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Aktisor® Wound Suspension in the Treatment of Ulcers with Multiple Etiologies

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ABSTRACT

Background: Aktisor® is a glycerol-based suspension which contains honey derived from Acacia, xanthan gum, and tannin-rich plant extracts from *Alchemilla vulgaris* (lady's mantle) and *Mimosa tenuiflora* (jurema). High levels of certain matrix metalloproteinases (MMPs) play a role in chronic wounds by constantly degrading the extracellular matrix (ECM) and thus preventing cell attachment and cell growth. Besides, tissue inhibitors of metalloproteinases (TIMPs) fail in the neutralization of MMPs. In addition to human MMPs, bacterial proteases have been found to influence tissue breakdown in infected wounds. Thus protease modulators are of a major importance and chronic wound treatment based on them is under active research. Objectives: The goal of the study was to evaluate the efficacy of dressings based on Aktisor® suspension in the treatment of chronic ulcers. Methods: Six patients with chronic ulcer [mean duration 1 year 5 months, (2 - 48 months)] who had received other than Aktisor® based treatment with no improvement over four weeks were included in this experiment. Results: Six patients experienced complete healing of their chronic ulcers. Conclusions: Aktisor® improved chronic wound healing and all the studied wounds healed after Aktisor® suspension was applied. Combination of tannin-rich plant extracts and honey might bring synergy thus adding bactericidal properties. This pilot study encourages for further studies.

1. INTRODUCTION

A chronic wound is one that has not progressed through all the wound healing stages—hemostasis, inflammation, proliferation, and tissue remodeling or resolution—necessary for the healing to become complete and ends up in a pathological stage of inflammation [1]. The most common etiologies are ische-

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mia, diabetes mellitus, venous stasis disease, or pressure. In addition, it has been shown that age (>60 years) is an independent risk factor leading to chronic wounds and the prevalence of chronic wounds will increase because people live longer, have several concurrent chronic diseases and are treated with polypharmacy [2]. Pain might be so severe that the use of compression therapy is contraindicated and, unfortunately, such patients become conditioned to pain, which then causes stress. Psychological stress impairs wound healing by up-regulating glucocorticoids and by reducing the levels of the pro-inflammatory cytokines at the wound site [3].

Most of the evidence-based treatments for chronic ulcers have focused on a certain type of intervention such as compression therapy for oedema or systemic treatment of venous ulcers with pentoxifylline [4]. Unfortunately, most patients with a chronic wound have multiple etiologies for their wound [5]. Moreover, wound bed screening has not yet been developed to the same extent as the analysis of certain other symptoms by means of laboratory tests and radiological examinations. At the moment, there is only one "wound bioanalyzer" of matrix metalloproteinases on the market, *i.e.* WoundChek™ ProteaseStatus (Systagenix, Gatwick, United Kingdom) [6].

Aktisor® is a glycerol-based suspension which contains honey derived from *Acacia*, xanthan gum, and tannin-rich plant extracts from *Alchemilla vulgaris* (lady's mantle) and *Mimosa tenuiflora* (jurema). Aktisor® represents a completely new class of therapeutic agents for the treatment of chronic wounds of diverse origins. The cumulative properties of Aktisor®, which consist of maintaining the wound surface hydrated, removing contaminants from the wound surface, and neutralizing the ECM-destroying matrix metalloproteinases (MMPs), are considered conducive to producing an accelerated healing process.

Glycerol is also known as an anti-microbial substance, often used in medicine for preserving tissues and cells, and is therefore an excellent choice as a cleansing and moisturizing ingredient, being totally safe for topical application on wounds and having also demonstrated wound healing properties [1997 patent N˚PCT/FR99/01340; 2013 patent N˚PCT/EP2013/061835] [7]. The tannin-rich plant extract component stops and prevents the destructive action of MMPs in the wound bed, thus preserving the cell matrix integrity crucial to cellular attachment and cellular growth [8] [9]. Additionally, medical honey products have proved to be effective because they cleanse the wound and accelerate wound healing, even in immune-compromised patients with colonization of multi-resistant bacteria [10] [11]. Interestingly, the minimum inhibitory concentration of honey against bacteria is generally less than 10% [12].

We wanted to test the product (Aktisor®) on patients whose wounds did not react to repeated conventional treatments based on the TIME (tissue, infection, moisture, edge) concept or whose wound location (heel) and general condition were not optimal for other treatment options [13].

2. PATIENTS

Six patients for the study were selected among those whose wounds showed no signs of improvement or healing after several attempts with conservative and surgical methods (**Table 1**). There were four male and two female patients and their mean age was 68 (54 - 83 years). Underlying pathologies included diabetes mellitus (n = 3), hypertonia (n = 3), and a range of other factors that influence wound healing (**Table 1**). The patients visited wound care specialist nurses regularly after their initial appointment with a multi-disciplinary team (plastic surgeon, vascular surgeon, dermatologist, nutritionist and infectious disease specialist). The patients were also asked whether they were allergic to honey before initiating the treatment. The standard criteria for the diagnosis of chronic wound were used (a wound had not healed after four weeks of standard care).

The wounds had been present in the patients for six months (range 2 - 48 months). During that period, the patients had been treated with a range of products and techniques both in primary and specialized health care centers (**Table 2**). Ointments and skin oil (Ceridal® GlaxoSmithKline, Ltd., Brentford, and Middlesex, United Kingdom) had been applied to the peri-wound area when necessary. Case number 4 had been treated with betamethasone and salicylic acid because of hyper-keratinized skin in her ankle to prevent further ulcerations in the lower legs. No topical or systemic antibiotics were used during the Aktisor® treatment.

Table 1. Patient demographics and characteristics while Aktisor® wound suspension was used for chronic wounds.

Patient	Sex	Age	Diseases	Wound duration	Aktisor® treatment in weeks	Wound localization	Wound size (in cms)
1	m	58	Juvenile diabetes (nephropathy, neuropathy, predialysis stage) Sleep apnea Hypertonia	5 months	0 4 6 12	a) Right heel b) Left heel	a) 4.5 × 4.0 b) 3.0 × 2.0 a) 3.0 × 2.5 b) 2.5 × 1.2 a) 2.0 × 1.0 b) 0.1 × 0.1 a) 0.3 × 0.1 b) -
2	m	71	ASO Type II diabetes, smoking history of 50 years,	6 - 7 months	0 2 4	Right leg, lateral and middle	a) 16.5 × 9.5 b) -
3	f	56	Sero negative rheumatoid arthritis, psoriasis	2 months	0 1	Right extremity a) Foot b) Lower, medial part of leg	a) 3.0 × 1.0 b)1.5 × 2.3 a)2.2 × 1.0 b)1.5 × 1.2
4	f	81	Obesity (BMI > 50), type II diabetes, recurrent erysipelas, (TRPA) carrier	4 years	0 6	Right leg Left leg	11 × 9 + 1.5 × 2 7 × 3.5 + 2 × 1.5 + 2 × 10
5	m	76	Chronic myeloid leukemia, ASO Venous insufficiency, MRSA carrier	2 years	0 1 2 5 7 8 14	Right leg Right ankle	a) 18.0 × 5.0 b) ? a) 15.5 × 4.5 b) 2.5 × 1.8 a) 15.2 × 3.8 b) 2.5 × 1.8 a) 15 × 3.0 − 4.8 b) ? a) 14.8 × 3.5 − 4.5 a) 14.5 × 3.3 − 4.0 a) 4.5 × 3.5

Continued

6	m	65	Dilated cardiomyopathy, Hypertonia Status post multiple injuries	2 months	0 2 5 8	Left heel	4.7 × 3.8 3.2 × 1.8 cm

Abbreviations: ASO = arteriosclerosis obliterans; TRPA = tobramycin resistant pseudomonas aeruginosa; MRSA = methicillin resistant staphylococcus aureus; ? = no records, - = no wound.

Table 2. Treatments used in chronic wounds before Aktisor® wound suspension was applied.

Case	NPWT	Debridement & Skin transplantation	Treatment Compression treatment	Silver	Maggot therapy	Potassium permanganate	Hydrogel	Allevyn®	Polymem®	Medihoney®
1	X	X		X			X	X		
2			X	X						
3	X			X			X			
4	X	X	X	X	X	X	X	X		X
5		X	X	X		X	X		X	
6	X			X			X	X		

Negative pressure wound therapy = NPWT.

3. MATERIAL AND METHODS

Aktisor® used in the study contained 1.5% dried extract of procyanidins from *Mimosa tenuiflora* (13.5% polyphenols) and 1.5% dried extract of procyanidins from *Alchemilla vulgaris* (12% polyphenols) in anexcipient containing 64% glycerol (vegetable origin, Pharma Grade, CAS no. 56-81-5, Undesa, Italy) and 33% honey (Acacia-derived, Miels Villeneuve, France) [14]. The product is developed by VITROBIO Pharma/Naturveda, Issoire, France.

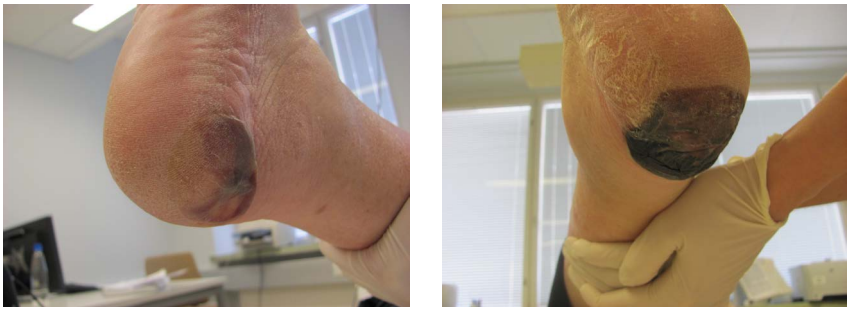
Aktisor® has been tested under in vitro conditions by Professor Heikki Arvilommi, MD (Referator Oy, Turku, Finland). The tests showed that in the presence of Aktisor®, gram-negative rods that are often cultured from chronic ulcers were killed within 24 hours (Supplemental data).

Wound preparation prior to application was carried out by mechanically removing visible necrosis or fibrin coat from the wound bed if necessary and by rinsing the wound with Prontosan® Wound Irrigation Solution, B Braun, Germany. The wounds of case 2 and case 4 were also pretreated with Xylocain 2% gel because of the pain. Aktisor® was applied 2 - 3 times a day to the wound at beginning of the treatment and later, after 2 - 3 days, once a day according to the manufacturer's instructions, and a low-adherent absorbent dressing [Melolin (Smith & Nephew Oy, England)] was used to cover the wound. The patients were regularly followed up by a wound care specialist, and in between their dressings were changed by public health nurses.

The study was approved by the Ethical Committee, Lappeenranta, Finland (1043/13.01.02/2013), and all patients gave their written informed consent to participation in the study and permission to publish their pictures.

4. RESULTS

Reduction in wound size was observed in six patients within a mean period of six weeks (range: 2 - 10 weeks) (Table 1, Figures 1-5). Case 1 had pressure ulcers on his heels due to neuropathy, and even though his angiography findings were negative, he probably had microangiopathy. The location of his ulcers on the heels was demanding, and special shoes were acquired to avoid physical irritation of the wound (Figure 1(a) and Figure 1(b)). The response to Aktisor® was good, and the healing took two months (Figures 1-3). Case 5 with an exuding wound experienced reduced pain within one week, and the amount of secretion decreased clinically (Figure 4 and Figure 5).



(a) (b)

Figure 1. Case 1 before any treatments.

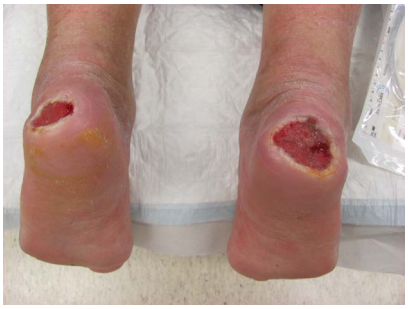


Figure 2. An angiogram performed two months later could not show signs of ASO. The wounds did not heal after debridement, skin transplantation and NWPT. One month later, treatment with Aktisor® suspension was started.

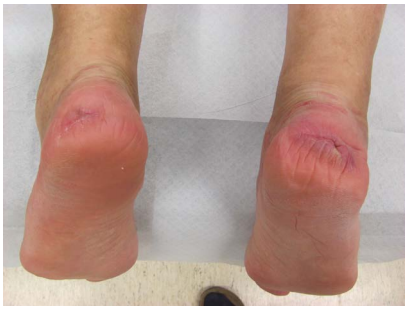


Figure 3. Case 1: After two months the wounds were healed.

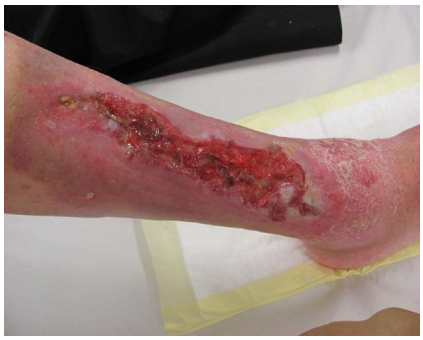


Figure 4. Case 5 with an exudative and painful leg ulcer.

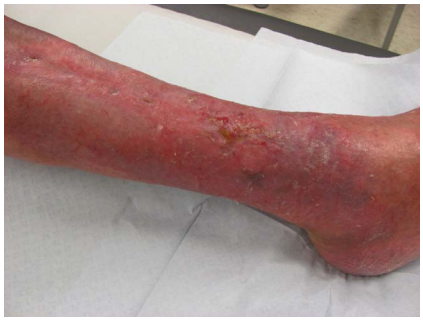


Figure 5. Case 5: The wounds were healed within four months.

All patients reported light or moderate smarting in their wounds for up to 20 minutes after Aktisor® application, a side effect usually limited to the beginning the treatment. No allergic reactions could be detected. Aktisor® was easy to use and both the wound care product itself and the suggested cover material, a low-adherent absorbent dressing (Meloline®), proved economical.

5. DISCUSSION

The published data on tannins and wound healing are surprisingly scant even though herbal medicines have been widely used around the world since ancient times. Modern research has only recently offered some evidence-based data on the molecular level. Tannins are water-soluble polyphenols that are present in many food plants. The dosage and type of tannins are critical to their beneficial effects, including antimicrobial, anticarcinogenic and antimutagenic effects [15]. According to the inventors of this product, the chosen plant extracts were selected on the basis of their affinity for the MMPs specifically involved in chronic wounds. It is likely that the tannins or their specific fractions bind to the MMPs responsible for the degradation of the cellular matrix components and thus help preserve the extracellular matrix onto which new daughter cells then attach. The more chronic the wound bed, the higher the MMP activity is. MMPs in the chronic wound are products of both the host and bacteria. Shrivastava *et al.* have shown that the MMPs in pressure ulcers, diabetic ulcers and venous leg ulcers are more or less identical, which might explain why the chronic wounds with diverse etiologies that were treated with Aktisor® suspension healed [8].

Honey facilitates the debridement of wounds by the autolytic action of tissue proteases. It creates a moist wound environment by drawing out lymph fluid from the wound tissues through powerful osmotic action. This provides a constant supply of proteases at the interface of the wound bed and the overlying necrotic tissue, which may help to explain the rapid debridement provided by honey [12] [16]. Honey (buckwheat, acacia and manuka) causes induction of keratinocytes, functions as a chemo attractant and enhances expression of syndecan-4 and MMP-9 [17]. Interestingly, the honeys of various floral origins use separate cell signal translation pathways for cell migration and wound healing.

The results of this case study of six patients clearly show that Aktisor® is highly effective for accelerating the healing process of chronic wounds, irrespective of diverse etiologies. Because of the limited number of patients in this descriptive report, we do not claim that Aktisor® is superior over similar products. However, combination of tannin-rich plant extracts and honey might bring synergy thus adding Aktisor®'s bactericidal properties. These observations encourage us for further studies.

DECLARATION OF INTEREST

Taina A. Broth, Arja Järvelä and Tuula Tiainen have no conflict of interest.

REFERENCES

1. Guo, S. and Dipietro, L.A. (2010) Factors Affecting Wound Healing. *Journal of Dental Research*, **89**, 219-229. https://doi.org/10.1177/0022034509359125
2. Sgonc, R. and Gruber, J. (2013) Age-Related Aspects of Cutaneous Wound Healing: A Mini-Review. *Gerontology*, **59**,159-164. https://doi.org/10.1159/000342344
3. Broadbent, E. and Koschwanez, H.E. (2012) The Psychology of Wound Healing. *Current Opinion in Psychiatry*, **25**, 135-140. https://doi.org/10.1097/YCO.0b013e32834e1424
4. Ubbink, D.T., Santema, T.B. and Stoekenbroek, R.M. (2014) Systemic Wound Care: A Meta-Review of Cochrane Systematic Reviews. *Surgical Technology International*, **24**, 99-111.
5. McCarty, S.M., Cochrane, C.A., Clegg, P.D. and Percival, S.L. (2012) The Role of Endogenous and Exogenous Enzymes in Chronic Wounds: A Focus on the Implications of Aberrant Levels of Both Host and Bacterial Proteases in Wound Healing. *Wound Repair and Regeneration*, **20**, 125-136. https://doi.org/10.1111/j.1524-475X.2012.00763.x
6. Snyder, R.J., Cullen, B. and Nisbet, L.T. (2013) An Audit to Assess the Perspectives of US Wound Care Specialists Regarding the Importance of Proteases in Wound Healing and Wound Assessment. *International Wound Journal*, **10**, 653-660. https://doi.org/10.1111/j.1742-481X.2012.01040.x
7. Saegeman, V.S., De Vos, R., Tebaldi, N.D., *et al.* (2007) Flow Cytometric Viability Assessment and Transmission Electron Microscopic Morphological Study of Bacteria in Glycerol. *Microscopy and Microanalysis*, **13**, 18-29. https://doi.org/10.1017/S1431927607070079
8. Shrivastava, R., Cucuat, N., Rousse, M., Weigand, T., Neto, P., Janicot, C. and Shrivastava, C. (2014) A New Generation of Topical Chronic Wound Treatments Containing Specific MMP inhibitors. *Chronic Wound Care Management and Research*, **1**, 31-40. https://doi.org/10.2147/CWCMR.S59946
9. Shrivastava, R. and John, G.W. (2006) Treatment of Aphthous Stomatitis with Topical *Alchemilla vulgaris* in Glycerine. *Clinical Drug Investigation*, **26**, 567-573. https://doi.org/10.2165/00044011-200626100-00003
10. Jull, A.B., Walker, N. and Deshpande, S. (2013) Honey as a Topical Treatment for Wounds. *Cochrane Database of Systematic Reviews*, **2**, CD005083. https://doi.org/10.1002/14651858.CD005083.pub3
11. Majtan, J., Kumar, P., Majtan, T., Walls, A.F. and Klaudiny, J. (2010) Effect of Honey and Its Major Royal Jelly Protein 1 on Cytokine and MMP-9 mRNA Transcripts in Human Keratinocytes. *Experimental Dermatology*, **19**, e73-e79. https://doi.org/10.1111/j.1600-0625.2009.00994.x
12. Molan, P. (2011) The Evidence and the Rationale for the Use of Honey as a Wound Dressing. *Wound Practice and Research*, **19**, 204-220.
13. Leaper, D.J., Schultz, G., Carville, K., Fletcher, J., Swanson, T. and Drake, R. (2012) Extending the TIME Concept: What Have We Learned in the Past 10 years? *International Wound Journal*, **9**, 1-19. https://doi.org/10.1111/j.1742-481X.2012.01097.x

14. Shrivastava, R. (2011) Clinical Evidence to Demonstrate that Simultaneous Growth of Epithelial and Fibroblast Cells Is Essential for Deep Wound Healing. *Diabetes Research and Clinical Practice*, **92**, 92-99. https://doi.org/10.1016/j.diabres.2010.12.021

15. Bonifacio, B.V., Silva, P.B., Ramos, M.A., Negri, K.M., Bauab, T.M. and Chorilli, M. (2014) Nanotechnology-Based Drug Delivery Systems and Herbal Medicines: A Review. *International Journal of Nanomedicine*, **9**, 1-15.

16. Molan, P.C. (2006) The Evidence Supporting the Use of Honey as a Wound Dressing. *The International Journal of Lower Extremity Wounds*, **5**, 40-54. https://doi.org/10.1177/1534734605286014

17. Ranzato, E., Martinotti, S. and Burlando, B. (2012) Epithelial Mesenchymal Transition Traits in Honey-Driven Keratinocyte Wound Healing: Comparison among Different Honeys. *Wound Repair and Regeneration*, **20**, 778-785. https://doi.org/10.1111/j.1524-475X.2012.00825.x