**ANNNOTATED**

**HOMEOSTASIS BIBLIOGRAPHY**

1 Acosta-Madrid, I.I., et al

Interaction between Heliopsis longipes extract and diclofenac on the thermal hyperalgesia test

Phytomedicine 16, pg, 336-341, 2009

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2 Aghamohammadi, A., et al

Natural products for management of oral mucositis induced by radiotherapy and chemotherapy.

Integrative Cancer Therapies 15(1), pg, 60-68, 2015

**Clinical trials of natural products for the relief of side effects of radiation therapy have been promising for down regulating the reactive oxygen species generated**.

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Blocking Chemokine Receptors

J. Exp. Med., 186(8) pg. 1189-1191, 1997

**New anti-inflammatory agents act on CXCR4 and CCR2 receptors that bind CXCL12 and MCP-1 respectively.**

4 Barbosa, A.F., et al

Spilanthol: occurrence, extraction, chemistry and biological activities

Brazilian Journal of Pharmacognosy, 26, pg. 128-133, 2016

**Spilanthol is found in many different plants around the world used as traditional remedies. Mouthwatering, antioxidant, analgesic, neuroprotective, anti-inflammatory and antimicrobial effects have been found.**

5 Bayer

Dexpanthenol Clinical Study Synopsis - clinical trial - NCT00859196

**Clinical trial of dexpanthenol on skin demonstrated wound healing and gene expression results consistent with beneficial wound healing.**

6 Boonen, J., et al

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Journal of Ethnopharmacology, 127, pg 77-84, 2010

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7 Bouffi, C., et al

IL-6-dependent PGE2 secretion by mesenchymal stem cells inhibits local inflammation in experimental arthritis

PLOS One, Dec. 5(12) pg. E14247, 2010

**MSCs mediate immunosuppressive effects by two modes of action: Secretion of anti-proliferative mediators NO and PGE2 and systemically switch form Th1/Th17 to Th2 immune profile**

8 Byun, J.Y., et al

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Mediators of Inflammation 2014, ID 463524, 17 pages

**Resolution of inflammation is initiated by recognition of apoptotic cells. COX-2/PGE2 and HGF play important roles in tissue repair process.**

9 Chen, J. et al

Notch1-promoted TRPA1 expression in erythroleukemic cells suppresses erythroid but enhances megakaryocyte differentiation

Scientific Reports 2017, DOI:10.1038/srep42883

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10 Daubeuf, F., et al

An antedrug of the CXCL12 neutraligand blocks experimental allergic asthma without systemic effect in mice

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Planta Med. 76, pg. 665-670, 2010

**Spilanthol (Affinin) gives pain relief dose dependently in a challenge by acetic acid and/or capsaicin in mice through NO effects.**

12 Diaz, M.F., et al

Biomechanical forces promote immune regulatory function of bone marrow mesenchymal stromal cells

Stem Cells 35, pg 1259-1272, 2017

**MSCs mobilize in response to inflammation and injury. Wall shear stress in vascular lumen modulates antioxidant and anti-inflammatory mediators acting through NFkB/COX2/PGE2 to down-regulate TNFa.**

13 Dorr, W., et al

Effects of dexpanthenol with or without aloe vera extract on radiation-induced oral mucositis: preclinical studies

Int. J. Radiat. Biol. 81(3), pg. 243-250, 2005

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Advances in Pharmacological Sciences, 2013, DOI:10.1155/2013/423750

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Protective effect of dexpanthenol on bleomycin-induced pulmonary fibrosis in rats

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16 Escobedo-Martinez, C., et al

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**Spilanthol, the main active principle in Helopsis longipes gave anti-inflammatory and anti-arthritic results orally similar to phenylbutazone.**

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The Functions of TRPA1 and TRPV1: moving away from sensory nerves

Brit. J. of Pharm., vol 166, pg 510-521

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PLOS One 11(5), e0156021, 2016

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Nature 453(15), pg 314-321, 2008

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PNAS, 105(36), pg. 13532-13537, 2008

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TAK1 regulates the NRF2 antioxidant system through modulation p62/SQSTM1

Antioxidants and redox signaling, 25(17), pg. 953-964, 2016

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Role of SDF-1/CXCR4 signaling in regulation of PKA activity during cell migration

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Dexpanthenol modulates gene expression in skin wound healing in vivo

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**Genes upregulated by dexpanthenol in human skin are IL-6, IL-1b, CXCL1, CCL18 and CYP1B1. This data was collected from skin biopsies of clinical subjects. These are consistent with improved wound healing.**

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Current Medicinal Chemistry, 19, pg 5768-5773, 2012

**Calcium ion is the most pervasive signaling molecule in living organisms. Positive and negative calcium effects on cAMP levels is found in every cell of every organ to control energy, immune response and homeostasis.**

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Molecular Pain, 13, pg 1-10, 2017

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J. Tissue Eng. Regen. Med. 5(8), pg228-238, 2011

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**Transient receptor potential ion channels are sensitive to reactive oxygen species(ROS). Pathological conditions are the result of overactive ion channels. Modulation of TRPA1 may alleviate symptoms of these conditions.**

29 Keeble, J., et al

Involvement of transient receptor potential vanilloid 1 in the vascular and hyperalgesic components of joint inflammation

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Cancer: A Cancer Journal for Clinicians, 51(5), pg 290-315, 2009

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Stem Cells, 35, pg 1416-1430, 2017

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Focal adhesion kinase: A key mediator of transforming growth factor beta signaling in fibroblasts

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Stem Cell Research & Therapy, 2018, DOI:10.1186/s13287-018-0865-6 , 15pages

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Scientific Reports, 2017, DOI:10.1038/srep40161 13 pages

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**TLR4 is important for pathogenesis of inflammatory reactions and for promotion of pain as indicated by IL-1b and TNFa. Treatments that reduced pain also reduced these cytokines.**

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**TGF-beta increases ROS and decreases glutathione in fibrotic diseases. Agents decreasing TGF-beta and increasing glutathione may help reverse fibrosis.**

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JBC, 282, pg. 29470-29481, 2007

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Stem Cells International, 2017, DOI:10.1155/2017/8178643 - 11 pages

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Advances In Wound Care, 7(2), pg 29-45, 2018

**Scars as a result of surgery, burns or injury constitute a major burden on the healthcare system. Recent discoveries have clarified the role of skin stem cells and fibroblasts in regeneration of injuries and in scarring.**

48 Marquez-curtis, L.A., et al

Enhancing the migration ability of mesenchymal stromal cells by targeting the

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Dermatopathology, 1, pg. 98-107, 2014

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CXCR4 signaling in macrophages contributes to periodontal mechanical hypersensitivity in Porphyromonas gingivalis-induced periodontitis in mice

Molecular Pain, 13, pg. 1-8, 2017

**CXCR4 is important in periodontal disease**

52 Nomura, E.C.O., et al

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Journal of Ethnopharmacology, 150, pg. 583-589, 2013

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53 North, T.E., et al

Prostaglandin E2 regulates vertebrate haematopoietic stem cell homeostasis

Nature, 447, DOI:10.1038/nature05883 - 6 pages, 2007

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**Cancer cells are activated by CXCL12 and CXCR4. This requires COX2 and PGE2. New therapies directed at PGE2 are anticipated in ovarian cancer therapy.**

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Cyclooxygenase-2: a role in cancer stem cell survival and repopulation of cancer cells during therapy

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**COX-2 is a target for new drug development in cancer therapy in cancer stem cell delayed activity.**

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Int. J. Burn Trama, 2(1), pg 18-28, 2012

**Approximately 6 million people experience a burn per annum. Scarring is a heavy burden to overcome and it controlled by TGF-beta isoforms 1,2 and 3. Altering the ratios of these will give scarless healing.**

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Science reports, 2017 DOI:10.1038/s41598-017-16317-1 14 pages

**Endogenous annexin A1 plays an important role in preserving heart function after a stroke. Loss of annexin A1 gives exaggerated inflammation. Genetically altered mice without annexin A1 gave increased infarction size.**

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Diabetes, 65: pg 129-139, 2016

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Innate immunity derived factors as external modulators of the CXCL12-CXCR4 axis and their role in stem cell homing and mobilization

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Stem Cell Reports, 10, pg. 1625-1641, 2018

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Densitization of Transient Receptor Potential Ankyrin 1 (TRPA1) by the TRP vanilloid 1-sellective cannabinoid Arachidonoyl-2 Chloroethanolamine

Mol. Pharmacol. 2011, vol. 80(1), pg 117-123

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Biochimica et Biohysica Acta, 1830, pg. 2280-2296, 2013

**These studies gave a better understanding of how TGF-beta regulates stem cells**

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Transforming growth factor-b superfamily, implications in development and differentiation of stem cells

BioMol Concepts, 3, pg. 429-445, 2012

**This review summarizes the mechanisms by which the TGF-beta family members control MSC differentiation.**

Serhan, C. N., et al

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Cold Spring Harbor Perspectives in Biology, DOI:10.1101/cshperspect.a016311

21 pages

**Mounting of acute inflammation is crucial for host defense and pivotal to development of chronic inflammation, fibrosis and abscess. Leukocyte trafficking governs the resolution of self-limited inflammation**.

66 Sharma, V., et al

Spilanthes acmella ethanolic flower extract: LC-MS alkylamide profiling and it effects on sexual behavior in male rats

Phytomedicine, 18, pg. 1161-1169, 2011

**Spilanthes extracts act on the sexual control systems in male rats to act as aphrodisiac in this experiment.**

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The physiology of wound healing

Surgery, 35(9), pg. 473-477, 2017

**Wounding healing is a complex and time differentiated process. Inflammation, proliferation and tissue remodeling are important steps for healing in a homeostatic manner.**

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Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics

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**Human lymphoblastic cells increase glutathione content under the agency of pantothenate, dexpanthenol. This was due to increase production of ATP and mitochondrial CoA.**

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Effect of **spilanthes** acmella hydrothanolic extract activity on the tumour cell actin cytoskeleton

Cell Biology Int. 38, pg. 131-135, 2014

**Spilanthes extract demonstrated toxicity to cancer cells at 500 ug/mL.**

70 Sonis, ST., et al

Prevention of chemotherapy-induced ulcerative mucositis by transforming growth factor beta3

Cancer Research, 54, pg. 1135-1138, 1994

**Mucositis as result of chemotherapy or radiation therapy limits the treatment levels due to painful side effects in the oral cavity. Topical administration of TGF-beta3 gave reduced lesions in the oral cavity, increased feeding and improved weight gain in Syrian Golden Hamsters.**

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Skin penetration enhancing properties of the plant N-alkylamide spilanthol

Journal of Ethnopharmacology, 148, pg. 117-125, 2013

**The dermal penetration of caffeine and testosterone were improved 4 fold under the influence of spilanthol.**

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Role of the CXCR4/SDF-1 chemokine axis in circulating neutrophil homeostasis

Blood, 104(2), pg. 565-571, 2004

**The SDF-1/CXCR4 axis is crucial in maintaining a neutrophil level in the normal homeostatic range.**

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Mucosal and blood-brain barrier transport kinetics of the plant alkylamide spilanthol using in vitro and in vivo models

BMC complementary and alternative med, DOI:10.1186/s12906-016-1159-0

12 pages

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N-alkylamides: from plant to brain

Functional foods in health and disease, 4(6), pg. 264-275, 2014

**Plant N-alkylamides are bio-active with broad functional spectrum. Kinetics of dermal, circulatory and brain penetration suggest they may be active in the brain.**

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Exosomes secreted by human adipose mesenchymal stem cells promot scarless cutaneous repair by regulating extracellular matrix remodeling

Scientific Reports, DOI:10.1038/s41598-017-12919-x 2017

**Scar formation is an intractable medical problem. Recent research shows stem cells secrete an agent that benefits wound healing. Exosome treatment down-regulated TGF-b1 and improved the TGF-b1/TGFb3 ratio leading to a high ratio of MMP3 to tissue inhibitors of MMP(TIMP1).**

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Stem cell autocrine CXCL12/CXCR4 stimulates invasion and metastasis of esophageal cancer

Oncotarget, 8(22), pg. 36149-36160, 2017

**Extracellular matrix is controlled by CXCL12/CXCR4 system to give a gain or loss of function through the ERK 1 and 2. Blocking of ERK may slow cancer development.**

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Roles of TGF-b family signaling in stem cell renewal and differentiation

Cell Research, 19, pg. 103-115, 2009

**TGF-beta control development and maintenance of various organs. Stem cell differentiation into myofibroblasts point to possible scarring**

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A new mesenchymal stem cell(MSC) paradigm: Polarization into a pro-inflammatory MSC1 or and immunosuppressive MSC2 phenotype

PLOS One, 5(4), e10088, 2010 - 14 pages

**Mesenchymal stromal cells can point to inflammation by action of TLR agents. TLR4 gives an inflammatory MSC, while TLR3 gave immunosuppressive action.**

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Epithelial-mesenchymal transition, TGF-b and Osteopontin in wound healing and tissue remodeling after injury

J. Burn Care Res. 33(3), pg. 311-318, 2012

**Epithelial to mesenchymal transition is essential to development and to wound healing. The time-line of healing is mediated by the differentiating aspect of local cells. Osteopontin and TGF-beta are controlling the differentiation called EMT.**

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Involvement of CXCR4/CXCR7/CXCL12 interactions in inflammatory bowel disease

Theranostics, 3(1), pg. 40-46, 2013

**The CXCR4 and its ligand CXCL12 act in the progress of inflammation and the migration of immune cells to the endpoint of homeostasis. Inflammatory bowel disease is controlled by the cytokines along with CXCR7.**

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Calcium pantothenate modulates gene expression in proliferating human dermal fibroblasts

Experimental Dermatology, 18, pg.969-978, 2009

**Pantothenate and dexpanthenol enhance migration and proliferation o fibroblasts to the wound site. Genes involved are IL-6,. IL-8, HO-1, CYP1B1 and HspB7.**

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Focal adhesion kinase links mechanical force to skin fibrosis via inflammatory signaling

Nature Medicine, 18(1), 148-154, 2012

**Healing of wounds are found in these experiments to involve mechanical action which is expressed int the upregulation of FAK/ERK/MCP1**

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Increased expression of TGF-b signaling components in a mouse model of fibrosis induced by submandibular gland duct ligation

PLOS One, 2015, DOI:10.1371/journal.pone.0123641 - 24 pages

**Signals of fibrosis such as E-cadherin, collagen 1 and fibronectin were upregulated in scarring. Blockage of TGF receptors by inhibitors gave reduced scarring and fibrosis.**

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Anti-inflammatory effect of spilanthol from Spilanthes acmella on murine macrophage by down-regulating LPS-induced inflammatory mediators

J. Agric. Food Chem. 56, pg 2341-2349, 2008

**The purification and biological activity were explored on murine RAW 264.7 macrophage cells. Inflammatory markers such as iNOS, COX2 and NFkB were down-regulated by purified spilanthol in these murine cells.**

85 Wu, Q., et al

Extracellular calcium increases CXCR4 expression on bone marrow-derived cells and enhances pro-angiogenesis therapy

Molecular Medicine, 13(9B), pg. 3764-3773

**Calcium control of expression of cell surface receptor CXCR4 was demonstrated while CXCL12 was controlled by bone marrow cells (BMC). Thus, calcium is a positive regulator of stem cell mobilization, homing and therapy.**

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Metformin is a novel suppressor for transforming growth factor (TGF)-b1

Science Reports, 2016, DOI:10.1038/srep28597 - 9 pages

**TGF-beta is a source of pathogenesis of numerous diseases and is a target of metformin. The results are that TGF-beta dimerization is blocked by metformin and this should have therapeutic potential in a number of diseases where TGF-beta1 hyperfunction is indicated.**

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A novel strategy to enhance mesenchymal stem cell migration capacity and promote tissue repair in an injury specific fashion

Cell Transplantation, 22, pg. 423-436, 2013

**IGF-1 improves migration and homing capacity of MSC and is possibly rational approach to organ repair.**

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Oxidative stress induces stem cell proliferation via TRPA1/RYR-mediated Ca2+ signaling in the drosophila midgut

eLIFE, 2017, DOI:10.7554/elife.22441 - 24 pages

**Oxidative stress such as ROS triggers stem cell proliferation to restore homeostasis.**

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Stromal Cell-derived Factor-1 receptor CXCR4-overexpressing bone marrow mesenchymal stem cells accelerate wound healing by migration into skin injury areas

Cellular Reprogramming, vol 15(3), pg. 206-215, 2015

**Stromal cell-derived factor -1 and its membrane receptor CXCR4 are involved int homing and migration of stem cells to speed wound healing.**

90 Yang, J.X., et al

CXCR4 receptor overexpression in mesenchymal stem cells facilitates treatment of acute lung injury in rats

JBC, 290(4), pg. 1994-2006, 2015

**The CXCR4 receptor is experimentally overexpressed in MSC to reduce fibrotic lung injury.**

91 Zeng Y., et al

Role of the stromal cell derived factor-1CXC chemokine receptor 4 axis in the invasion and metastasis of lung cnacer and mechanism

Journal of Thoracic Disease, 9(12), pg. 4947-4959, 2017

**Enhanced CXCR4 in cancer cells correlates with more vigorous metastatic action. Blockage of CXCR4 may give a cancer control point.**

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Cytokines regulating hematopoietic stem cell function

Curr. Opin. Hematol, 15(4), pg. 307-311, 2008

**Review of stem cell experiments in genetic manipulation gives incite into the control points for stem cells.**

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CXCR4/CXCL12 axis counteracts hematopoietic stem cell exhaustion through selective protection against oxidative stress

Scientific Reports, 2016, DOI:10.1038/spre37827 - 13 pages

**Expression of CXCR4 and CXCL12 acting by ROS blocks stem cell exhaustion. CXCL12 rescues stem cells form oxidative stress.**

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Prostaglandin E2 inhibits collagen synthesis in derma fibroblasts and prevents hypertrophic scar formation in vivo

Experimental Dermatology, 25, pg. 604-610, 2016

**The anti-scar effect of PGE2 is acting by upregulating cAMP thought the EP2 receptor. Scar reduction is achieved through balancing the MMP/TMP expression and thus decreasing collagen.**

95 Huang, C-H, et al

Spilanthol inhibits TNF-a-induced ICAM-1 expressions and pro-inflammtory responses by inducing heme oxygenase-1 expression and suppressing pJNK in HaCaT keratinocytes.

Molecular Medicine Reports, vol. 18,pg2987-294

**AntiInflammatory action of Spilanthol on TNFa is consistent with the homeostatic observations in herbal/Vit. Formulations in WhiteHill testing.**

96 Cho, Y-C, et al

Spilanthes acmella inhibits inflammatory responses via inhibition of NFkB and MAPK signaling pathways in RAW 264.7 macrophages

Molecular Medicine Reports, vol. 16, pg 339-346, 2017

**This paper shows NFkB reduction under the influence of Spilanthes Extract, presumably by the action of spilanthol. These anti-inflammatory actions are consistent with the results of returning to homeostatic levels on application of gels, skin creams, lozenges to inflammatory conditions.**

97 Huang, W-D., et al

Spilanthol inhibits COX-2 and ICAM-1 expression via suppression of NFkB and MAPK signaling in interleukin-1b-stimlated human lung epithelial cells

Inflammation, vol 41, pg 1934-1944, 2018

**Spilanthol suppresses expression of major inflammatory genes for COX-2, NFkB and thus PGE2, along with MCP-1 are reduced. This pathway is consistent with healing observed in WhiteHill formulatons.**

98 De Spiegeleer, B., et al

Skin penetration enhancing properties of the plant N-alkylamide spilanthol

Journal of Ethnopharmacology, vol. 148, pg 117-125, 2013

**Levels of spilanthol as low as 0.5 to 1% spilanthol give up to 400% increase in skin penetration of a wide range of lipophilic characteristics. This activity may be helping the herbal actives and pro-vitamin B5 to penetrate the skin more efficiently, which we see in rapid pain relief.**

99 Olah, Z. et al

Pellitorine, an extract of Tetradium daniellii, ,is an antagonist of the ion channel TRPV1

Phytomedicine, vol 34, page 44-49, 2017

**Pellitorine blocks pain through limiting Ca++ ions entry into the cellular cytoplasm. WhiteHill formulations with pellitorine has shown rapid pain relief in osteoarthritis, burns and migraine headaches.**

100 Lee, W., et al

Vascular barrier protective effects of pellitorine in LPS-induced inflammation in vitro and in vivo

Fitoterapia, vol. 92, pg 177-187, 2014

**Vascular integrity is crucial for vascular and tissue homeostasis. Pellitorine blocks permeability of cytokines to limit anaphylactic shock. WhiteHill has several examples of the skin cream acting like an epi-pen for allergic insect time reaction blockage.**

101 Lieder, B., et al

The alkamide trans-pellitorine targets PPARgamma via TRPV1 and TRPA1 to reduce lipid accumulation in developing 3T3-L1 adipocytes.

Frontiers in Pharmacology, vol 8, article 316, 2017

**Pellitorine treated fat cells show reduced fat accumulation caused by blockage of fatty acid synthase and expression of PPAR-gamma gene and protein. This has applications in diabetes and up-expression of TRPA1 and TRPV1.**

102 Veryser, L. et al

Quantitative transdermal behavior of pellitorine from Anacyclus pyrethrum extract.

Phytomedicine, vol 21, pga 1801-1807, 2014

**Pellitorine shows penetration of the stratum corneum in a Franz diffusion cell fitted with human skin. This predicts local and systemic effects of pellitorine in human use, consistent with WhiteHill case histories.**

103 Kim, S-J., et al

Mechanism of anti-nociceptive effects of Asarum sieboldii Miq. Radix: potential role of bradykinin, histamine and opioid receptor-mediated pathways.

Journal of Ethnopharmacology, vol. 88, pg 5-9, 2003

**Asarum sieboldii extract gives pain relief apparently through the opioid receptor with inhibition of bradykinin and histamine-mediated action. The homeostatic effects could be expressed in pain relief with reduced opioid side-effects.**

104 Ku, S-K, et al

Anti-septic effets of pellitorine in HMGB1-induced inflammatory responses in vitro and in vivo

Inflammation, vol. 37, pg 338- 348, 2013

**Pellitorine suppressed the release of TNFa, IL-6 and NFkB by release of bound HMGB1 which may have application to treatment of various severe vascular inflammatory diseases.**

105 Veryser, L., et al

Quantitative In Vitro and In Vivo evaluation of intestinal and blood-brain barrier transport kinetics of the plant N-alkylamide Pellitorine

BioMed Research International, vol 2016, article ID5497402, 11 pages

**Pellitorine has good gut permeation and rapidly permeates the blood-brain barrier once in the blood holding promise for central nervous system diseases.**

106 Rohm, B., et al

Capsaicin, nonivamide and trans-pellitorine decrease free fatty acid uptake without TRPV1 activation and increase acetyl-coenzyme A synthase activity in Caco-2 cells

Food and Function, volt 6, page 173-187,2015

**trans-Pellitorine increases acetyl-coenzyme A synthetase. Dexpanthenol up-regulates acetyl-CoA and supports pellitorine.**

107 Riera, C.E., et al

Compounds from Sichuan and Melegueta peppers activate, covalently and non-covalently, TRPA1 and TRPV1 channels

British Journal of Pharmacology, vol. 157, pg 1398-1409, 2009

108 Rios, M., Olivo, H.

Natural and synthetic alkamides: Applications in Pain Therapy,

Studies in Natural Products Vol. 43, Chapter 3, pg 79-121 2014

**Alpha-hydroxylsanshool acts on TRPV1 and TRPA1 to cause these channels to open and deliver Ca++ to the cytoplasm. Ca++ is a second messenger that modulates the activities of kinases, the molecular switches of the immune and nervous system to relieve pain and itch. WhiteHill’s homeostatic formulations give the same result on pain and itch.**

109 Nilius, B. and Appendino, G.

Spices: The savory and beneficial science of pungency

Rev. Physiol. Biochem. Pharmacol. Doi: 10.1007/112\_2013\_11 76 pages

**The antioxidant system, operating through the NRF2, HO-1 and glutathione pathways is initiated through the TRPV1 and TRPA1 ion channels to down-regulate the immune response and return the mammalian system to homeostatic conditions**

110 Jain, S.K., et al

Glutathione stimulates vitamin D regulatory and glucose-metabolism genes, lowers oxidative stress and inflammation, and increases 25-hydroxy-vitamin D levels in Blood: A novel approach to treat 25-hydroxy-vitamin D deficiency.

Antioxidants and Redox Signaling, vol. 29(17), pg 1792-1807, 2018

**Glutathione implementation assists the immune function of Vit. D3. Dexpanthenol should be synergistic with Vit. D3 in modulating the immune system and restoring homeostasis**

111 Griffith, J.W., et al

Chemokines and Chemokine receptors: Positioning cells for Host Defense and Immunity

Annual Reviews in Immunology, vol. 32, pg 659-702

**The chemokine system orchestrates immune cell migration and positioning at the organismic level in homeostasis. CXCR4, CXCL12, MCP-1, CCR2 all act to regulate the immune system. Dexpanthenol, spilanthol and pellitorine act on these systems to restore homeostasis.**

112 Oetjen, L.K., et al

Sensory Neurons Co-opt classical immune signaling pathways to mediate chronic itch

Cell, vol. 171, pg 217-228, 2017

**Chronic itch is controlled by JAK signaling. Inhibitors of JAK block itch. TRPV1 and TRPA1 activation blocks JAK and itch also. WhiteHill’s spilanthol and pellitorine act on both of these ion channels to stop itch rapidly.**

113 Zouboulis, C.C.

Human Skin: An independent Peripheral Endocrine Organ

Hormone Research, vol. 4, pg 230-242, 2000

**Skin plays a role in activating Vit. D3 at the epidermal level in normal and diseased skin to restore homeostasis.**

114 Roseborough, I.E., et al

Prevention and treatment of excessive dermal scarring

Journal of the National Medical Associaton, vol 96(1), pg 108-116, 2004

**Blockers of inflammatory agent NFkB reduce scarring. Vit. D3, spilanthol, pellitorine and dexpanthenol all reduce NFkB and could be the reason WhiteHill’s skin cream has almost eliminated scarring after incisions.**

115 Montovani, A., et al

The chemokine system in diverse forms of macrophage activation and polarization

TRENDS in immunology, vol 25(12), pg 677-686, 2004

**Homeostatic systems are modulated in WhiteHill’s system. MCP-1, CCR2, CXCR4, CXCL12, all are working to restore macrophages to M2, anti-inflammatory status, ie, homeostasis.**

116 Ito, S., et al

1a,25-Dihydroxyvitamin D3 enhances cerebal clearance of human amyloid-beta peptide(1-40) from mouse brain across the blood-brain barrier

Fluids and Barriers of the CNS, vol 8(20), pg 1-10, 2011

**Cerebral blockage of amyloid-beta transport across the blood-brain barrier is considered a vascular disfunction associated with Alzheimer’s disease. Vit. D3 appears to enhance to transport of amyloid-beta and possibly alleviate symptoms of the disease.**

117 Li-Mei, W., et al

Anti-Inflammatory and Anti-oxidative effects of Dexpanthenol on Lipopolysaccharide induced acute lung injury in mice.

Inflammation, vol. 39(5), pg 1757-1763, 2016

**Dexpanthenol protects against the damage caused by the bacterial polysaccharide LPS through glutathione enhanced expression and through reduced TNFa, NFkB and IL-6**

118 Karapinar, O.S., et al

The protective role of dexpanthenol on the endometrial implants in an experimentally induced rat endometriosis model

Reproductive Sciences, vol 24(2), pg 285-290, 2016

**Dexpanthenol has free-radical scavenging effects and showed reduced oxidative damage and reduced TNFa.**

119 Ebner, F. et al

Topical use of dexpanthenol in skin disorders

American Journal of Clinical Dermatology, vol. 3(6), pg 427-433

**Good skin penetration of dexpanthenol and high local concentrations allow reduced inflammation, itching, dryness, roughness and fissures when applied over 3-4 weeks.**

120 Martinelli-Klay, C.P., et al

Modulation of MCP-1, TGF-beta1 and a-SMA Expressions in granulation tissue of cutaneous wounds treated with local Vit. B complex: An experimental study.

Dermatopathology, vol. 1, pg 98-107, 2014

**Wound models in mice showed enhanced healing expressed though reductions in MCP-1, TNFa and TGF-beta1. Dexpanthenol is rapidly converted in the skin to Vit. B5**

121 Chan, R.J., et al

Prevention and treatment of acute radiation-induced skin reactions: A systematic review and meta-analysis of randomized controlled trials.

BMC Cancer, vol. 14, 1-19, 2014

**Reviews of many pallative treatments show no important benefits for all agents used. This is in contrast to WhiteHill’s skin cream which gave immediate itch results and total reduction in redness over 3 weeks with twice daily applications.**

122 boehncke, W-H., et al

Animal models of psoriasis

Clinics in Dermatology, vol. 25, pg 596-605, 2007

**T-lymphocytes were activated to model psoriasis. Steroids and Vit. D were effective. Our case histories give examples of healing over several weeks with 5-7 lozenges daily with spilanthol and pellitorine**

123 Ngo, Q.M., et al

# Alkaloids from Piper nigrum exhibit anti-inflammatory activity via activating the NRF2/HO-1 pathway.

Phytotherapy Research, doi: 10.1002/ptr.5780

**Pellitorine shows a 9 fold increase in HO-1 expression and blocked iNOS with IC50 of 14.5 uM.**

124 Gouin, O., et al

TRPV1 and TRPA1 in cutanious neurogenic and chronic inflammation: Pro-inflammatory response induced by their activation and their sensitization

Protein Cell, vol 8(9), pg 644-661, 2017

**Inflammation and pain sensors act through TRPV1 and TRPA1 and use ionic calcium to shift immune function**

125 Gertsch, J.

Anti-Inflammatory cannabinoids in diet

Cummunicative and Integrative Biology, vol 1(1), 26-28, 2008

**CB2 agonists down-regulate p38MAPK, ERK1/2 and JNK1/2 to inhibit inflammation and pain**

126 Wegiel, B., et al

Heme as a danger molecule in pathogen recognition

Free Radical Biology and Medicine, vol. 89, pg 651-661

**Pattern recognition molecules, PAMP, act through the HO-1 which is now recognized as the master gene critical to appropriate host response to inflammation and pain**

127 Munoz, L. et al

Targeting p38 MAPK pathway for the treatment of Alzheimer’s disease

Neuropharmacology, vol. 58, pg 561-568, 2010

**p38 MAPK has emerged with new roles in cognition and memory decline. Alzheimer’s patients may benefit from p38 MAPK inhibitors.**

128 Scott, J.F., et al

Oral Vitamin D rapidly attenuates inflammation from sunburn: an interventional study

Journal of Investigative Dermatology, vol. 137, pg 2078-2086, 2017

**Massive doses of Vit. D one hour after sunburn gave reduced TNFa and iNOS along with reduced redness. WhiteHill’s skin cream applied several hours after beach sunburn at low concentrations reduced redness.**

129 Gildea, L.A. et al

Anti-Inflammatory action of stannous fluoride

IADR poster #1156, March 21-24, 2007

**Stannous fluoride is shown to express significant inhibition of matrixmetalloproteinases, MMP, commonly found in the oral cavity of gingivitis patients.**

130 Vasconcelos, R.M., et al

Host-Microbiome Cross-talk in oral mucositis

Critical Reviews in Oral Biology & Medicine,

J. Dent. Res. 2016 doi: 10..1177/0022034516641890

**Mucositis presents with TNFa, IL-1b, IL-6 and MMP**’s

131 Barnes, L.A., et al

Mechanical forces in cutaneous wound healing: Emerging therapies to minimize scar formation

Advances in Wound Healing, vol.7(2), pg 47-56, 2018

**Focal Adhesion Kinase uses mechanical force to help close wounds. TGF-beta is used at two time points to close wounds with minimal scarring.**

132 Chen, L. and DiPietro, L.A.

Toll-like receptor function in acute wounds

Advances in wound care, vol 6(10), pg 344-355, 2017

**The HMGB1 and TNFa are involved in wound healing at different time points. Both are modulated in WhiteHill’s homeostasis pathway.**

133 Taylor, P.C., et al

Reduction of chemokine levels and leukocyte traffic to joints by tumor necrosis factor a: Blockade in patients with rheumatoid arthritis

Arthritis and Rheumatism,vol 43(1), pg 38-47, 2000

**Blocking TNFa significantly reduced swelling and chemokines TNFa and MCP-1 in RA joints. Spilanthol and Pellitorine reduce these also.**

134 Shemer, A., et al

Efficacy of a mucoadhesive patch compared with an oral solution of treatment of aphthous stomatitis

Drugs R&D 2008, vol 9(1), pg 29-36

**Reduction in TNFa leads to healing of ulcers. WhiteHill’s action on these ulcers most likely reduces TNFa also as it heals them.**

135 Schurks, M., et al

Tumor Necrosis Factor gene polymorphisms and Migraine: A systematic review and meta-analysis

Cephalalgia, vol 31(13), pg 1381-1404, 2012

**Certain gene mutants of the TNFa gene were more highly expressed in the migraine population. The action of WhiteHill’s homeostasis formulas rapidly stop migraines**

136 Saito, K., et al

Epigallocatechin gallate inhibits oxidative stress-induced DNA damage and apoptosis in MRL-Fas mice with autoimmune sialadenitis via upregulation of heme oxygenase-1 and Bcl-2

Automunity, vol. 47(1), pg 13-22, 2014

**The NRF2 herbal agent EGCG fights dry mouth by up-regulating HO-1. This mechanism is HO-1 increase seen in the WhiteHill homeostasis composition.**

137 Straub, J.M., et al

Radiation-Induced fibrosis: mechanisms and implications for therapy.

Journal of Cancer Research and Clinical Oncology, Doi: 10.1007/s00432-015-1974-6 2015

**Radiation damages cells increase oxidative stress and inflammatory cytokines such as TNF-a. The herbal composition of WhiteHill down-regulates TNF-a**

138 Sah, S.K., et al

Effects of human mesenchymal stem cells transduced with superoxide dismutase on imiquimod-induced psoriasis-like skin inflammation in Mice.

Antioxidants & Redox Signaling, vol. 24(5), pg 233-248, 2016

**Psoriasis expresses TNFa , NFkB, p38 MAPK and JNK. The herbal composition of WhiteHill down-regulates these cytokines and chemokines**

139 Tyurin, Y.A., et al

Cytokine profile of patients with allergic rhinitis caused by pollen, mite and microbial allergen sensitization.

Journal of Immunology Research, <http://doi.org/10.1155/2017/3054217>

**Pollen allergy up-regulates TNFa and IL-1 beta. The herbal composition of WhiteHill down-regulates the TNFa and IL-1 beta**

140 Chen, Y., et al

Vitamin D receptor inhibits NFkB activation b interacting with IKKbeta protein

Journal of Biological Chemistry, <http://www.jbc.org/cgi/doi/10.1074/jbc.M113.467670>

**Vitamin D3 rapidly blocks NFkB acting through TNFa. WhiteHill’s homeostatic composition containing Vitamin D3 is expected to down-regulate allergies from environment and food.**