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Aloe vera—Mechanisms of Action, Uses, and Potential Uses in Plastic Surgery and Wound Healing

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Abstract

Aloe vera has been used for centuries for medicinal purposes. Clinical and experimental evidence indicates usefulness for skin moisturization, promoting wound healing, thermal skin injury, frostbite, and ischemic skin insults. *Aloe vera* has anti-inflammatory, vasodilatory, antimicrobial, and proliferative actions, which have been investigated in various experimental models and in various *in vitro* studies. This extensive literature review of the properties and actions of *Aloe vera* finds substantial evidence for the reported and also likely clinical usefulness for *Aloe vera* in Plastic Surgery and in wound care and wound healing. Though further clinical investigation is warranted, *Aloe vera* use may likely be indicated in situations where its effects could positively influence outcomes, such as wound healing, flap vascularity, and inflammatory skin pathologies.

Keywords

Aloe vera, Wound Healing, Anti-Inflammatory, Prostaglandin, Anti-Microbial, Anti-Oxidant, Angiogenesis

1. Introduction

Aloe vera is a succulent tropical plant native to the Arabian Peninsula. Early documented usage of the plant dates back to ancient Greece and Egypt, where it was used to alleviate sunburns and as skin beauty care [1]. *Aloe vera* was utilized regularly to aid in wound healing during times of war and exploration, from

Alexander the Great's conquests to Christopher Columbus's journeys to the New World [2]. While *Aloe vera* has been regularly used in alternative and complementary medicine, it has not yet been widely incorporated into the clinical practice of western medicine.

The skin is the largest organ in the human body and serves as a protective barrier from the outside environment. It functions in homeostasis and thermoregulation and is the first line of defense against foreign pathogens. Skin disease and injury may be the result of many pathophysiologies. In those which result in local tissue ischemia and cell death, the microcirculation in dermal tissue is affected. In injuries due to heat, cold, chemicals, electricity, crush, friction, radiation, or other wound etiologies, ischemic microvascular changes occur in non-reversible damage zones of dermal tissue, resulting in cell death. However, reversible and relatively ischemic areas are potentially salvageable [3] [4] [5]. Thus, an agent that would inhibit ischemia, microbes, and inflammation would be of positive value to support and augment wound healing.

The mucilaginous tissue in the *Aloe vera* leaf contains phytochemicals, and its anti-oxidative, anti-inflammatory, anti-microbial, and proliferative properties have been shown to promote wound healing in both animal and human models [6] [7] [8] [9]. Enhancing these properties can help augment blood supply and tip the scale of relative ischemia to adequate perfusion, thereby salvaging reversible ischemic skin injury.

This review describes and identifies the effects and mechanisms that *Aloe vera* has on skin care and wound healing. We then propose uses and the potential utility of *Aloe vera* in the field of plastic surgery as it pertains to wound healing.

2. Review

The myriad of compounds that make up the composition of *Aloe vera* gel has been shown to have positive therapeutic properties in skin wound healing as well as other acute and chronic disease processes [10]. **Table 1** lists the constituents that have been isolated from *Aloe vera.* We discuss *Aloe vera*'s anti-inflammatory and vasodilatory, anti-microbial, anti-oxidant, and proliferative effects on skin healing. We also propose clinical uses based on the available data of its mechanisms of action.

2.1. Anti-Inflammatory and Vasodilatory Effects

Prostaglandins and thromboxanes are eicosanoid compounds formed from arachidonic acid. They serve as signaling molecules that are present in most tissues and organs, and they are necessary to orchestrate complex inflammatory reactions [11] [12] [13]. Eicosanoids are synthesized using two isoforms of cyclooxygenases. Knockout of cyclooxygenase (COX) genes in mice has been shown to impair inflammatory responses [14]. Clinically, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are used to reduce the inflammatory response by targeting the arachidonic pathway that produces these molecules.

Table 1. Known compounds isolated from *Aloe vera* Leaf [10] [61].

Anthraquinones	**Inorganic compounds**
Aloe-emodin	Calcium
Aloetic acid	Chlorin
Aloin A and B	Chromium
Anthranol	Copper
Barbaloin	Iron
Chrysophanic acid	Magnesium
Emodin	Manganese
Emolin	Potassium sorbate
Ester of cinnamic acid	Sodium
Isobarbaloin	Zinc
Resistannol	
	Enzymes
Saccharides	Alkaline phosphatase
Aldopentose	Amylase
Cellulose	Carboxypeptidase
Glucose	Catalase
L-rhamnose	Cyclooxygenase
Mannose	Glutathione peroxidase
	Lipase
Vitamins	Oxidase
B1 Thiamine	Phosphoenolpyruvate carboxylase
B2 Riboflavin	Superoxide dismutase
B6 Pyridoxine	
B9 Folic acid	**Essential amino acids**
C Ascorbic acid	Isoleucine
Choline	Leucine
E α-tocopherol	Lysine
β-carotene	Methionine
	Phenylalanine
Miscellaneous	Threonine
Arachidonic acid	Valine
β-sitosterol	
Campesterol	**Nonessential amino acids**
Cholesterol	Alanine
Gibberellin	Arginine
Lignins	Aspartic acid

Continued

Salicylic acid	Glutamic acid
Triglycerides	Glycine
Triterpenoid	Histidine
Uric acid	Hydroxyproline
γ-linolenic acid	Proline
	Tyrosine
Carbohydrates	
Acemannan	**Chromones**
Acetylated glucomannan	8-*C*-glucosyl-(2'-*O*-cinnamoyl)-7-*O*-methylaloediol A
Acetylated mannan	8-*C*-glucosyl-(*S*)-aloesol
Arabinogalactan	8-*C*-glucosyl-7-*O*-methyl-aloediol
Cellulose	8-*C*-glucosyl-7-*O*-methyl-(*S*)-aloesol
Galactan	8-*C*-glucosyl-noreugenin
Galactogalacturan	Aloesin
Galactoglucoarabinomannan	Isoaloeresin D
Glucogalactomannan	Isorabaichromone
Peptic substance	Neoaloesin A
Pure mannan	
Xylan	**Proteins**
	Lectins
	Lectin-like substance

There is a balance between the vasodilatory actions of certain prostaglandins and the vasoconstricting actions of thromboxanes. Found at the endothelial border, prostaglandin E_1 (PGE_1) and prostaglandin I_2 (PGI_2) are vasodilators that counteract the vasoconstricting effects of thromboxane B_2 (T_xB_2) and prostaglandin F_{2a} (PGF_{2a}) [15] [16]. Robson *et al.* demonstrated histologic imbalances of the two forces in burned tissues [4]. As perfusion is paramount for the viability of the burn wound zone of stasis, reducing vasoconstricting prostaglandins and increasing vasodilatory endogenous prostaglandin mediators reduce areas of dermal ischemia. Exogenous prostaglandins (specifically PGI_2) delivered intravenously to an experimental axial skin flap model showed significantly greater flap survival compared to controls [17]. Inhibition of thromboxane (specifically T_xB_2) has been shown to support perfusion of the dermal and subdermal plexuses [3] [18]. When used in combination, synergistic effects of inhibiting thromboxane and injecting prostaglandin I_2 resulted in an even higher percentage of skin flap survival by promoting increased perfusion to ischemic flap tissue compared to control [19]. Subsequently, use of selective thromboxane inhibitors such as thromboxane synthetase inhibitors and cyclooxygenase inhibitors have been shown to increase wound perfusion [18].

Cera *et al.* reported *Aloe vera*'s effects of inhibiting T_xB_2 in burn injuries [20]. *Aloe vera* cream (Dermaide Aloe®) and aspirin have been shown to prevent progression of frostbite injuries following rapid rewarming [21]. DelBeccaro *et al.* and Heggers *et al.* both attributed increased tissue survivability in frostbite, electrical, intra-arterial drug, and thermal injuries to the vasodilatory effects of *Aloe vera* and other anti-thromboxane agents such as methimazole and imidazole [18] [22]. Use of *Aloe vera* alone and when combined with another specific anti-thromboxane agent (methimazole) were shown to have the greatest effects of tissue survival, wound healing, and decreased morbidity in dermal injury with associated ischemia [22].

Extracts of the phytochemical constituents present in *Aloe vera*, have demonstrated anti-inflammatory and vasodilatory activity through COX inhibition [23]. Salicylic acid, a known COX inhibitor, is present in large quantity in fresh *Aloe vera* [24]. Anthraquinones are aromatic organic compounds found in numerous plants. Emodin and emolin, anthraquinone derivatives found in Aloe, act as competitive inhibitors of thromboxane synthetase and have significant anti-inflammatory properties [25].

Other *Aloe vera* compounds have been shown to modulate the inflammatory response. Aloesin appears to affect migration of both fibroblasts and leukocytes [26]. In early phases of wound healing, Aloesin promotes leukocyte extravasation and cytokine and growth factor release. Aloesin is thought to act on leukocyte migration via phosphorylation of Cdc42 and Rac1, signaling proteins that coordinate and regulate actin dynamics and cell polarization [27]. The inflammatory markers TNF-α, IL-1β, IL-6, and TGF-β1 mediate leukocyte signaling, migration, and phagocytosis, and are significantly increased in the presence of aloesin. Another Aloe pro-inflammatory compound is acemannan. Acemannan activates macrophages and enhances bactericidal activity [28] [29]. Additionally, Aloe extracts have been shown to decrease inflammatory markers and affect DNA repair capacity [30] [31]. Wahedi *et al.* demonstrated significant decreases in macrophage and neutrophil activity in later phases of inflammation with Aloesin administration [26]. Use of Aloe on experimental burn wounds demonstrated a significant decrease in TNF-α and IL-6 levels and reduction in leukocyte adhesion on postcapillary venules [31]. NAE-8®, an *Aloe vera*-based extract, has been shown to decrease levels of TNF-α and IL-1β [30].

2.2. Anti-Microbial Effects

Because injury site is prone to infection, topical treatment with antimicrobial agents is frequently utilized in burn wound treatment. Silvadene® cream contains 1% micronized silver sulfadiazine. It is an antimicrobial agent commonly used for partial and full thickness burns. However, silver sulfadiazine can negatively affect wound healing time [32]. Heggers *et al.* demonstrated that the wound retardant effect of silver sulfadiazine could be reversed with the addition of Aloe gel [33]. This is likely due to anthraquinone derivatives emodin,

Aloe-emodin, aloin, and chrysophanic acid, which have both antimicrobial and anti-inflammatory activity [20] (**Table 2**).

Anthraquinones have been shown to exhibit antimicrobial properties by altering solute transport through membranes, cell walls, and fatty acid elongation [10] [34]. Reports vary, but some studies demonstrate up to 18 species of microorganisms inhibited by Aloe preparations [6]. *Aloe vera* was able to inhibit

Table 2. *Aloe vera* compounds listed by mechanisms of action [7] [8] [20] [24]-[30] [45] [46] [47] [48] [49].

Immunomodulatory compounds
Acemannan
Aloe-emodin
Aloesin
Anthraquinones
Arabinogalactan
Arachionic acid
Cyclooxygenase
Emodin
Emolin
Glucomannan
Lectin-like substance
Neoaloesin A
Salicylic acid
Anti-microbial compounds
Aloe-emodin
Aloin
Chrysophanic acid
Emodin
Anti-oxidant compounds
C Ascorbic acid
Catalase
Chromones
E α-tocopherol
Glucomannan
Glutathione peroxidase
Superoxide dismutase
Proliferative compounds
Aloesin
F3 Fraction
β-sitosterol

growth at extract concentrations as low as 60% of bacterial strains, such as *Citrobacter sp.*, *Serratia marcescens*, *Enterobacter cloacae*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *S. aureus*, *S. pyogenes*, and *S. agalactiae*. Other species such as *E. coli, Enterococcus,* and *Candida albicans* were more resistant, requiring higher concentrations for significant inhibition; however, all bacterial species responded to treatment [35].

2.3. Anti-Oxidant Effects

Reactive oxygen species (ROS) are naturally formed as a byproduct of cellular oxidative phosphorylation in cytochrome oxidation, phagocytosis, and the inflammatory process. Normally, the body maintains a balance of anti-oxidant enzymes, mainly superoxide dismutase and glutathione synthetase. In the presence of increased oxidants (tissue injury), the balance is shifted, which may cause local or systemic healing and homeostatic dysfunction [36].

Formation of reactive oxygen species in the presence of significant traumatic or metabolic injury is of concern due to the potential for sepsis and organ failure [36] [37]. As a tissue metabolite, the reactive species causes local vascular changes to redirect tissue perfusion. In the presence of pathologic stimulus, redirection of perfusion can be significant enough to cause ischemia to distant organs. Additional insult produces more ROS to be released systemically, which may lead to worsening distant ischemia, sepsis, and tissue inflammation [36] [38].

The role of antioxidants is important as a complement to primary intervention to prevent systemic effects of oxidative species. Enhancing native enzymatic defenses against ROS have been shown to reduce tissue ischemia and oxidative injury [39]. A dose-dependent anti-oxidant effect is observed in *Aloe vera* due to its glutathione peroxidase activity, superoxide dismutase enzymes, and phenolic anti-oxidants [8] [10]. NAE-8® similarly promotes a reduction of lipid peroxidation and supports the maintenance of cellular integrity. Akgun *et al.* demonstrated reduction in elevated malondialdehyde, glutathione, and myeloperoxidase levels in burns with this extract, indicating decreased inflammatory response secondary to Aloe's potent antioxidant effects [30].

2.4. Proliferative Wound Healing Effects

Aloe vera extract influences initial short-term inflammation promoting neutrophil infiltration and cytokine release. Activated leukocytes, macrophages, and fibroblasts release cytokines and growth factors to initiate angiogenesis and wound healing. While tissue inflammation is eventually reduced in the presence of Aloe extracts, the presence of growth factors is sustained. Transforming growth factor-Beta 1 (TGF-β1) is a major growth factor in wound healing [40]. Some functions include: increasing migration and mitosis of fibroblasts and keratinocytes, angiogenesis, formation of extracellular matrix, and differentiation of cells [41] [42]. Wahedi *et al.* described aloesin's positive effects on upregulat-

ing SMAD and MAPK signaling pathways, which are critical for collagen development and angiogenesis [43]. By upregulating these signaling pathways, *Aloe vera* can stimulate increased rates of re-epithelialization and angiogenesis by increasing TGF-β activity [44].

Other growth factors affected by Aloe extracts include vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Moon *et al.* attributed increased expression of VEGF with β-sitosterol, a compound found in *Aloe vera* [45]. β-sitosterol is known to enhance expression of other angiogenic proteins, such as van Willebrand Factor (vWF), VEGF receptor (Flk-1), and matrix laminin [46]. With dichloromethane extraction of *Aloe vera* gel, Lee *et al.* isolated an active fraction (F3) which appears to increase proliferation of endothelial cells and increases extracellular matrix proteolytic enzymes for vascular remodeling [47] [48]. Aloe has also been shown to increase bFGF and TGF-β levels at wound sites [49].

The Rho family GTPases are important in regulating actin cytoskeleton and cellular migration. Specifically, Rho, Rac, and Cdc42 have been shown to have essential roles in normal wound closure and healing [50]. Wounds treated with aloesin demonstrated significant increases in keratinocyte migration rate and upregulated expression of activated Rac1 and Cdc42 in a dose-dependent manner of aloesin. This resulted in increased rates of wound closure and dermal regeneration compared to untreated mice models [26]. NAE-8® treatment showed similar effects on migration of fibroblasts, which act synergistically with keratinocytes; their proliferation increased matrix protein, fibronectin, proteoglycan, hyaluronan, and collagen production [30].

Wahedi *et al.* demonstrated a qualitative and quantitative improvement in collagen production in wounds treated with aloesin. The treated group exhibited increased amounts of collagen deposition after days 5 and 10, and improvement in the organization of collagen complexes, compared to control groups [26]. Heggers *et al.* found that lectins from *Aloe vera* increased collagen activity, which increased wound contraction and breaking strength [22]. Collagen synthesis by fibroblasts also depends on the presence of oxygen, which is further augmented by *Aloe vera* due to its vasodilatory effects [7] [51].

Aloe vera decreases wound healing time in skin wound and injuries due likely to the interplay of the above processes. An efficacy study on wound healing times indicated a summary weighted mean difference in healing time that was 8.79 days shorter in the *Aloe vera* group [52]. Results were most improved in first and second degree burns, where perfusion is salvageable. Additional experimental models have demonstrated modulation of inflammation, increased wound contraction and epithelialization, decreased and better organized scar, that ultimately results in a greater maximum wound strength and elasticity, when wounds were treated with *Aloe vera* [53]. *Aloe vera* and its extract isolates are associated with decreased pain, shorter healing time, improved wound contracture, and increased breaking tensile strength [22] [52] [53]. Proliferative

compounds found in *Aloe vera* are listed in **Table 2**.

3. Discussion

Aloe vera Uses and Potential Uses

Due to the relatively limited side effect profile from the use of *Aloe vera* compared to systemic drugs such as steroids or COX inhibitors, *Aloe vera* topical cream is a favorable complement for skin injuries. Steroids and COX inhibitors reduce the initial phase of inflammation and proliferation. Aloe extracts have been able to modulate inflammatory response to best promote healing [28] [29] [30]. Use of some topical antimicrobials can negatively impact wound healing time due to inhibitory effects on keratinocytes and fibroblasts. When used in conjunction with these treatments, *Aloe vera* extracts can negate some of their adverse effects [33] [54].

Some studies have shown a lack of significant results with *Aloe vera* application versus control groups assessing wound healing [55] [56]. Cuttle *et al.* demonstrated little evidence in decreasing microflora concentrations or improving scar maturation of burn wounds [57]. Topman *et al.* determined no significance in fibroblast migration kinematics, while Coelho *et al.* observed no difference in wound repair between the sample groups [55] [56]. This is likely due to a common issue with many natural product medications: a lack of standardization of extract concentrations. It is possible that some of these studies used Aloe extracts with insufficient concentrations of active compounds that have the known anti-inflammatory and proliferative effects. The study performed by Cuttle *et al.* also had the *Aloe vera* mixed further with other alternative therapies such as saliva and tea tree oil impregnated dressing [57].

Because the concentration of active ingredients in plants may vary depending on age, growing environment, and extraction methods, it is beneficial to extract the ingredients as a concentrate before application [52] [58]. This is seen with the use of Dermaide Aloe®, a commercially purified extract, which when compared to other crude extracts, was shown to have higher antimicrobial effects with lower doses of the product [59]. Active ingredients in Aloe extracts also deteriorate with time [52] [60]. Auto-degradation of the mucilage polysaccharides can be retarded with the addition of microalgae polysaccharides [60].

What also differentiates *Aloe vera* products and its derivatives from other topical medications is low side effect profile and a lack of serious adverse reactions. Adverse effects noted by patients include transient burning sensation after application, skin hyperpigmentation, contact dermatitis, mild itching, and transient leukocytosis [6] [52] [61]. Some of the skin irritation such as the itching and burning may be associated with wound inflammation itself. The transient leukocytosis is likely due to the immunostimulating compounds, such as acemannan. Reynolds *et al.* noted some cytotoxic effects found in several other studies, but these were more associated with chemical solvents used during commercial processing [6].

The use of *Aloe vera* is not limited to high temperature thermal injuries. Much of the tissue damage caused by frostbite is due to partial thawing and re-freezing—or recurring frostbite—which is the result of progressive thrombosis of microvasculature [62]. The frostbite pathophysiology of progressive tissue ischemia is not unlike the mechanisms of other burn wounds. Evaluation of frostbite blister fluid revealed similar enzymes and inflammatory mediators [12] [62]. Similar to thermal burn wounds, there is a balance between vasodilatory prostaglandins and vasoconstricting thromboxane present with frostbite injuries. When comparing *Aloe vera* cream used in controlled rabbit frostbite wound models, tissue survival was up to four times greater when utilized as a cream [63]. *Aloe vera* is not effective in all types of thermal injuries. Liquid propane freeze injuries damage tissue differently than thermal burn wounds. Skin was unsalvageable and use of Dermaide Aloe® did not significantly improve outcomes [64].

A randomized controlled trial on split-thickness skin graft (STSG) donor site wound healing time was performed by comparing *Aloe vera* gel with a medical lubricant [65]. Similar in pathology to partial thickness burn injury, STSG donor site wounds require regular moist dressing changes as skin re-epithelialization occurs. The authors found statistical significance in the times to complete epithelialization, which demonstrated *Aloe vera*'s efficacy in wound healing [65]. There is some evidence for potential *Aloe vera* use in the treatment of radiation-induced dermatitis [66]. However, this evidence seems inconclusive, as several other studies indicate damage from radiation therapy did not improve significantly with *Aloe vera gel* compared to control group [67] [68]. Given oral lyophilized Aloe powder dissolved in purified water, rat models with radiation exposure had significantly accelerated wound contraction [69]. *Aloe*-treated rats were shown to have increased TGF-β1 and bFGF activity with significantly less inflammatory cells, more fibroblasts and blood vessels 15 days post-wounding when compared to radiation exposure only rats [69].

Aloe vera's vasodilatory and angiogenic properties along with its other proliferative anti-inflammatory effects may have a role in microcirculatory disease and injury. *Aloe vera* has already been shown to decrease leukocyte adhesion and maintain increased arteriolar diameter and permeability in microcirculation of burn models [70]. Maintaining proper perfusion to skin flaps is a common challenge in plastic surgery, and microvascular thrombosis and endothelial cell injury have been implicated in ischemia [71]. Thrombogenic factors are increased at the anastomosis sites in the animal models with skin flaps. It has been shown that antithrombotic treatment modalities have an effect on thrombus formation and preventing ischemia-related injury [71] [72]; these modalities were further demonstrated to increase skin flap survival and decrease necrosis [73]. The antithrombotic effects of *Aloe vera* can be a similarly effective means of maintaining perfusion in thermal injuries [3] [18] [21]. Further studies may show a possible use of *Aloe vera* topical agents in maintaining skin flap perfu-

sion and viability.

The microvasculature is a location affected by certain systemic and autoimmune diseases. In particular, cutaneous involvement of systemic diseases such as scleroderma (systemic sclerosis, SSc) and systemic lupus erythematosus (SLE) will often begin with microvascular manifestations. Conditions such as Raynaud's phenomenon, livedo reticularis, and acrocyanosis are common in these diseases due to vasospasm and inhibition of vessel dilation upon cold exposure [74] [75] [76]. The vasospasm and lack of perfusion for long periods may eventually lead to digital ulcers, gangrene, and cutaneous infarction [5].

The pathophysiology of these disease processes is similar. As autoimmune disease processes, SSc and SLE produce autoantibodies against endothelial cells, causing vasculopathy, digital infarcts, thrombosis, and vasoconstriction [5] [77] [78] [79]. Endothelial damage and autoantibodies also lead to leukocyte recruitment and extravasation through the upregulation of adhesion molecules (E-selectin, ICAM-1, VCAM-1) and cytokines [79]. With elevated oxidized-LDL, scleroderma can induce a pro-inflammatory response and generation of free radicals, along with a pro-coagulative state from increased thrombogenic factors, to form atherosclerotic plaques [80] [81]. Vasospasm may occur in SSc, as damaged cells have decreased expression of nitric oxide (NO) and increased endothelin-1 (ET), leading to a vasoconstrictive, ischemic state.

Aloe vera may have efficacy in managing skin manifestations of these disease processes. Topical application of nitroglycerin paste has been shown to reduce digital ulcers and ischemia through localized venodilation and smooth muscle relaxation [82]. When comparing nitroglycerin with *Aloe vera* in wound healing, topical Aloe compound (Dermaide Aloe®) appeared to promote wound healing faster than nitroglycerin while also having less systemic adverse effects [83] [84]. The progression of these diseases is related to the vasculopathy that occurs through endothelial damage, coagulation, vasospasm, inflammation, and dysregulated angiogenesis. It is possible that *Aloe vera* may be effective for treatment of cutaneous manifestations of systemic sclerosis and systemic lupus erythematosus, acting upon multiple patho-mechanisms with the expectation of positive results.

4. Conclusion

Aloe vera's complex chemistry has been shown to act directly on wound and pathological sites or synergistically with other medications. Its properties as an anti-inflammatory, anti-microbial, anti-oxidative, antithrombotic, vasodilatory, and tissue proliferative agent have been shown to significantly decrease skin wound healing time and improve wound contracture and strength. Aloe is most efficacious with superficial and partial thickness burn wounds. There is some evidence that different preparations of Aloe can have many other therapeutic uses in management of plastic surgery and wound healing. Potential applications include use for frostbite, skin flap and graft surgery, cutaneous manifestations of

systemic autoimmune diseases, and skin ischemia.

Disclaimer

The contents of this work do not represent the views of the Department of Veterans Affairs or the United States Government.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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