treat an integumentary wound according to the method of any one of paragraphs 50 to 86.

125. The kit of any one of paragraphs 122 to 124, further comprising instructions for using the materials in the plurality of containers to prepare the topical formulation.

126. The kit of any one of paragraphs 122 to 125, further comprising one or more applicators for applying the topical formulation onto a wound bed.

127. The kit of any one of paragraphs 122 to 126, further comprising one or more wound dressings of any one of paragraphs 46 to 49.

128. A method comprising instilling a topical formulation comprising cannabidiol or cannabidiolic acid, and a liquid carrier, onto an integumentary wound, and optionally the periwound area of the integumentary wound, of a subject.

129. The method of paragraph 128, wherein the topical formulation consists of cannabidiol or cannabidiolic acid, and the liquid carrier.

130. The method of paragraph 128 or 129, wherein the topical formulation is instilled onto an integumentary wound.

131. The method of any one of paragraphs 128 to 130, wherein the liquid carrier comprises an aloe vera gel, a hyaluronic acid gel, a vegetable oil, a medium-chain triglyceride, pluronic lecithin organogel, or a transdermal base comprising a liposomal component.

132. The method of paragraph 131, wherein the liquid carrier comprises an aloe vera gel or a hyaluronic acid gel.

133. The method of any one of paragraphs 50 to 86, wherein the treatment period is 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months or until the wound healing is complete.

134. The use of any one of paragraphs 128 to 132, wherein the treatment period is 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months or until the wound healing is complete.

EXAMPLES

Example 1: Preparation of A Topical Formulation of Cannabinoids, Terpenes and Flavonoids

[0159] The formulation was prepared in 30ml aliquots using sterile technique. 10 ml of aloe vera gel (purchased under the commercial name "Aloe Gel" from Realaloe Canada, British Columbia, Canada) and 10 ml of hyaluronic acid gel (containing 8 mg/ml of hyaluronic acid; purchased under the commercial name "PRO HA + C" from Naka Professional, Toronto, Canada M9W 5S2) were decanted into a sterile container. The dried powder forms of diosmin (purchased under the commercial name "Diovasc" from Xymogen Inc, 32819 USA), and quercetin (purchased under the commercial name "Quercetin Capsules" from Alpha Science

Laboratories, Toronto, Canada), equivalent to 500 mg of each, were then added to the gel mixture. Then, 1.5 ml of THC oil (containing 20 mg/ml of THC; purchased under the commercial name "Red Cannabis Oil" from Tweed Inc, Smiths Falls, Ontario, Canada) and 3.5 ml of CBD oil (containing 20 mg/ml of CBD; purchased under the commercial name "Yellow Cannabis Oil" from Tweed Inc, Smiths Falls, Ontario, Canada) were added. Finally, 3 ml of beta-caryophyllene (containing 814.5 mg/ml of beta-caryophyllene; purchased from True Terpenes Inc, 2416 N Hayden Island Drive, Portland, Oregon, USA, 97217) and 1 ml of linalool (containing 852.9 mg/ml of linalool; purchased from True Terpenes Inc, 2416 N Hayden Island Drive, Portland, Oregon, USA, 97217) were added. The mixing container was then closed and shaken for 30 seconds. The mixing container was covered with dark tape in order to protect from the light. The prepared formulation contained a) 2.3 mg/ml of cannabidiol and 1.0 mg/ml of tetrahydrocannabinol; (b) 81.5 mg/ml of beta-caryophyllene and 28.4 mg/ml of linalool; and (c) 16.7 mg/ml of micronized diosmin and 16.7 mg/ml of micronized quercetin.

Example 2: A Case Report of Topical Formulation of Cannabinoids, Terpenes and Flavonoids in Wound Healing

[0160] This example demonstrated the efficacy of the topical formulation prepared in Example 1, which was topically instilled upon wound beds of chronic and recalcitrant wounds. The treatment was found to promote healing in chronically recalcitrant wounds.

[0161] A compounded mixture of cannabinoids, terpenes and flavonoids was topically instilled onto the wound bed of an 85-year-old woman with a large chronic wound on her right leg since 2013. This patient also suffered from CHF, Atrial Fibrillation, and Osteoarthritis. The wound had clinical signs of idiopathic Pyoderma Gangrenosum, identified with histopathologic and immunofluorescent features. The patient refused traditional medicines such as Prednisone, Imuran, Cyclosporine, and Inflixamab.

[0162] The treatment started from November 1, 2017. The highly heterogeneous wound has seen rapid granulation and later epithelium growth inside the original necrotic area, and significant shrinking of the wound area over the course of 90 days. In addition to wound granulation, the patient also reported that the patient experienced reduced wound-related pain and exudation.

[0163] During the treatment of the patient, color photos of the wound were routinely taken at the patient's residence. As an alternative, the longest length and widest width of the wound were manually recorded.

[0164] During the period from November 1, 2017 to January 30, 2018 (total: 90 days), there were 35 visits to the patient (average frequency: 2.6 days/visit). 119 images (average: 3.4

images/visit) were analyzed. Multiple images were taken on each visit due to the large surface extent of the wound which could not fit into one camera field of view (FOV).

[0165] Wound boundaries were manually contoured on each image. The wound area was extracted from the contour using a polygon area mask defined by the contour points. This area is defined as the region of interest (ROI). A color space transformation from the Red-Green-Blue (RGB) space to the Hue-Saturation-Value (HSV) space was performed on the image. The HSV space (or other similar approaches) is commonly used to perform segmentation of different objects, including skin, due to its much higher contrast between semantically different objects. The hue space value is commonly represented by a non-dimensional value from 0 to 360 and wraps around. 0 and 360 represent red color while green is at 120 and blue is at 240. Since the color of interest is around the red wavelength, a different period in the hue space from -180 to 180 was taken. As a result, 0, 120 were still red and green respectively, but blue is shifted one period to (240−360)=−120, and most importantly, all pixels with red color would be next to each other for histogram analysis, allowing much more convenient binning. Finally, the range (−180,180) is normalized to (−0.5,0.5) for interoperability between different software platforms which may choose a different range for hue space (e.g. some may choose to let hue range from 0 to 255 to fit within a traditional 8-bit data structure). All pixels in the hue channel inside the ROI were counted on a histogram. Empirical thresholds were applied to classify the pixels inside the wound as "necrosis," "granulation," "epithelium," and "no label."

[0166] Assume the areas of necrosis, granulation, and epithelium would be rather contiguous, morphological operations were performed to improve accuracy of classification. First, an image erosion structuring element of appropriate size was applied so that small misclassified regions would be eliminated. Then, a dilation filter using the same structuring element is applied to recover the correct size of classified areas.

[0167] For visualization, a small dilation structuring element was applied to each area, followed by a subtraction of the area. This series of operation allows one to draw out the outer contour of the classified area. Areas of difference classifications were delineated by different contour colors.

[0168] Finally, the percentage of each type of pixel classification inside the wound was calculated to be interpreted as the percent of area inside the wound being the labeled type of tissue:

$$\%\ granulation = number\ of\ "granulation"\ pixels / total\ number\ of\ pixels\ in\ wound$$

$$\%\ epithelial = number\ of\ "epithelial"\ pixels / total\ number\ of\ pixels\ in\ wound$$

[0169] The entire pipeline of the analysis was implemented in the Python programming language using the OpenCV computer vision library.

[0170] In addition to the image analysis data, an upper-bound estimate of the wound area is provided by the measured widest length and longest length: $wound\ area \approx longest\ length \times widest\ width$.

[0171] Statistical analysis was performed in Python (version 3.6.2, SciPy version 0.19.1) and MATLAB (version R2016a).

[0172] Representative images on days 15, 41, and 87 and their analysis are shown in FIGS. 3a-c. The upper left image of each figure was taken with the classified area contoured (dark grey: granulation, white: epithelial tissue). The upper right image of each figure shows the hue channel (the area enclosed within the solid line) calculated from each image. The bottom graph of each figure shows the hue value histogram inside the wound area. Note the peak becomes significantly higher and narrower from day 15 to 41 due to the increased percentage of granulation tissue, and the peak becomes slightly wider on day 87 due to the growing amount of epithelial tissue. The wound healing can be distinguished into two distinct phases: the first phase before day 30 when tissue started a rapid granulation before day 30, and the second phase after day 30 when granulation process has saturated at close to 100% and epithelium growth starts. This division can be seen clearly observed in the summarized statistics shown in FIG. 4.

[0173] As discussed in the Background section, the initial phase of granulation is characterized by the narrowing of the histogram peak and the increase in magnitude of the peak. In the second phase of healing where granulation saturates and epithelium starts to form, the histogram gradually grows into the yellow region with a decreased magnitude of peak, representing granulation tissue turning into epithelial tissue.

[0174] The trend of the wound size and proportion of granulation and epithelium tissue is shown in FIGS. 5a-c and FIG. 4 respectively. In FIGS. 5a-c, a linear regression line of all the data points represented by "X" is shown as a dotted line in each figure. The equation of the linear regression line of FIG. 5a is y=-0.106x+19.6 with a coefficient of determination (R^2) of 0.774; the equation of the linear regression line of FIG. 5b is y=-0.059x+9.6 with a coefficient of determination (R^2) of 0.930; and the equation of the linear regression line of FIG. 5c is y=-1.545x+175.8 with a coefficient of determination (R^2) of 0.903.

[0175] It is important to note that the two indices measure different quantities: while the total wound size is considered in FIGS. 5a-c, the composition inside the wound is considered in

FIG. 4. This difference manifests in the strong linear decreasing trend in FIG. 5c where the product of length and width has $R^2 = 0.903$. In comparison, FIG. 4 shows rapid initial granulation and epithelium growth and saturation of the growth after a few days. This suggests that these two metrics are best to be observed in conjunction to fully understand the healing process of a wound.

[0176] The dramatic wound healing results observed in this case suggest the occurrence of a potentiated and synergistic effect between cannabinoids, terpenes and flavonoids.

Example 3: An Open-Label Trial

[0177] An open-label trial was initiated on a cohort of stalled recalcitrant wounds, composed of cases with an average chronicity of over 2 years, which were treated with topical formulations of the present invention. The topical formulations were directly applied to wound beds, and in some cases, to wound beds and the periwound areas. All cases were previously afforded with all available Evidence Based Medicine treatments that conformed with local best practices and wound-bed preparation principles. All patients provided informed consent to be subjected to the experimental therapy.

[0178] The patient recruitment information is summarized below:

- "Complex Wounds" affecting "Complex Patients"
- 33 patients with 42 recalcitrant wounds
    - 31 patients with wounds involving cutaneous membranes
    - 2 patients with wounds involving mucous membranes
- Wound Diagnoses:
    - Venous Leg Ulcers (16 wounds)
    - Autoimmune (including Pyoderma Gangrenosum, Rheumatoid Arthritis, Microscopic Polyangiitis, and Polyarteritis Nodosa) (10 wounds)
    - Non-uremic Calciphylaxis (3 wounds)
    - Uremic Calciphylaxis (2 wounds)
    - Diabetic foot ulcers (1 wound)
    - Pressure Ulcers (2 wounds)
    - Post-surgical wounds (2 wounds)
    - Sickle Cell Disease (3 wounds)
    - Malignant Wound (1 wound)
    - Mucous Membrane (including vaginal and peri-anal membranes) (2 wounds)

- Wound Duration: more than 6 months (Range 6 months to 12 Years)
    - Gender:
        - 24/33female
        - 9/33 male
    - Age:
        - Average = 70.5 years
        - Range: 28.5 to 90.5
    - Performance Status: (*Entirely healthy people score 100%*)
        - Average = 70.0%
        - Range: 30% to 100%
    - M3 Multimorbidity Index: (*Entirely healthy people score 0*)
        - Average = 3.16
        - Range: 0.12 – 6.91

[0179] The topical formulations used for treatment are identified in the table below.

FORMULA	Aloe Vera Gel	Hyaluronic Acid Gel	Liposomal Base	Pluronic Lecithin Organogel	Normal Saline	Quercetin	Diosmin	Hesperidin	Kaempferol	Apigenin	CBD	THC	Beta-Caryophyllene	Linalool
F1-2	10 ml	10 ml				500 mg					10 mg		3 ml	
F3	10 ml	10 ml				500 mg					7.5 mg	5 mg	3 ml	
F4	10 ml	10 ml				500 mg					30 mg	20 mg	3 ml	
F5	10 ml	10 ml				500 mg			500 mg	500 mg	10 mg		3 ml	
F6	20 ml					1,000 mg					50 mg		10 ml	
F7	10 ml	10 ml				500 mg	450 mg	50 mg			7.5 mg	5 mg	2 ml	2 ml
F8	10 ml	10 ml				500 mg	450 mg	50 mg			55 mg	10 mg	3 ml	3 ml
F9	10 ml	10 ml				500 mg	450 mg	50 mg	500 mg	500 mg	55 mg	10 mg	3 ml	3 ml
F10	10 ml	10 ml				500 mg	450 mg	50 mg			60 mg			3 ml
F11	10 ml	10 ml				500 mg	450 mg	50 mg			70 mg	20 mg	2 ml	
F12	10 ml	10 ml				500 mg	450 mg	50 mg			60 mg		3 ml	
F12B	10 ml	10 ml				500 mg			500 mg	500 mg	60 mg		3 ml	3 ml
F13	10 ml	10 ml				500 mg	450 mg	50 mg			60 mg	30 mg	3 ml	
F14			10 ml			500 mg	450 mg	50 mg			60 mg		3 ml	
F15				10 ml		500 mg	450 mg	50 mg			60 mg		3 ml	
F16	20 ml					1,000 mg					60 mg		3 ml	
F17			10 ml			500 mg	450 mg	50 mg			50 mg	50 mg	5 ml	
F18			10 ml			500 mg	450 mg	50 mg			100 mg		10 ml	
F19			10 ml			500 mg	450 mg	50 mg			50 mg	25 mg	5 ml	3 ml
F20					100 ml	1,000 mg	450 mg	50 mg			100 mg	50 mg	10 ml	5 ml

[0180] Among the 33 patients treated, complete wound closure was observed in 23 patients, progressive wound closure was observed in 7 patients, and no significant wound closure was observed in 2 patients (one with severe diabetic charcot foot and osteomyelitis and the other with diagnosed malignancy). One patient with two wounds was lost to follow up. All patients, other than the one lost to follow up, experienced clinically relevant pain relief within 5-7 days. Reduced utilization of opioid analgesics and reduced utilization of systemic antibiotics were also observed, while no systemic or local adverse reactions were observed. No patient underwent amputation.

Example 4: Further Trials of Topical Formulations of Cannabinoids, Terpenes and Flavonoids

[0181] Topical formulations were prepared in aliquots using the following proportions – in F21, F22, and F27 to F30, the specified amounts of CBD and THCa were supplied in 2 ml of total oil volume; in F23 and F24, the specified amount of THCa was supplied in 2 ml of total oil volume and the specified amount of CBD was supplied in 4 ml of total oil volume; in F25 and F26, the specified amount of CBD was supplied in 3 ml of total oil volume:

FORMULA	Aloe Vera Gel	Hyaluronic Acid Gel	Liposomal Base	Quercetin	Diosmin	Hesperidin	CBD	THCa	THC	Beta-Caryophyllene	Linalool
F21	5 ml	5 ml		500 mg	405 mg	40 mg	40 mg	42.4 mg	< 2 mg	2 ml	
F22			10 ml	500 mg	405 mg	40 mg	40 mg	42.4 mg	< 2 mg	2 ml	
F23	2.5 ml	2.5 ml		500 mg	405 mg	40 mg	80 mg	42.4 mg	< 4 mg	1 ml	
F24			5 ml	500 mg	405 mg	40 mg	80 mg	42.4 mg	< 4 mg	1 ml	
F25	5 ml	5 ml		500 mg	405 mg	40 mg	60 mg		< 3 mg	3 ml	
F26			10 ml	500 mg	405 mg	40 mg	60 mg		< 3 mg	3 ml	
F27	5 ml	5 ml		500 mg	405 mg	40 mg	40 mg		< 2 mg	2 ml	2 ml
F28			10 ml	500 mg	405 mg	40 mg	40 mg		< 2 mg	2 ml	2 ml
F29	5 ml	5 ml		500 mg	405 mg	40 mg	40 mg	42.4 mg	< 2 mg	2 ml	2 ml
F30			10 ml	500 mg	405 mg	40 mg	40 mg	42.4 mg	< 2 mg	2 ml	2 ml

[0182] Recalcitrant wounds of nine were treated with Formulations F21 to F30. Formulations F21, F23, F25, F27 and F29, compounded in a mixture of hyaluronic acid and aloe vera gel, were applied to wound beds. Formulations F22, F24, F26, F28 and F30, compounded in liposomal base, were applied to periwound areas.

[0183] The nine patients suffered from the following diseases:

- Vasculitic diseases
    - Pyoderma gangrenosum (2 patients treated with F23 and F24 – 3 wounds; 1 patient treated with F27 and F28)

- Vasculopathic diseases
    - Uremic Calciphylaxis (1 patient treated with F25 and F26; 2 legs with multiple wounds; see case report later in this Example)
    - Non-Uremic Calciphylaxis (2 patients treated with F25 and F26; 3 legs with multiple wounds; see case report later in this Example)
    - Sickle Cell Disease (1 patient treated with F21 and F22; 2 legs with 3 wounds; see case report later in this Example)
    - Leukocytoclastic Vasculitis (1 patient treated with F27 and F28)
    - Porokeratosis (1 patient treated with F29 and F30; see case report later in this Example)

[0184] The following therapeutic benefits were observed:

- Relief of wound-related pain (WRP): clinically significant relief of pain (>30% on an 11-point pain scale) was observed within 5-10 minutes of topical application, which lead to a 30% to 50% reduction in utilization of systemic opioids;
- Promotion of wound closure and wound healing/maturation; and
- Reduced scar tissue formation and reduced skin fibrosis: no hypertrophic scars were formed; no induration was observed; and the treatments displayed excellent cosmetic effect with no bevel defects.

[0185] The combined use of a wound bed formulation and a periwound formulation was associated with an average 1.3 times (from 1.2 times to 1.5 times) more rapid closure of wounds (cm^2/day) compared to the use of a wound bed formulation alone. Moreover, the use of THCa was associated with an average 5.3 times (from 2 times to 7 times) more rapid closure of wounds (cm^2/day) compared to no use of THCa. Moreover, the use of linalool was associated with an average 3.8 times (from 3.2 times to 4.3 times) more rapid closure of wounds (cm^2/day) compared to no use of linalool.

Treatment of sickle cell disease leg ulcers

[0186] This case report of the sickle cell disease patient referred to above illustrates the efficacy of the topical formulations disclosed in this Example. The treatments were found to promote wound closure in refractory non-healing wounds that were over 6 months in duration and had failed all available best practice treatments.

[0187] A 44-year-old woman was a chronically ill patient with 12-year history of chronic recurrent ulcerations involving both lateral ankles and left medial ankle. She has a palliative performance scale score of 60% (healthy persons score 100%) and a M3 multimorbidity index of 3.35 (two thirds of persons from typical populations score zero). The patient also suffered from

right heart failure and peripheral vascular disease, with hemoglobin concentrations ranging between 65-75 g/L and oxygen saturation that was consistently less than 90%.

[0188] The patient was treated with daily topical applications of F21 and F22 to three wound sites located on her right lateral ankle, left medial ankle, and left lateral ankle. To each wound site, she first applied F21 to the wound beds and F22 to a 4 to 6 cm radial cuff of periwound integument. She then applied one layer of Jelonet™ and one layer of Mesorb™ on top, followed by a spiral bandaging of her lower limbs using, sequentially, gauze kling roll, Comprilan, and Easifix. Smartphone photography was used daily to estimate wound size.

[0189] On Day 0 of treatment, the size of the patient's right lateral, left medial, and left lateral wounds were estimated to be 11.0cm^2, 1.8cm^2, and 5.4cm^2, respectively. On Day 24, the left medial ankle wound closed completely. On Day 45, the right and left lateral wounds were 97% and 98.5% closed, respectively. Using a linear regression model, the rates of wound closure were 0.30cm^2/day, 0.062cm^2/day, and 0.15cm^2/day for the right lateral, left medial, and left lateral ankle wounds, respectively. When expressed in percentages, the three wounds closed at a rate of 2.7%/day, 3.5%/day, and 2.8%/day, respectively.

[0190] After Day 45, the patient stopped the treatment and was lost to follow-up until Day 97, when she was admitted to the hospital with sepsis from cholecystitis. Her right lateral and left lateral ankle wounds deteriorated to 11.14cm^2 and 7.46cm^2, which were larger than the size of the wounds on Day 0. Her left medial ankle wound remained closed. The patient agreed to resume the same daily topical applications of F21 and F22 to her two remaining wound sites.

[0191] After 53 days of treatment from the date of admission, both remaining wounds closed completely. The rates of closure for the right lateral ankle and left lateral ankle wounds were 0.22cm^2/day (or 1.9%/day) and 0.13cm^2/day (or 1.7%/day). Treatment progression is depicted in FIG. 7.

Treatment of recalcitrant non-uremic calciphylaxis (NUC) leg ulcers

[0192] This study involved two elderly Caucasian females with recalcitrant NUC leg ulcers of greater than 6 months duration. F25 and F26 were applied daily to both the wound bed and peri-wound tissues until complete wound closure was achieved. Wounds were photographed regularly, and the digital images were subjected to planimetric analysis to objectively quantify the degree of granulation and epithelization. Analgesic utilisation, as a surrogate/proxy for pain scores, was also tracked. The cohort had a mean M3 multimorbidity index score of 3.31. Complete wound closure was achieved in a mean of 76.3 days. Additionally, no analgesics were required after a mean of 63 days. The treatments were well tolerated with no adverse reactions.

Methods

[0193] Two female patients with painful and non-healing leg ulcers, of greater than 6 months duration, were referred to a regional consultative wound management clinic in Toronto, Canada. Both patients failed all available best practices in accordance with WBP. Topical formulations F25 and F26 were applied daily to the wound beds and peri-wound tissues:

[0194] F25 and F26 are chemically equivalent but compounded in separate vehicles that promote absorption through a wound bed and intact integument, respectively. The daily treatments were continued until complete wound closure, defined as the wound bed being 100% epithelialized.

[0195] On their initial visits, their degrees of global medical complexity were calculated using the M3 multimorbidity index tool. Additionally, both patients consented to 4 mm punch biopsies of their wounds for histopathologic and immunofluorescent evaluation that confirmed NUC. Following gentle cleansing with sterile normal saline, each patient underwent daily application of evenly applied thin layers of F25 to the wound beds, and F26 to a 4 to 6 cm radial cuff of peri-wound integument. Tissues were then covered with one layer each of Jelonet and Mesorb, followed by spiral bandaging of the lower limb, sequentially, using gauze kling roll, Comprilan, and Easifix, between the level of the metatarsal phalangeal joints and the infra-popliteal space.

[0196] To track the treatment outcomes and perform statistical analyses, images of the wound were taken with a smartphone camera (iPhone 6 and XS, Apple Inc.). Using a simple planimetric wound image analysis technique, the wound area on each image was manually contoured, and the relative wound area change and relative wound composition change, in terms of granulation and reepithelization, was calculated. Data were also fitted to a linear regression model to report the general trend and the estimated time to complete wound closure. The daily utilisation of opioid analgesics was prospectively documented as a proxy/surrogate to monitor and gauge pain severity. Laboratory results for each patient described below are given in the following table:

Lab Tests	Normal Ranges	Patient A	Patient B
Hb (g/L)	115 to 160	123	113
Albumin (g/L)	35 to 50	30	30
eGFR (mL/min)	>60	73	89
Creatinine (μmol/L)	49 to 90	66	57
Calcium (mmol/L)	2.02 to 2.62	2.32	2.43
Phosphate (mmol/L)	0.70 to 1.50	0.75	1.27
Rheumatoid factor (IU/L)	<20	<20	92.3
Cardiolipin IGM (CU)	<20	23.0	<2.6
Arterial toe-brachial iIndex	>0.65	R leg 0.7	R leg 0.63 L leg 0.52
Venous reflux	-	R leg +	R leg ++ L leg ++

Patient A

[0197] An 85-year-old Caucasian woman presented with a 6-month history of painful ulcerations involving her right leg. Her medical history included chronic congestive heart failure, valvular heart disease, pulmonary hypertension, moderate dementia, Type 2 diabetes mellitus, atrial fibrillation (Xarelto 2.5 mg bid), systemic hypertension, osteoarthritis, surgically fused right ankle, and hyperlipidemia. Her M3 comorbidity index was 3.59. Patient A could not express her pain level in terms of numeric rating scores. However, her caregiver indicated that at the onset of this study, the patient had previously never been in a similar level of distress. Her caregiver shared a questionable history of "allergy" to strong opioids and thus elected to only use TYLENOL with Codeine No. 3 tablets, USP (300 mg/30 mg) for pain relief.

[0198] On clinical examination, Patient A had five necrotic ulcerations involving the antero-lateral aspect of her right leg. Mild veno-lymphedema was noted.

[0199] 27 good-quality images of this wound region, captured over 74 days, were available for analysis, with representative images at different stages of treatment shown in FIG. 8A. The wound area was 50% closed on day 37 and completely closed on day 74 (2.5 months). According to the linear regression model, the wound was expected to close in 77.0 days (fitted slope = –1.4%/day), illustrated in FIG. 8B.

[0200] Planimetric wound image analysis assessed the gross phenotypic changes in the wound bed during the treatment phase, with results illustrated in FIG. 8C. A characteristic two-phase wound closure process is observed: during the first half of the treatment, granulation dominates the wound healing landscape with relatively small decrease in the total wound area

(slope of granulation for first 34 days = +1.8%/day). During the second half of the treatment, the reepithelization process quickly caught up by replacing the granulated tissue and rapidly contracting the wound area, achieving ultimate wound closure (slope of reepithelization from day 34 till closure = +1.8%/day).

[0201] Regarding pain management, Patient A initially required 10 tablets of TYLENOL with Codeine No. 3 tablets per day. A 33% reduction in analgesic requirements, analogous to a clinically significant degree of pain relief occurred on day 18. On day 57 of treatment, TYLENOL with Codeine No. 3 tablets were no longer required by the patient for analgesia.

Patient B

[0202] A 69-year-old Caucasian woman presented with an 8-month history of painful ulcerations involving her right leg, and a 4-month history of ulcerations involving her left leg. Her medical history reflected Type 2 diabetes mellitus, rheumatoid arthritis, systemic hypertension, osteoarthritis, and hyperlipidemia. Her M3 comorbidity index was 3.02. During the 3 weeks prior to the start of the trial, Patient B had been rendered completely bed-bound and dependent on others for personal care owing to her extreme pain.

[0203] On clinical examination, Patient B had numerous necrotic ulcerations involving both legs that were circumferential. Mild veno-lymphedema was noted.

[0204] About 44 good-quality images of the posterior aspects of both legs, captured over 81 days, were included in the analysis for each of the two legs, shown in FIG. 9A and 9B respectively. As illustrated in FIG. 9C, the left leg wound area was 50% closed around day 36 to 41 and was seen completely closed on day 79 (2.6 months) (fitted slope = –0.8%/day). The right leg wound healed slightly faster overall (FIG. 9D). It was 50% closed at approximately day 32 to 36 and was completely closed on day 74 (2.4 months) (fitted slope = –1.2%/day).

[0205] Planimetric wound image analysis, as shown in Figure 9E, demonstrated a very similar two-phase wound healing response to Patient A described above. The first half of the treatment was characterised by increase in granulation tissue (slope of granulation for first 25 days: left leg = +2.3%/day, right leg = +1.1%/day), and the second half was characterised by rapid reepithelization and closure of wound (slope of reepithelization from day 25 till closure: left leg = +1.5%/day, right left = +1.8%/day).

[0206] Patient B initially required 188 mg of oral morphine sulfate equivalents per day. A 33% reduction in analgesic requirements, analogous to a clinically significant degree of pain relief occurred on day 19. She began to ambulate with assistance on day 21 and became fully mobile and independent on day 54. On day 68 of treatment, she no longer required any form of analgesia.

[0207] Throughout the entire course of this trial, there were no significant side effects, systemically, regionally, or locally, experienced by either of the patients.

Treatment of uremic calciphylaxis leg uclers

[0208] This case report of a patient with uremic calciphylaxis leg ulcers further illustrates the efficacy of the topical formulations disclosed in this Example. The treatments were found to promote wound healing in patients with high levels of co-morbid illness afflicted with intractable, non-healing wounds.

[0209] A 74-year-old woman with bilateral leg ulcers of more than 12-month in duration presented at the study with large necrotic wounds involving both legs that were debrided. Biopsies confirmed the diagnosis of uremic calciphylaxis. The patient also suffered from end-stage cardiac failure and peripheral vascular disease while undergoing hemodialysis for end-stage diabetic nephropathy. She was extremely frail and sarcopenic, with a palliative performance scale score of 50% (healthy persons score 100%) and a M3 multimorbidity index of 4.79 (two thirds of persons from typical populations score zero). During the course of her treatment in the study, her average hemoglobin was 91g/L and her oxygen saturation was consistently less than 90%. The patient had medical contraindications to other available experimental treatments.

[0210] The patient was treated with daily topical applications of F25 and F26 to two wound sites located on the lower portion of her left and right legs. To each wound site, she first applied F25 to the wound beds and F26 to a 4 to 6 cm radial cuff of periwound integument. She then applied one layer of Jelonet™ and one layer of Mesorb™ on top, followed by a spiral bandaging of her lower limbs using, sequentially, gauze kling roll, Comprilan™, and Easifix™. The patient passed away from her cardiac conditions before the end of treatment, resulting in a treatment period totaling 21 days. Her tri-weekly hemodialysis sessions limited her to only 11 applications of the formulations over the 21-day period. Digital images were taken on Day 0, Day 7, and Day 21 of treatment to estimate wound size. Images were analyzed using planimetric image analysis.

[0211] Retrospective review of the images demonstrated a decrease in overall wound size of 9% and 5% on the left and right leg, respectively, by the end of the 3-week treatment. A much large increase in granulation of tissue in the wound bed was also observed, where 59% and 78% of the total wound size on the left and right leg, respectively, was granularized on Day 21. Throughout the course of the treatment, the patient did not experience any local or systemic adverse reactions.

Treatment of a chronic arterial-venous ulcer with superimposed porokeratosis

[0212] A 90 year-old man presented with a recalcitrant circumferential right leg ulcer of duration greater than two years. The patient developed widespread porokeratosis from the chronicity of his arterial-venous ulcer. The wound was treated with daily topical application of formulation F29 to the wound bed and F30 to periwound areas. The wound was photographed regularly and the digital images were subjected to planimetric analysis to quantify the degree of epithelization. The initial size of the wound was estimated to be about 176 cm^2. Using a linear regression model, the rate of wound closure was 1.57 cm^2/day over the treatment period, or 0.87%/day expressed as a percentage of total wound area (FIG. 10).

Example 5: A Case Report of Medical Cannabis in the Palliation of Malignant Wounds

[0213] A 44-year-old man with an exophytic (fungating) wound involving his right cheek area was diagnosed with a squamous cell cancer of his right buccal cavity three years earlier. He had the tumor surgically resected, followed by external beam radiotherapy and chemotherapy. Despite this appropriate cancer treatment, he developed a buccal recurrence that eventually eroded through his cheek, creating an oral cutaneous fistula and associated exophytic lesion. Over the two-year period before treatments with medical cannabis (MC), he had elected to forego further conventional oncologic therapies in favor of mostly naturopathic treatments. Despite using high-dose hydromorphone, pregabalin, and dexamethasone, he continued to experience continuous (background) generalized right hemifacial pain along with volitional incident pain (wound-related procedural pain) occurring with wound dressing changes. He rated his average daily pain score as 9 of 10. In addition, he also reported having side effects from his analgesics, such as constipation and drowsiness. He also reported suffering severe aesthetic distress from his facial disfigurement along with right-sided trismus, depression, insomnia, nausea, and anorexia.

[0214] At the beginning, he was offered a trial of vaporized MC (ARGYLE™; THC 7.25% + CBD 8.21%) from TWEED, Inc. delivered through a certified Volcano™ vaporizer unit. The particular strain was strategically chosen to maximize the analgesic potential of both THC and CBD while mitigating against the sedation and psychotomimetic side effects commonly experienced with high-dose THC strains.

[0215] On his second clinic visit, he reported significant reductions in both baseline and volitional incident pain. He indicated that he used 0.5-1.0 g of dried cannabis per day and vaporized every two to four hours and 15 minutes before his daily wound dressing change. His pain relief was so significant that he was able to discontinue pregabalin and dexamethasone while reducing hydromorphone to approximately 25% of his pre-MC dosage. He also reported

experiencing less trismus and nausea, along with improved appetite, sleep, and effect. Importantly, he reported no negative effects from the MC. Furthermore, his overall performance status and symptom control was good enough to allow him to be working modified hours as a health care professional.

[0216] During his third and fourth clinic visits, his malignant wound was observed to have increased in size, yet his performance status only marginally declined, and his average daily pain scores remained within tolerable limits, while needing only small increases in daily opioid utilization. Unfortunately, his trismus and oral cutaneous fistula rendered the continued use of vaporized MC technically difficult.

[0217] Because the patient had experienced such positive outcomes with MC therapy, he was eager to continue it through an alternate delivery system. Thus, he was offered a trial of topical MC compounded in nongenetically modified organic sunflower oil (ARGYLE THC 5.24% + CBD 8.02% from TWEED, Inc.). He was instructed to apply, and digitally spread, 1-2 cc of the MC oil to the entire malignant wound, both externally and intrabuccally. He also was advised to swish any residual oil throughout his oral cavity and swallow any residual.

[0218] On his fifth clinic visit, he reported having consistently used the topical MC four times daily. He stated that pain relief commenced with 10-15 minutes after application and lasted for up to two hours after application. He did not report any negative experiences from the use of topical MC. Between his fourth and fifth clinic visits, his condition began to globally deteriorate, and he required a doubling in his daily opioid utilization. Interestingly, the size of his malignant wound decreased by about 5% over the four week interval.

[0219] Four weeks after his last clinic visit, he was admitted to an acute general hospital with hypovolemia. As a result, he was lost to follow-up and ceased to use MC on his admission. He expired three weeks later.

[0220] His clinical course over five months of treatments with MC is summarized in Table 1.

Table 1
Clinical Data

Date	Tumor Size (cm^2)	Average Daily Pain Score (0–10)	Analgesics	MC Therapy	PPSv2 (%)
November 12, 2015	8.75	9	Hydromorphone 30 mg/day Pregabalin 150 mg/day Decadron 4 mg/day	Vaporized	90
December 10, 2015	12.38	3	Hydromorphone 8 mg/day	Vaporized	90
January 21, 2016	26.44	3	Hydromorphone 8 mg/day	Vaporized	80
March 17, 2016	44.16	4	Hydromorphone 10 mg/day	Topical Oil	70
April 21, 2016	41.90	4	Hydromorphone 20 mg/day	Topical Oil	60

MC = medical cannabis; PPSv2 = Palliative Performance Scale, version 2.

[0221] This case report demonstrates the potential for MC to provide effective pain and symptom management in the setting of malignant wounds. The rapid onset of analgesia after

topical placement suggests that the effects were mediated through absorption of the THC and CBD cannabinoids that subsequently interacted with peripheral nociceptors, immune cells, and cancer cells. The post application analgesia may be because of the gastrointestinal absorption of ingested residual MC oil.

Example 6: 3 Case Reports of Topical Medical Cannabis in the Treatment of Patients with Pyoderma Gangrenosum

[0222] Pyoderma gangrenosum (PG) is a rare inflammatory neutrophilic skin disease. Although 50-70% of cases occur in the setting of inflammatory arthritis, inflammatory bowel disease, hematologic diseases, and solid neoplasms, the remainder are idiopathic. Classically, it presents as cutaneous ulcerations that most commonly occur on the lower extremities. PG represents a significant challenge from both diagnostic and therapeutic perspectives. PG is frequently misdiagnosed as cellulitis, venous leg ulcers, and arterial ulcers. Pain is a universal symptom of PG and most patients suffer high levels of pain that is often refractory to high-dose systemically administered opioid analgesics. Because the lesions of PG tend to be chronic and relapsing, they have the potential to substantially compromise quality of life over a protracted period.

Methods

[0223] Before the initiation of topical medical cannabis (TMC), all patients underwent a complete medical workup and providing informed consent for the use of this experimental treatment. All patients were also subjected to wound biopsies for histopathology and immunofluorescence studies to rule out other pathologies. For all three cases, patient reported average daily pain scores, based on an 11-point numeric rating scale (0-10), and average daily opioid use (morphine sulfate equivalents in mg/day) were assessed before and after initiating treatment with TMC. Using a paired t-test, the mean pre-TMC average daily pain score was compared with the mean post-TMC value for all three cases. The percent decrease in average daily pain score after the initiation of TMC was also determined for each case. For average daily opioid dosage, a paired t-test was used to compare the mean pre-TMC morphine sulfate equivalents (MSE) used to the mean post-TMC values for cases 1 and 2 only. In Case 3, the mean MSEs used was nil both before and after initiating treatment with TMC, precluding comparison with a paired t-test. For all hypothesis testing, a P-value <0.05 was considered significant and a decrease in average pain score greater or equal to 30% was accepted to be clinically significant. All statistical analyses were carried out using GraphPad QuickCalcs Software (GraphPad Software Inc., La Jolla, CA).

Case 1

[0224] A 50-year-old woman presented with a painful left medial leg ulcer of at least 12 months' duration. This PG was superimposed on an area of lipodermatosclerosis resulting from a post-phlebitic syndrome in the setting of Factor V Leiden deficiency. She was initially treated with systemic corticosteroids, intralesional corticosteroids, opioid analgesics, and inelastic compression systems. In view of her continued high levels of pain, she agreed to a trial of topical MC oil (ARGYLE™ THC 5 mg/mL + CBD 6 mg/mL) from TWEED Inc (Ontario, Canada). One milliliter of TMC was applied to wound bed daily followed by application of inelastic compression bandaging. The use of the multilayered inelastic compression system precluded the use of TMC for breakthrough pain in this case. After the initiation of TMC, she did not require further corticosteroids.

Case 2

[0225] A 76-year-old man, with no concomitant illnesses, presented with the first-ever occurrence of a painful right lateral ankle ulcer. He was prescribed opioid analgesics and systemic corticosteroids both before and after the initiation of TMC. Before initiating TMC, he was also administered intralesional corticosteroids. He continued to experience high levels of pain and, thus, he agreed to a trial of MC oil (Bedrolite™ THC 7 mg/mL + CBD 9 mg/mL) from Bedrocan Inc. He applied 0.5-1.0 mL of MC oil to the wound bed two times per day plus one to three times daily for breakthrough pain. The wound was dressed with nonadherent dressings.

Case 3

[0226] A 60-year-old woman with systemic lupus erythematosus presented with a recurrent painful right lateral leg ulcer. She was prescribed systemic corticosteroids both before and after the initiation of TMC. She had a history of side effects with opioid analgesics and, thus, refused to use them. She used acetaminophen 325-650 mg every 6 hours as needed for pain. Given her high levels of pain, she agreed to a trial of MC oil (Bedrolite™ THC 7 mg/mL + CBD 9 mg/mL) from Bedrocan Inc. She applied 0.5-1.0 mL of MC oil to the wound bed two times per day plus one to three times daily for breakthrough pain. The wound was dressed with nonadherent dressings.

Results

[0227] The data in Tables 2 and 3, collected prospectively, reflect clinical observations over a total of 17, 21, and 12 weeks for cases 1-3 pre-TMC, respectively, and over 33, 9, and 21 weeks for cases 1-3 post-TMC, respectively. Each of the three patients reported consistently experiencing the onset of analgesia within three to five minutes of each application. After the initiation of treatment with TMC, there was a statistically significant ($P < 0.05$) decrease in the

average daily pain score in cases 1 and 2 (Table 2). In addition, all cases demonstrated ''clinically significant'' pain reductions of greater than 30% which is the generally accepted threshold quoted in international pain research (Younger et al., *Curr. Pain Headache Rep.* 2009;13:39-43). In Case 1, the mean pain score decreased from 8.25 to 2.76, a 66.5% decrease that is both clinically and statistically significant ($P = 0.0007$). For Case 2, the pre-TMC mean pain score was 8.75, which decreased by 73.4% to 2.33, a clinically and statistically significant ($P = 0.0006$) change. Finally, for Case 3, the mean pain score decreased from 4.29 to 1.50, a 65% change that was clinically significant but did not quite reach the threshold for statistical significance ($P = 0.0720$). The average daily opioid dose in cases 1 and 2, measured as MSE (mg), decreased in a statistically significant manner after starting the application of TMC (Table 3). For Case 1, the mean MSE decreased from 26.00 to 0.24 mg, a statistically difference ($P = 0.0013$). In Case 2, mean MSE decreased from 27.33 mg to 12.50, a decrease that was also statistically significant ($P = 0.0001$).

[0228] This case series demonstrates the potential for TMC to provide effective analgesia that was opioid sparing in the setting of PG. The rapid onset of analgesia after topical application suggests that the effects were mediated through absorption of the cannabinoids THC and CBD that subsequently interacted with cannabinoid receptors expressed on peripheral nociceptors and immune cells.

Table 2

Comparison of Mean Daily Pain Scores Before and After Initiating Treatment With TMC

Case	Mean Daily Pain Score Pre-TMC ± SD (*n*)	Mean Daily Pain Score Post-TMC ± SD (*n*)	*P*-Value	Percent Change (%)
1	8.25 ± .50 (4)	2.76 ± 1.34 (25)	0.0007	66.5
2	8.75 ± .46 (8)	2.33 ± 1.97 (6)	0.0006	73.4
3	4.29 ± .95 (4)	1.50 ± 1.60 (7)	0.0720	65.0

TMC = topical medical cannabis.

Table 3

Comparison of Mean MSE Before and After Initiating Treatment With TMC

Case	Mean MSE (mg/day) Pre-TMC ± SD (*n*)	Mean MSE (mg/day) Post-TMC ± SD (*n*)	*P*-Value
1	26.00 ± 5.16 (4)	0.24 ± .88 (25)	0.0013
2	27.33 ± 2.18 (8)	12.50 ± 1.23 (6)	0.0001
3	0 (4)	0 (7)	n/a

MSE = morphine sulfate equivalents; TMC = topical medical cannabis; n/a = not applicable.

Example 7: Oral formulations for wound management

[0229] The following tabulated oral formulations promote wound healing and/or relieve wound-related pain, when used alone or in conjunction with topical formulations of the invention:

FORMULA	Quercetin	Diosmin	Hesperidin	CBD	THCa	THC	Beta-Caryophyllene	Linalool
F31	500 mg	500 mg	50-100 mg	20-25 mg		< 1 mg	150-250 mg	150-250 mg
F32	500 mg	500 mg	50-100 mg	20-25 mg	20-25 mg	< 1 mg	150-250 mg	150-250 mg

The oral formulations can be taken once or twice daily depending on the extent of the wound size, wound complexity, and level of pain.

[0230] Use of F31 and F32 was associated in 30-50% reduction in the utilization of analgesics by patients, a proxy or surrogate measure for patient-reported pain scores. Use of F31 and F32 improved wound closure times by 25-50%.

[0231] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the scope of the appended claims.

[0232] The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers such as E and Z), enantiomers or diastereomers. The present disclosure includes each of the isolated stereoisomeric forms (such as the enantiomerically pure isomers, the E and Z isomers, and other alternatives for stereoisomers) as well as mixtures of stereoisomers in varying degrees of chiral purity or percentage of E and Z, including racemic mixtures, mixtures of diastereomers, and mixtures of E and Z isomers.

[0233] Accordingly, the compounds described herein encompass all possible enantiomers and stereoisomers thereof including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The present disclosure includes each of the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity, including racemic mixtures. It also encompasses the various diastereomers.

[0234] When the chemical name does not specify the isomeric form of the compound, it denotes any one of the possible isomeric forms or mixtures of those isomeric forms of the compound. The compounds may also exist in several tautomeric forms. Accordingly, the compounds depicted herein encompass all possible tautomeric forms thereof.

[0235] The term "tautomer" is generally understood to refer to isomers that change into one another with great ease so that they can exist together in equilibrium; the equilibrium may

strongly favor one of the tautomers, depending on stability considerations. For example, ketone and enol are two tautomeric forms of one compound.

[0236] It must be noted that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Unless defined otherwise all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs.

[0237] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[0238] As used herein in the specification and in the claims, "or" should be understood to encompass the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items.

[0239] As used herein, whether in the specification or the appended claims, the transitional terms "comprising", "including", "having", "containing", "involving", and the like are to be understood as being inclusive or open-ended (i.e., to mean including but not limited to), and they do not exclude unrecited elements, materials or method steps. Only the transitional phrases "consisting of" and "consisting essentially of", respectively, are closed or semi-closed transitional phrases with respect to claims and exemplary embodiment paragraphs herein. The transitional phrase “consisting of” excludes any element, step, or ingredient which is not specifically recited. The transitional phrase “consisting essentially of” limits the scope to the specified elements, materials or steps and to those that do not materially affect the basic characteristic(s) of the invention disclosed and/or claimed herein.

CLAIMS:

1. A topical formulation comprising:

(a) 0.1 mg/ml to 40 mg/ml of one or more cannabinoids;

(b) 25 mg/ml to 1000 mg/ml of one or more terpenes;

(c) 10 mg/ml to 500 mg/ml of one or more flavonoids; and

(d) a liquid carrier,

wherein the one or more cannabinoids comprise at least 0.1 mg/ml tetrahydrocannabinolic acid.

2. The topical formulation of claim 1, wherein the one or more cannabinoids further comprise cannabidiol or cannabidiolic acid.

3. The topical formulation of claim 1 or claim 2, wherein the one or more terpenes comprise beta-caryophyllene, and the concentration of beta-caryophyllene is 50 mg/ml to 500 mg/ml.

4. The topical formulation of any one of claims 1 to 3, wherein the one or more terpenes further comprise linalool, and the concentration of linalool is 25 mg/ml to 500 mg/ml.

5. The topical formulation of any one of claims 1 to 4, wherein the one or more flavonoids comprise at least one of diosmin, quercetin, and hesperidin.

6. The topical formulation of any one of claims 1 to 5, wherein the one or more flavonoids comprise diosmin, quercetin, and hesperidin.

7. A topical formulation for direct application to an integumentary wound, comprising:

(a) 0.1 mg/ml to 40 mg/ml of one or more cannabinoids;

(b) 25 mg/ml to 1000 mg/ml of one or more terpenes; and

(c) 10 mg/ml to 500 mg/ml of one or more flavonoids,

wherein the one or more cannabinoids comprise at least 0.1 mg/ml tetrahydrocannabinolic acid.

8. The topical formulation of claim 7, wherein the one or more cannabinoids further comprise cannabidiol or cannabidiolic acid.

9. The topical formulation of claim 7 or 8, wherein the one or more terpenes comprise beta-caryophyllene, and the concentration of beta-caryophyllene is 50 mg/ml to 500 mg/ml.

10. The topical formulation of any one of claims 7 to 9, wherein the one or more terpenes further comprise linalool, and the concentration of linalool is 25 mg/ml to 500 mg/ml.

11. The topical formulation of any one of claims 7 to 10, wherein the one or more flavonoids comprise at least one of diosmin, quercetin, and hesperidin.

12. The topical formulation of any one of claims 7 to 11, wherein the one or more flavonoids comprise diosmin, quercetin, and hesperidin.

13. The topical formulation of any one of claims 7 to 12, further comprising a liquid carrier selected for instillation of the topical formulation onto an integumentary wound.

14. Use of a first topical formulation for the treatment of an integumentary wound of a subject, wherein the first topical formulation comprises one or more cannabinoids; one or more terpenes; and one or more flavonoids, and is for application onto the integumentary wound, and wherein the one or more cannabinoids comprise at least 0.1 mg/ml tetrahydrocannabinolic acid.

15. The use of claim 14, further comprising use of a second topical formulation comprising one or more cannabinoids; one or more terpenes; and one or more flavonoids, wherein the second topical formulation is for application onto a periwound area around the integumentary wound.

16. The use of claim 15, wherein the first topical formulation comprises an aloe vera gel and a hyaluronic acid gel, and the second topical formulation comprises pluronic lecithin organogel or a transdermal base comprising a liposomal component.

17. The use of any one of claims 14 to 16, wherein the first topical formulation is a topical formulation according to any one of claims 1 to 6.

18. The use of claim 17, wherein the second topical formulation is a topical formulation according to any one of claims 1 to 6.

19. The use of any one of claims 14 to 18, further comprising use of an oral formulation comprising one or more cannabinoids; one or more terpenes; and one or more flavonoids.

20. The use of any one of claims 14 to 19, wherein the integumentary wound is caused by a skin disease or condition, wherein the skin disease or condition is Skin Cancer (e.g., Primary Neoplasms, Metastatic Neoplasms, or Bowen's Disease), Vasculopathic Ulcers and Erosions (e.g., Sickle Cell Disease, Martorell's Ulcer, Uremic Calciphylaxis, Non-Uremic Calciphylaxis, Venous Leg Ulcers, or Arterial Ulcers), Integumentary Ulcers and Erosions caused by microbes (e.g., a bacterium, fungus, virus, or mycobacterium), Ulcers and Erosions related to diabetes (e.g., Diabetic Foot Ulcers, Necrobiosis Lipoidica Diabeticorum, or Diabetic Dermopathy), Blistering Skin Conditions (e.g., Epidermolysis Bullosa, Pemphigus, or Bullous Pemphigoid), Ulcers and Erosions caused by autoimmune diseases (e.g., Pyoderma Gangrenosum, Rheumatoid arthritis, Systemic Lupus Erythematosis, Scleroderma, or Morphea), Vasculitic Ulcers and Erosions (e.g., Cutaneous vasculitis, Leukocytoclastic Vasculitis, Cutaneous polyarteritis nodosa, or Microscopic polyangiitis), or Ulcers and Erosions caused by other complex diseases (e.g., Hidradenitis Suppurativa, Lichen Simplex Chronicus, Lichen Sclerosus, Lichen Planus, Wegener's Granulomatosis, Cryoglobulinemia, Behcet's Disease, Cryofibrinogenemia, Antiphospholipid Syndrome, Allergic Dermatitis, Psoriasis, or Porokeratosis).

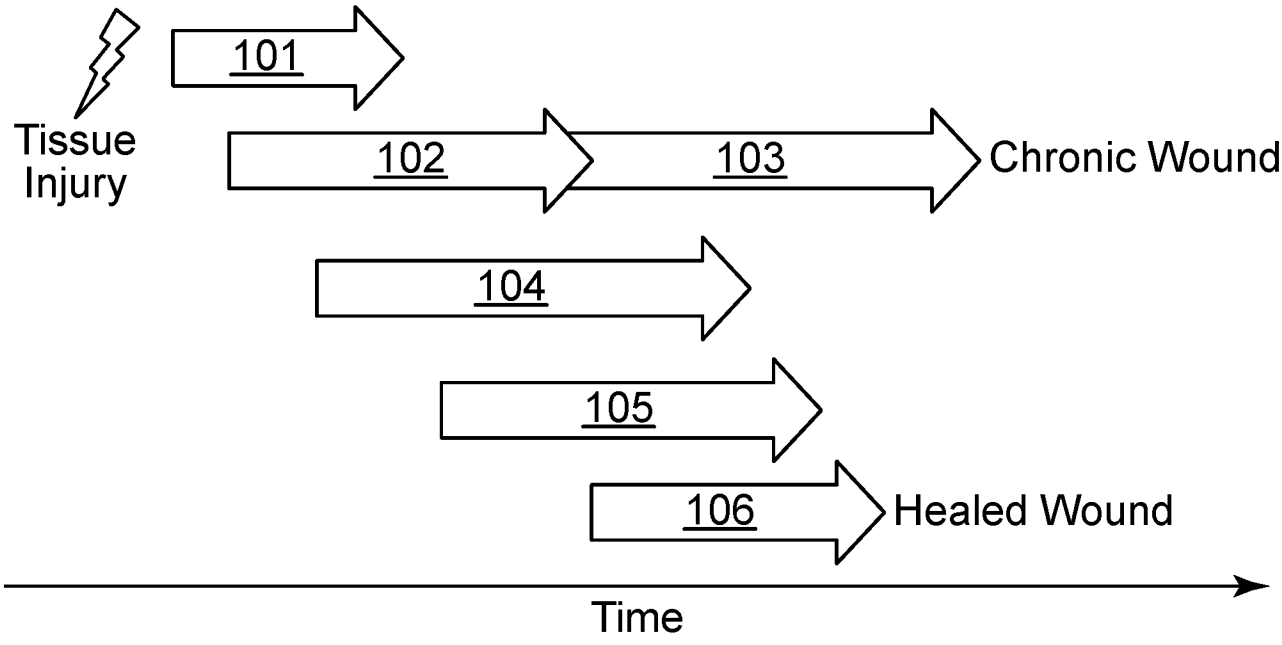


FIG. 1
(Prior Art)

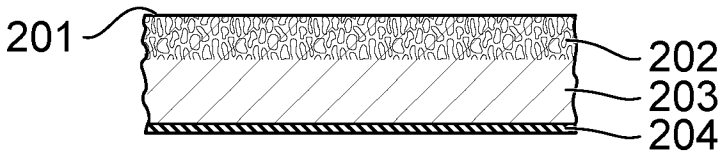


FIG. 2a

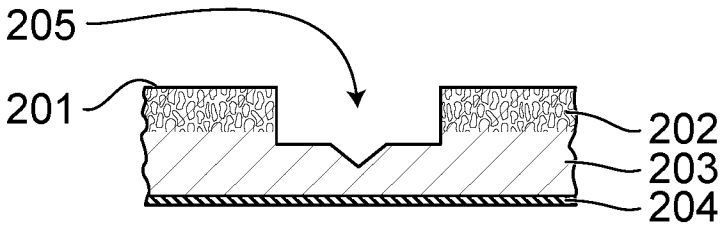


FIG. 2b

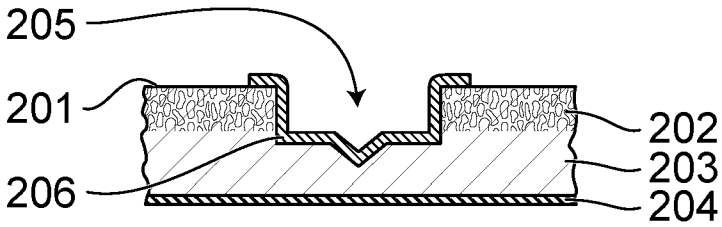


FIG. 2c

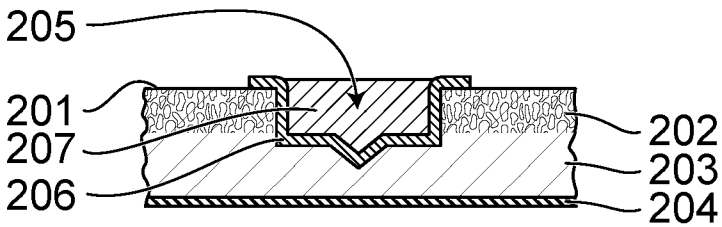


FIG. 2d

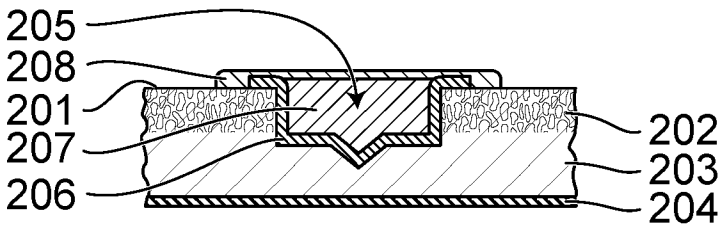


FIG. 2e

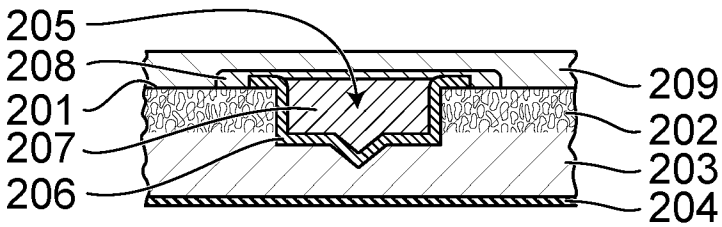


FIG. 2f

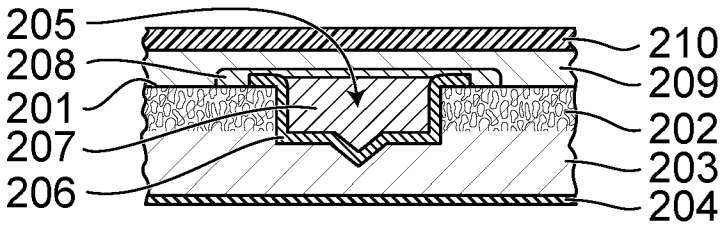
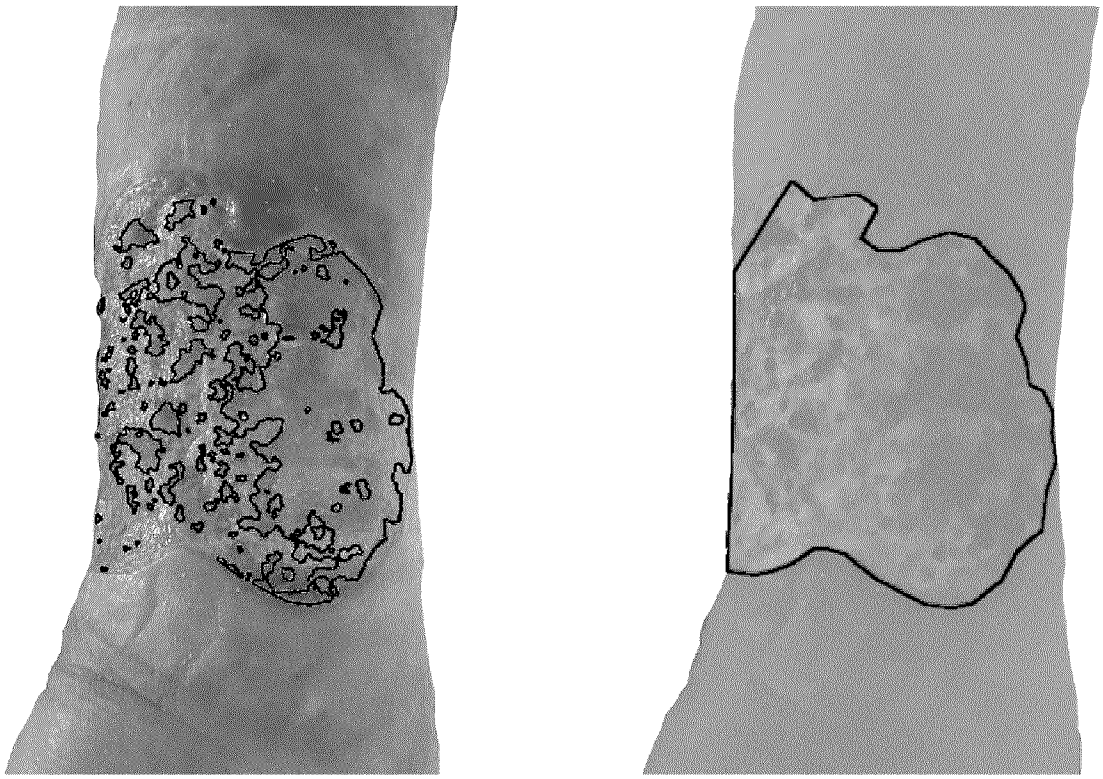


FIG. 2g



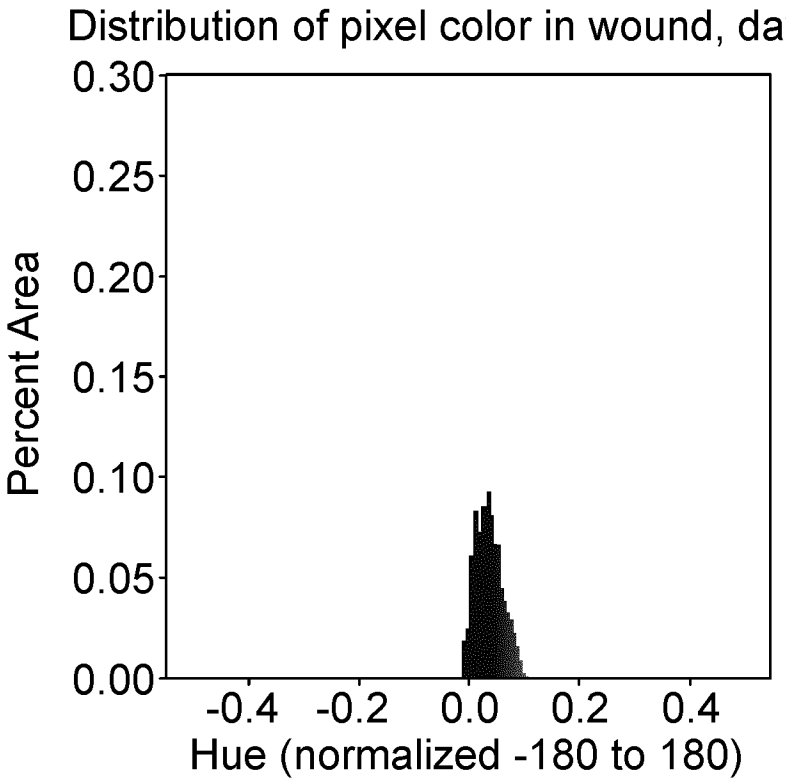
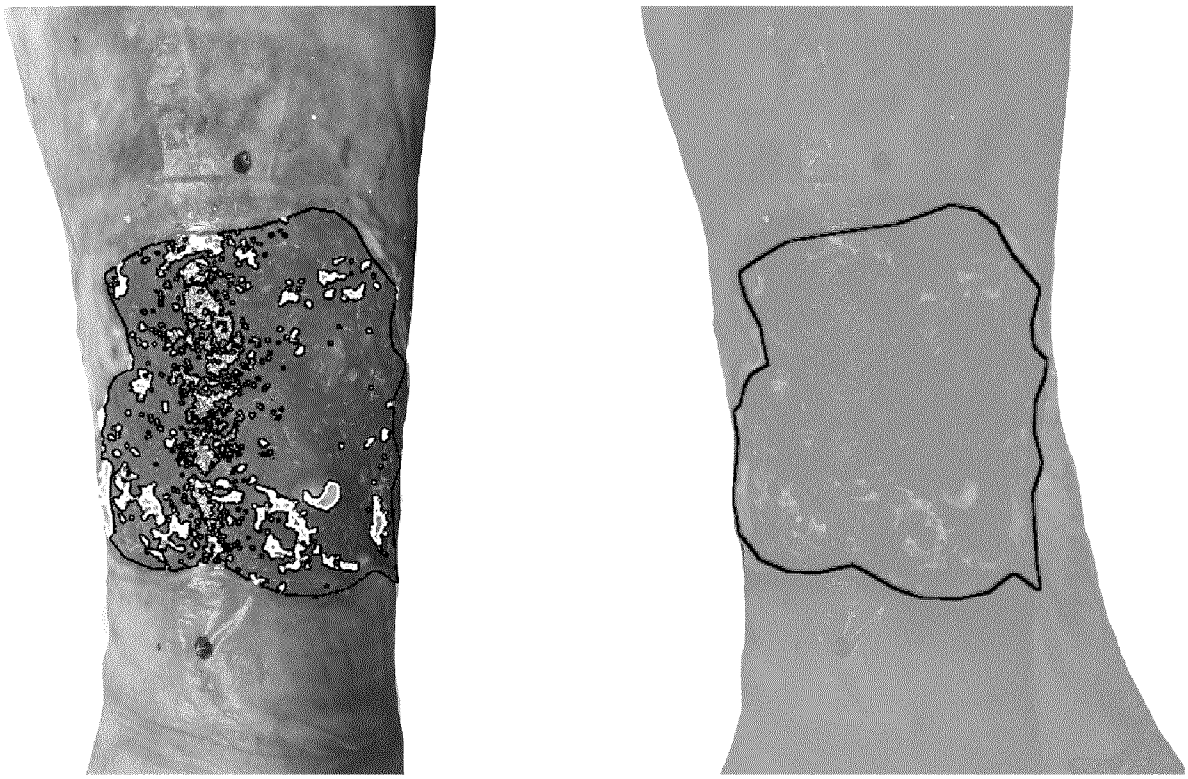

Distribution of pixel color in wound, day 15
Percent Area
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.4
-0.2
0.0
0.2
0.4
Hue (normalized -180 to 180)

FIG. 3a



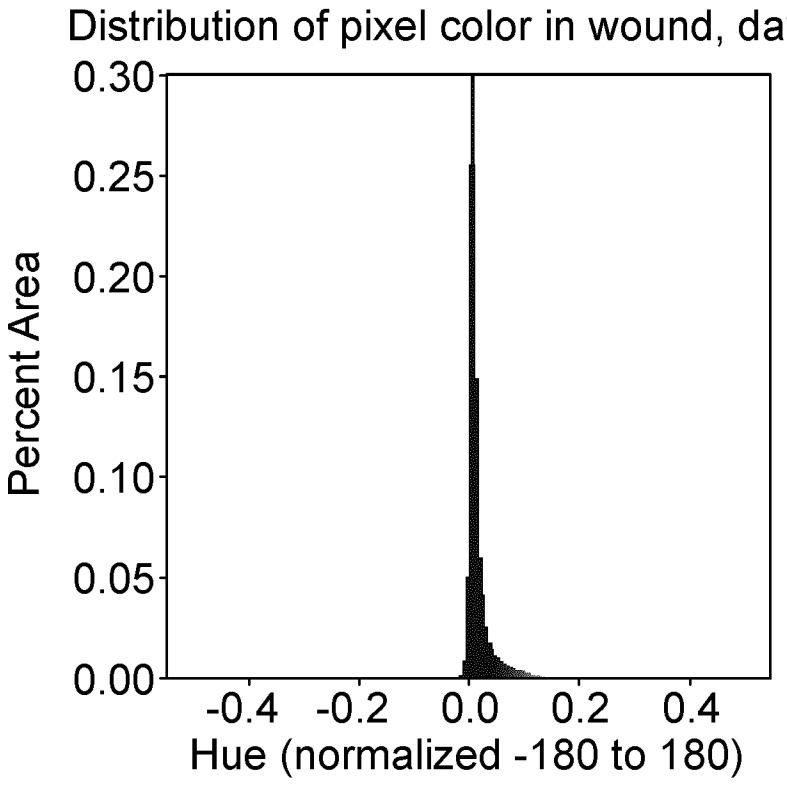
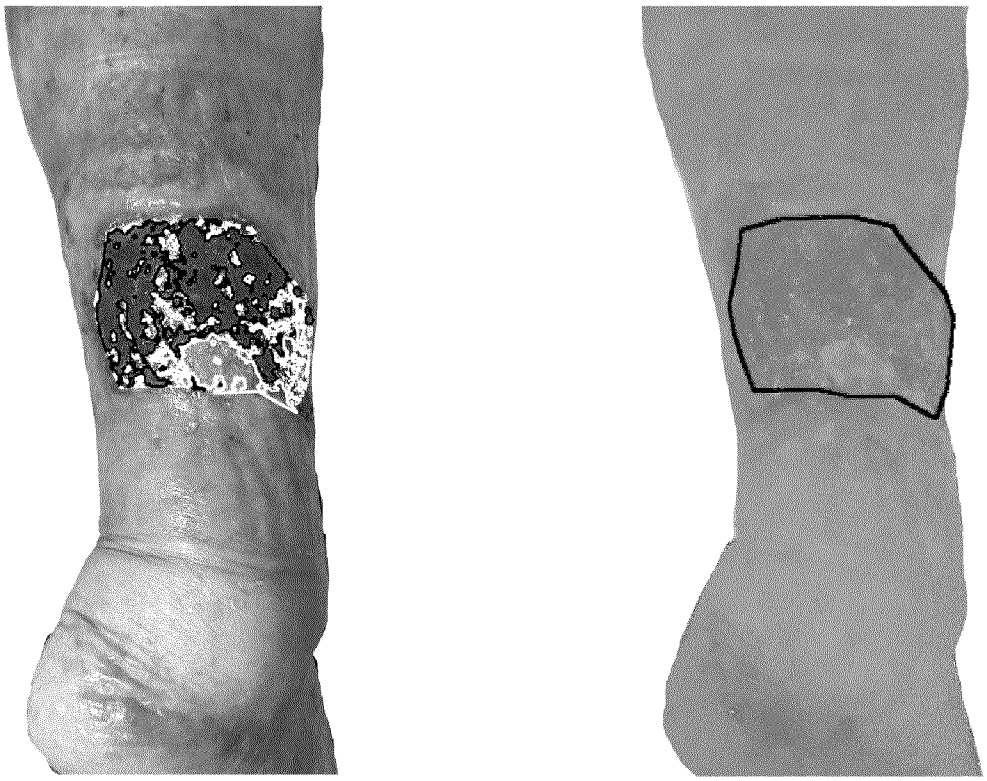

Distribution of pixel color in wound, day 41
Percent Area
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.4
-0.2
0.0
0.2
0.4
Hue (normalized -180 to 180)

FIG. 3b



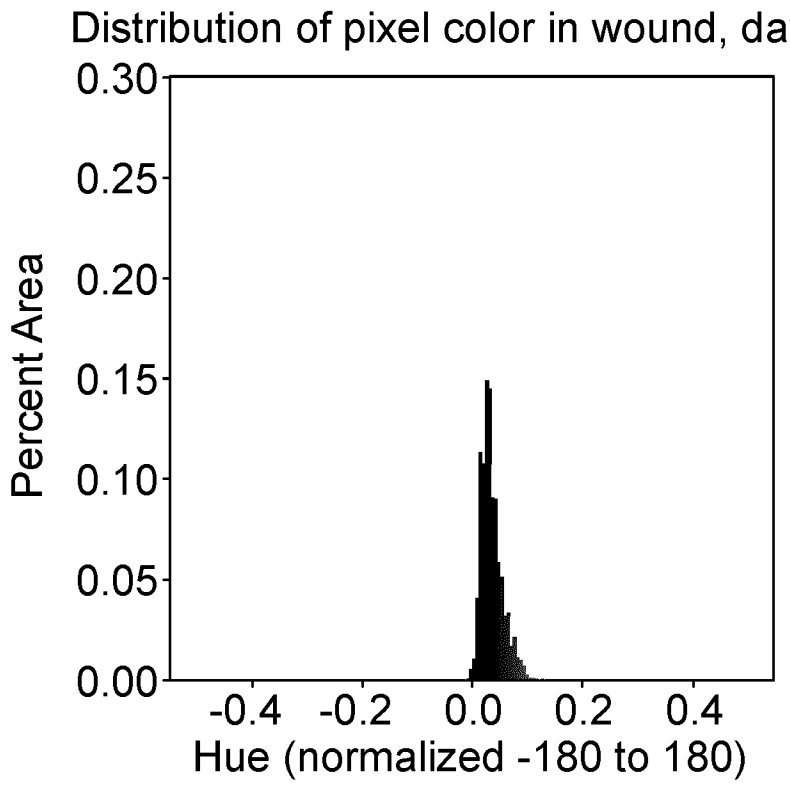

Distribution of pixel color in wound, day 87
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Percent Area
-0.4
-0.2
0.0
0.2
0.4
Hue (normalized -180 to 180)

FIG. 3c

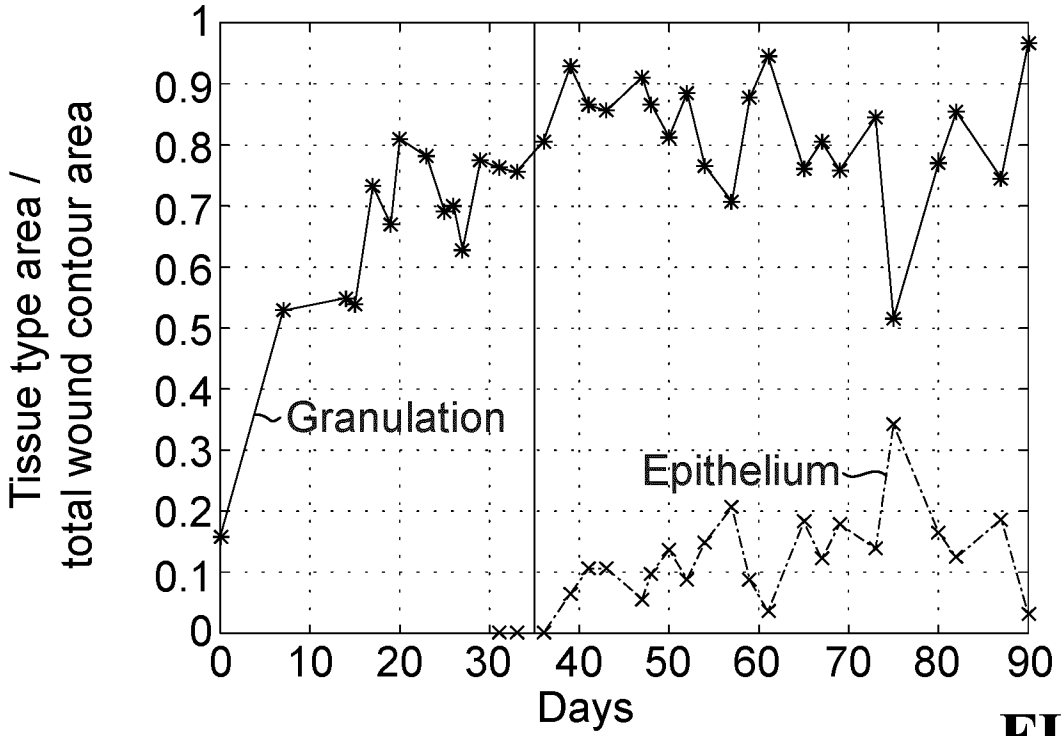

Tissue type area / total wound contour area
Granulation
Epithelium
Days
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80
90

FIG. 4

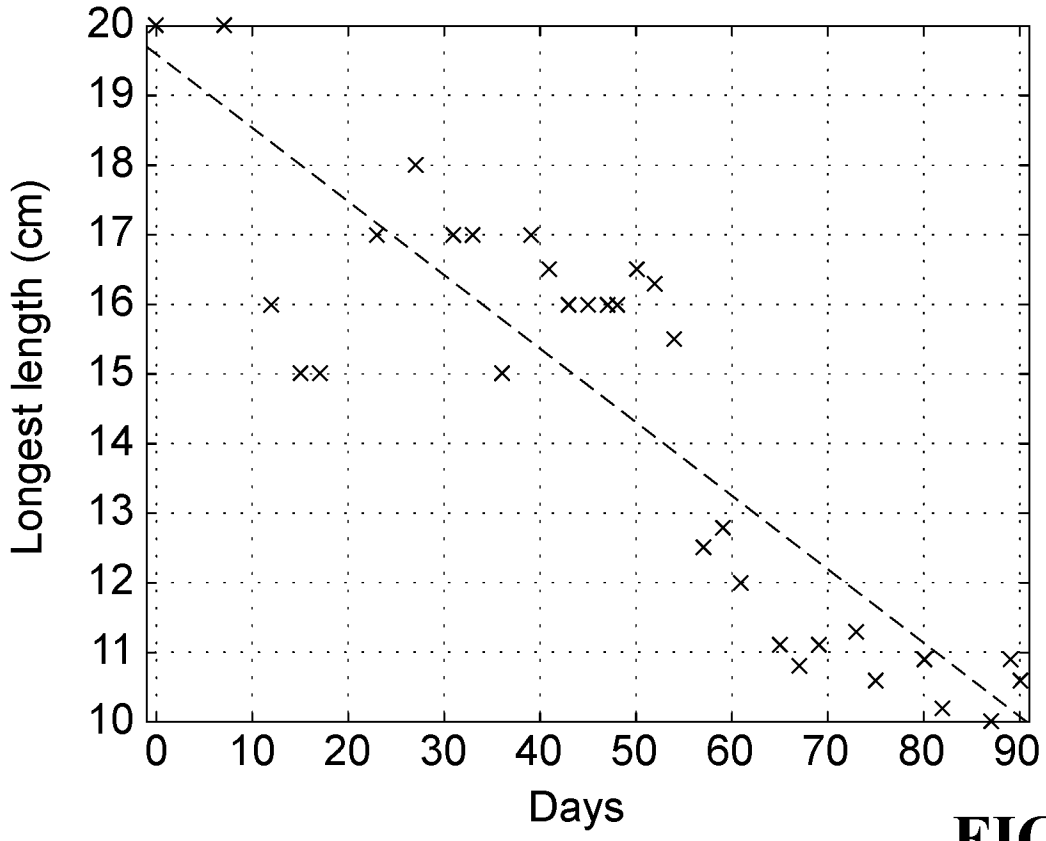

Longest length (cm)
Days
10
11
12
13
14
15
16
17
18
19
20
0
10
20
30
40
50
60
70
80
90

FIG. 5A

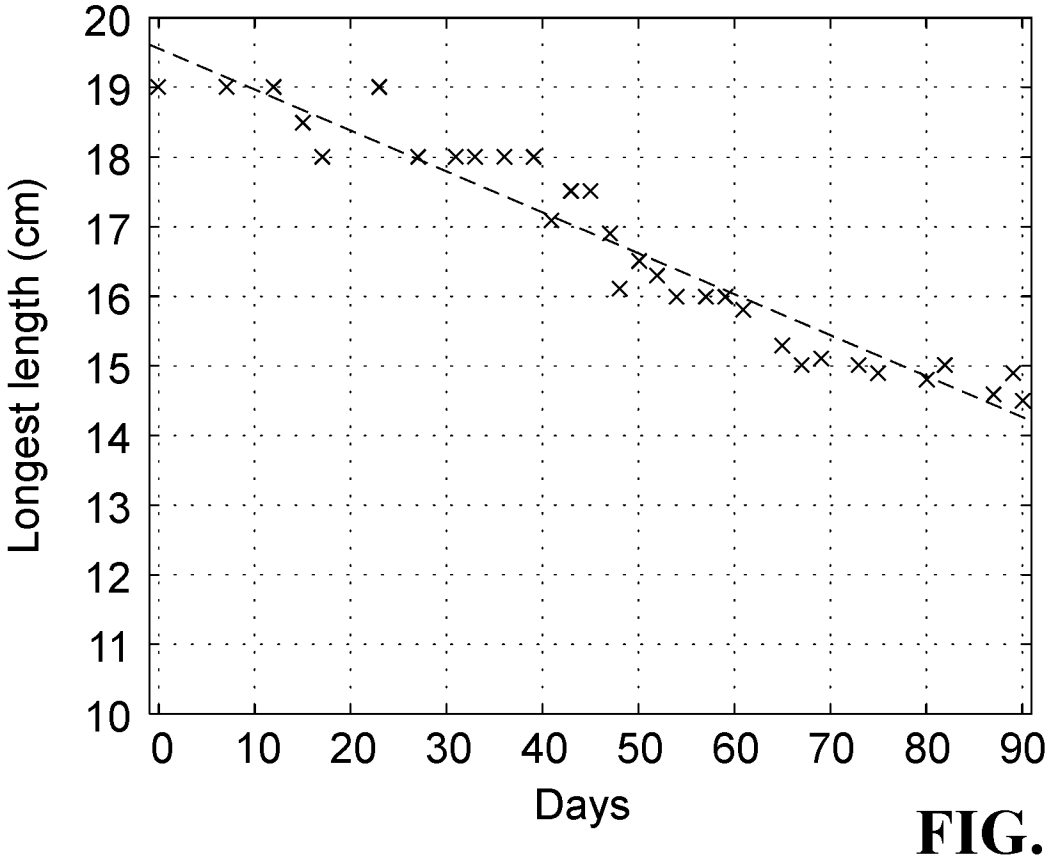

Longest length (cm)
20
19
18
17
16
15
14
13
12
11
10
0
10
20
30
40
50
60
70
80
90
Days

FIG. 5B

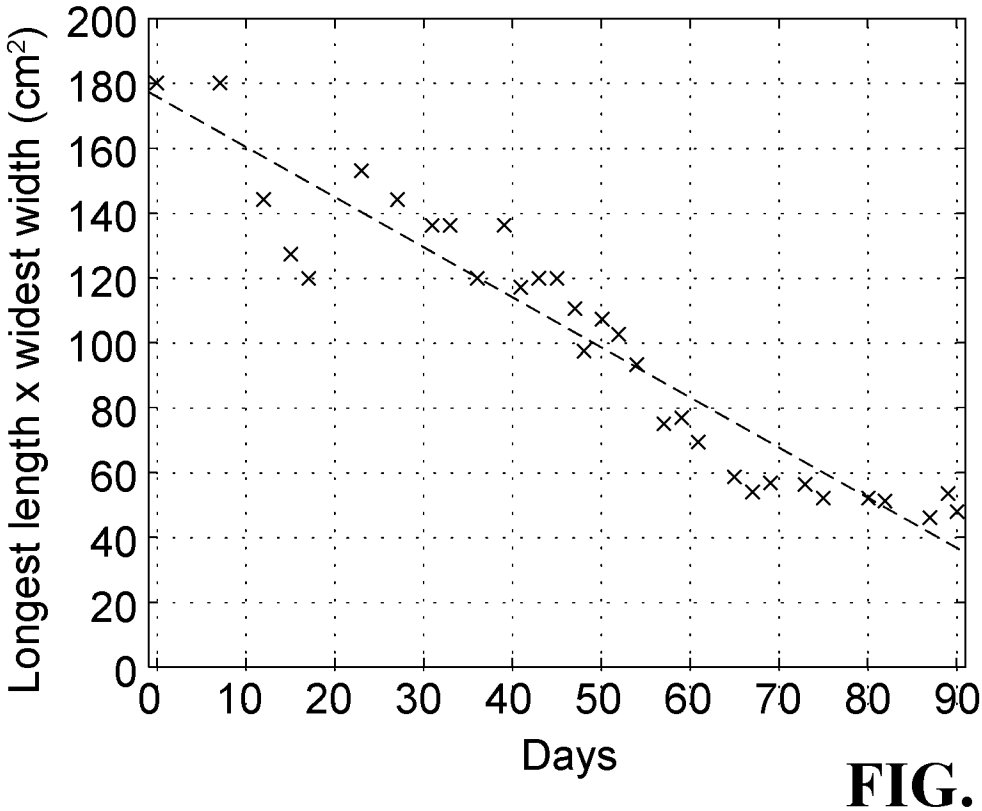

Longest length x widest width (cm²)
200
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
Days

FIG. 5C

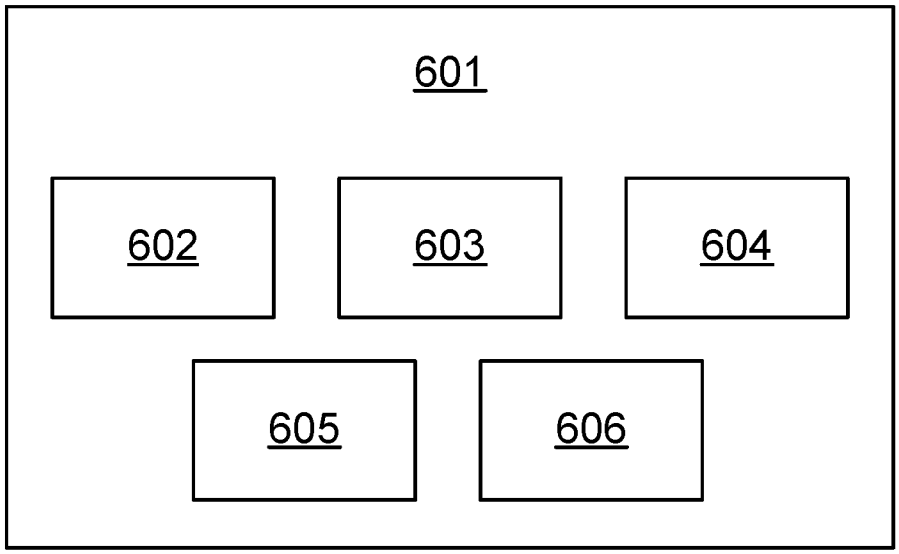


FIG. 6



FIG. 7

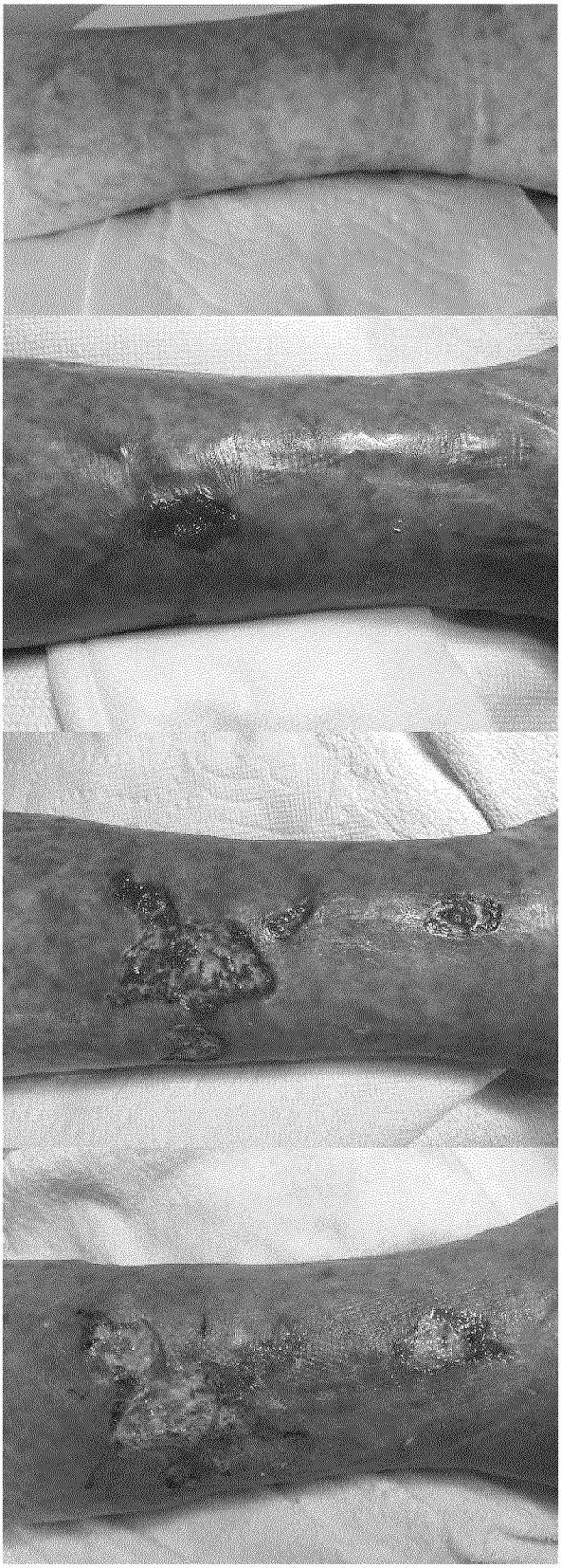


FIG. 8A

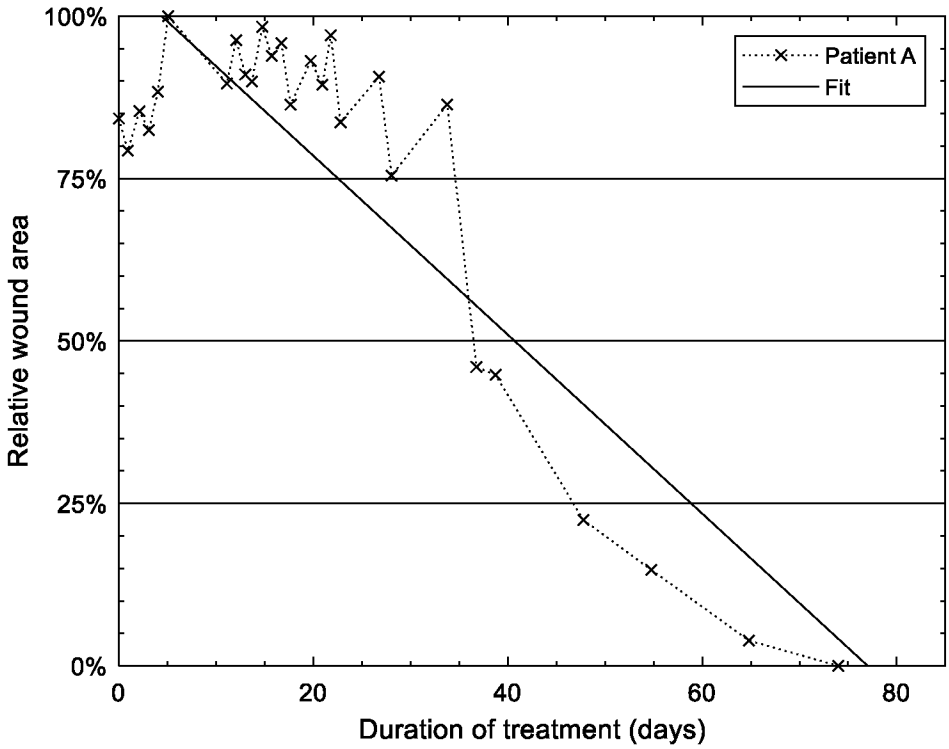

100%
75%
50%
25%
0%
Relative wound area
0
20
40
60
80
Duration of treatment (days)
Patient A
Fit

FIG. 8B

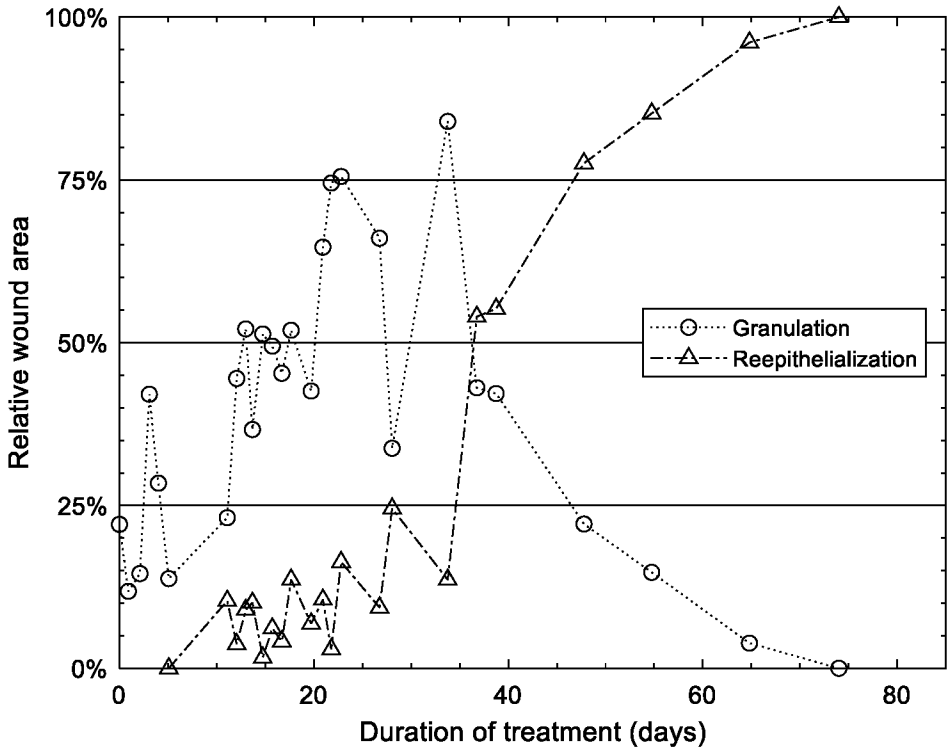

100%
75%
50%
25%
0%
Relative wound area
0
20
40
60
80
Duration of treatment (days)
Granulation
Reepithelialization

FIG. 8C



FIG. 9A



FIG. 9B

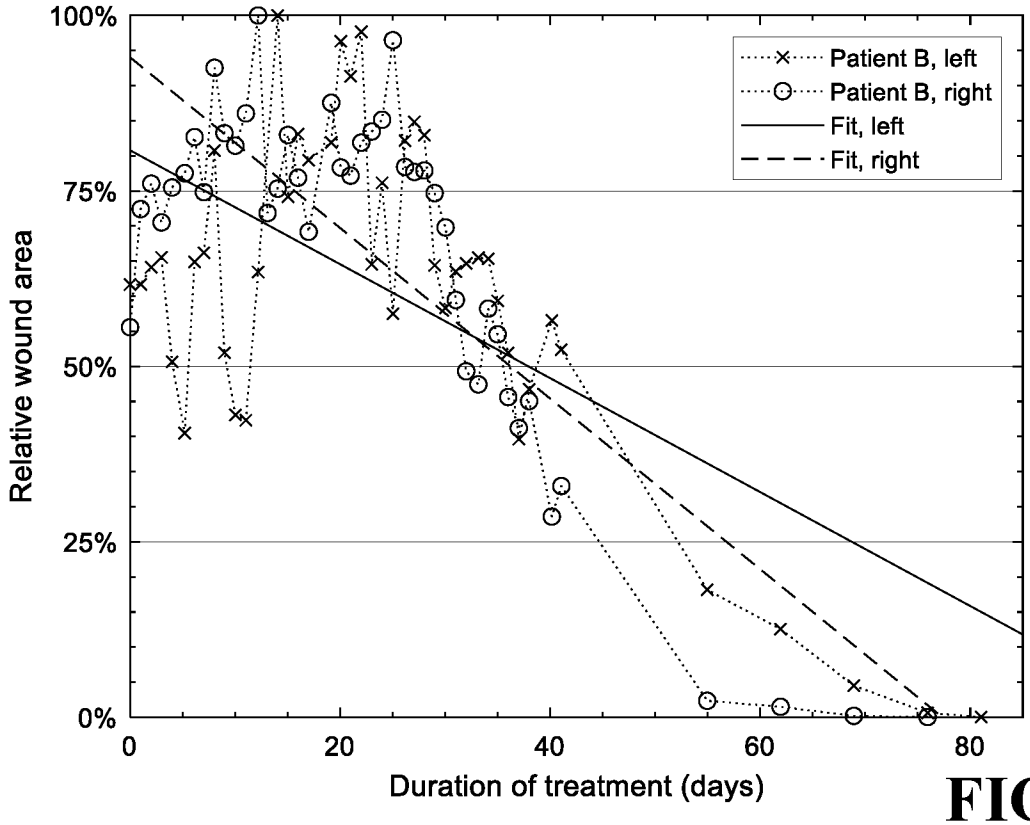

100%
75%
50%
25%
0%
Relative wound area
0
20
40
60
80
Duration of treatment (days)
Patient B, left
Patient B, right
Fit, left
Fit, right

FIG. 9C

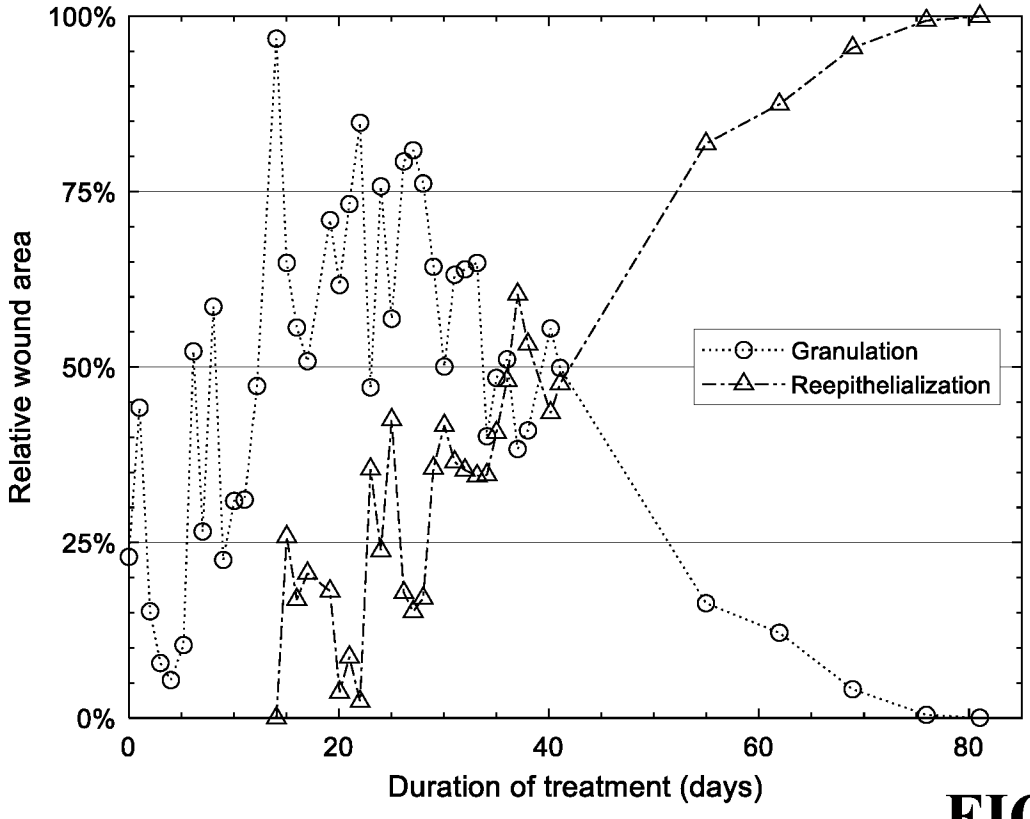

100%
75%
50%
25%
0%
Relative wound area
0
20
40
60
80
Duration of treatment (days)
Granulation
Reepithelialization

FIG. 9D

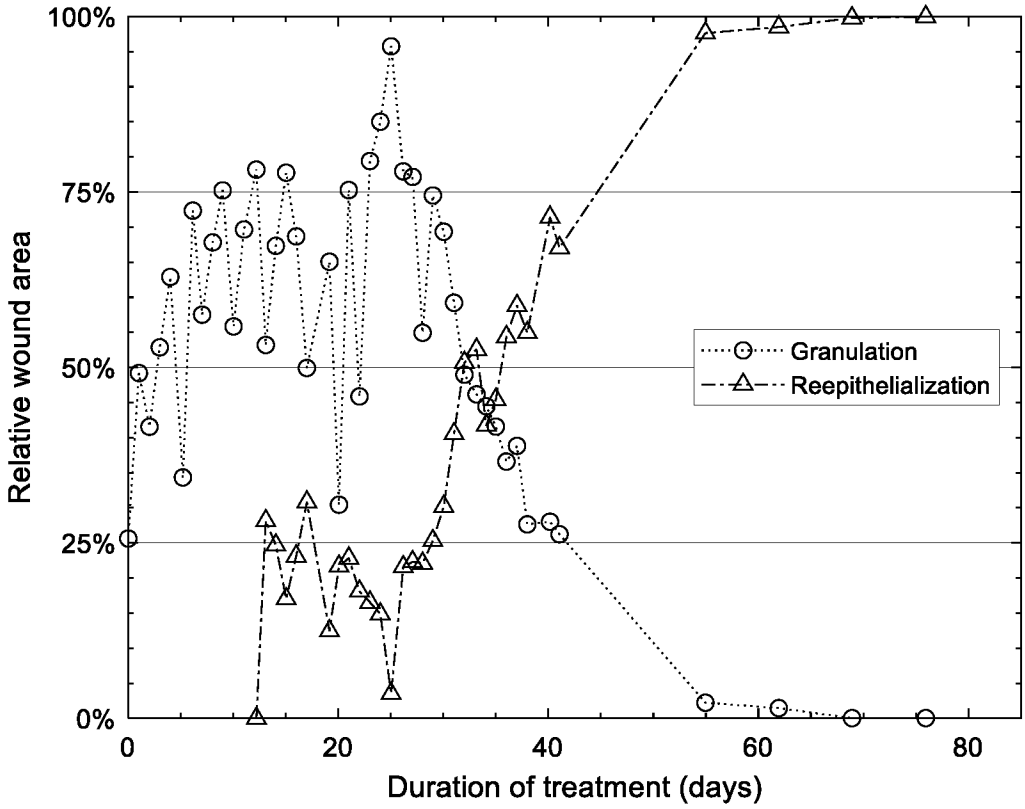

100%
75%
50%
25%
0%
Relative wound area
0
20
40
60
80
Duration of treatment (days)
Granulation
Reepithelialization

FIG. 9E

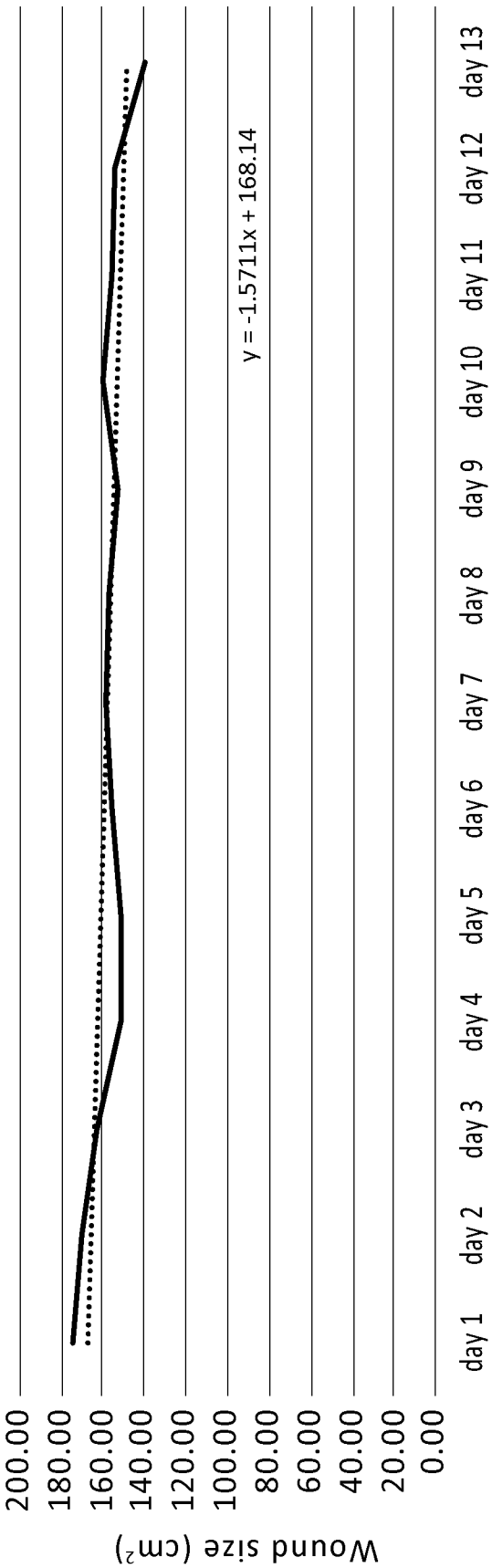

Wound size (cm²)
200.00
180.00
160.00
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
y = -1.5711x + 168.14
day 1
day 2
day 3
day 4
day 5
day 6
day 7
day 8
day 9
day 10
day 11
day 12
day 13
Day of treatment

FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2020/051326

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 31/352** (2006.01) , ***A61K 31/015*** (2006.01) , ***A61K 31/7048*** (2006.01) , ***A61K 31/728*** (2006.01) , ***A61K 36/185*** (2006.01) , ***A61K 36/886*** (2006.01) (more IPCs on the last page)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 2006.01: **A61K 31/352** , ***A61K 31/015*** , ***A61K 31/7048*** , ***A61K 31/728*** , ***A61K 36/185*** , ***A61K 36/886, A61K 9/10*** , ***A61P 17/02*** , ***C07C 13/32***, ***C07D 311/74*** , ***C07D 311/80***, ***C07H 17/07***, ***C08J 3/075***, ***C08L 5/08***

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STNext (Registry, CAPlus), Canadian Patent Database, Scopus

Keywords: thca, tetrahydrocannabinolic acid, beta caryophyllene, linalool, diosmin, quercetin, hesperidin, wound, integumentary

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2019056128A1 (MACNAIR L. et al.), 28 March 2019 (28-03-2019) **see the claims and Table 5**	
A	WO2017190249A1 (HOSSAIN Sazzad), 09 November 2017 (09-11-2017)	
A	WO2016138505A1 (COOPER J. et al.), 01 September 2016 (01-09-2016)	
P, A	WO2019191830A1 (MAIDA Vincenzo), 10 October 2019 (10-10-2019)	

☐ Further documents are listed in the continuation of Box C.

☑ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
"D"	document cited by the applicant in the international application
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search 26 November 2020 (26-11-2020)	Date of mailing of the international search report 09 December 2020 (09-12-2020)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Guillaume Tessier (819) 639-8671

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2020/051326

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2019056128A1	28 March 2019 (28-03-2019)	WO2019056128A1	28 March 2019 (28-03-2019)
		CA3076929A1	28 March 2019 (28-03-2019)
		EP3687527A1	05 August 2020 (05-08-2020)
		US2020281890A1	10 September 2020 (10-09-2020)
		WO2019056129A2	28 March 2019 (28-03-2019)
WO2017190249A1	09 November 2017 (09-11-2017)	WO2017190249A1	09 November 2017 (09-11-2017)
		AU2017260706A1	22 November 2018 (22-11-2018)
		CA3023049A1	09 November 2017 (09-11-2017)
		CN109689045A	26 April 2019 (26-04-2019)
		EP3452036A1	13 March 2019 (13-03-2019)
		EP3452036A4	06 November 2019 (06-11-2019)
		IL262702D0	31 December 2018 (31-12-2018)
		JP2019518075A	27 June 2019 (27-06-2019)
		SG11201809688RA	29 November 2018 (29-11-2018)
		US2019142788A1	16 May 2019 (16-05-2019)
WO2016138505A1	01 September 2016 (01-09-2016)	WO2016138505A1	01 September 2016 (01-09-2016)
		AU2016225026A1	07 September 2017 (07-09-2017)
		AU2018227544A1	29 August 2019 (29-08-2019)
		BR112017018316A2	17 April 2018 (17-04-2018)
		BR112019018088A2	24 March 2020 (24-03-2020)
		CA2977802A1	01 September 2016 (01-09-2016)
		CA3027108A1	14 December 2017 (14-12-2017)
		CA3054690A1	07 September 2018 (07-09-2018)
		CN107405314A	28 November 2017 (28-11-2017)
		CN110582206A	17 December 2019 (17-12-2019)
		CO2019009413A2	09 September 2019 (09-09-2019)
		EP3261629A1	03 January 2018 (03-01-2018)
		EP3261629A4	05 December 2018 (05-12-2018)
		EP3589129A1	08 January 2020 (08-01-2020)
		IL254025D0	31 October 2017 (31-10-2017)
		IL268929D0	31 October 2019 (31-10-2019)
		MX2017010872A	07 May 2018 (07-05-2018)
		MX2019010370A	22 October 2019 (22-10-2019)
		PE20200383A1	24 February 2020 (24-02-2020)
		US2019030101A1	31 January 2019 (31-01-2019)
		US10821147B2	03 November 2020 (03-11-2020)
		US2016250270A1	01 September 2016 (01-09-2016)
		US2017266153A1	21 September 2017 (21-09-2017)
		US2019192993A1	27 June 2019 (27-06-2019)
		WO2017100369A1	15 June 2017 (15-06-2017)
		WO2017214529A1	14 December 2017 (14-12-2017)
		WO2018160827A1	07 September 2018 (07-09-2018)
WO2019191830A1	10 October 2019 (10-10-2019)	WO2019191830A1	10 October 2019 (10-10-2019)
		AU2018417229A1	15 October 2020 (15-10-2020)
		CA3028706A1	04 October 2019 (04-10-2019)

A61K 9/10 (2006.01) , ***A61P 17/02*** (2006.01) , ***C07C 13/32*** (2006.01) , ***C07D 311/74*** (2006.01) , ***C07D 311/80*** (2006.01) , ***C07H 17/07*** (2006.01) , *C08J 3/075* (2006.01) , *C08L 5/08* (2006.01)