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# The Efficiency of BIOAPIFIT® Wound Care Ointment in the Treatment of Venous Ulcers

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**Abstract**

**Objective / Purpose:** The objective of this study was efficacy assessment of Bioapifit® wound care ointment consisted of honey, *Cera flava,* glycerin, the oil macerates of astringent and soothing herbs combined with three essential oils for the treatment of venous ulcers. **Materials and methods**: 50 patients with total 112 venous ulcers with the total surface area of 572.5 $cm^2$ were treated 60 days (twice a day) with Bioapifit® wound care ointment applied on conventionally cleaned wound and covered with bandage during the whole course of the study. The healing process was assessed by Venous Clinical Severity Score (VCSS) tool twice a month. **Results:** At baseline the mean value and standard deviation of the VCSS score was 25.03 ± 4.37 and 25.53 ± 3.36 for females and males, respectively. The surface area ranged from 1.6 to 28.1 $cm^2$ for females and from 1.60 to 29.20 $cm^2$ for males. The mean value and standard deviation of the total VCSS score following the treatment decreased to 6.26 ± 4.0 and 6.47 ± 3.9 for females and males, respectively. Total number of active ulcers decreased from 112 to 17 and the total surface area of all ulcers from 572.5 $cm^2$ to 7.6 $cm^2$. No side-effects were observed during the course of the study. **Conclusion / Discussion:** Two months application of Bioapifit® wound care ointment resulted in complete closure of 84.8% of the ulcers and reduction in their surface area for 98.7% with the mean healing time of 37.2 days.

**Key Words:** Venous Ulcers, VCSS Tool, Honeybee's Products, Herbal Macerate



## 1. Introduction

Venous ulcer, the latest stage of the chronic venous disease, represents the area of discontinuity of the skin, most often located in the distal parts of the lower limbs (Marinović Kulišić, 2016). It differs in size and shape, sometimes including the entire circumference of the extremities. Possible causes of venous ulcers include inflammatory processes resulting in leukocyte migration, plasma cell and granulocyte activation, increased activity of metalloproteinase, endothelial damage, platelet aggregation, and intracellular edema. Impaired muscle activity represents another important risk factor involved in the patophysiology of venous ulcers (Collins and Seraj, 2010; Marinović Kulišić, 2016).

The important risk factors are older age (>50), body mass index (BMI) gender,

multiple childbirths, previous leg injuries, deep venous thrombosis, inadequate physical activity, smoking, static foot disorders, family history, phlebitis (Collins and Seraj, 2010; Marinović Kulišić, 2016).

Various management options were developed so far for the treatment of chronic venous disease (Collins and Seraj, 2010; Marinović Kulišić, 2016) and include: conservative treatment (compression therapy, leg elevation, dressings), mechanical treatment (vacuum- assisted closure), medications (natural venoactive drugs, pentoxifylline, glycosaminoglycans, prostaglandine E1, aspirin, iloprost, oral zinc, antibiotics/antiseptics), hyperbaric oxygen therapy, surgical intervention (debridement, human skin grafting, artificial skin, surgery for venous insufficiency). The latest was applied to the large ulcers with prolonged duration not responded to the conservative treatment. Since 1994 clinical assessment of the severity of the chronic venous disease is based on the CEAP (clinical, etiology, anatomy, and pathophysiology) classification system ranging from C0 with no disease present to C6 with the presence of active ulcers assessment of chronic venous disorders (Marinović Kulišić, 2016).

Based on the elements of CEAP classification the American Venous Forum, in 2000 developed the Venous Severity Score (VSS) grading tool as the complementary system to the CEAP classification. VSS classification is necessary for the longitudinal monitoring of the clinical condition of the patient during and after the intervention. This classification is combined with the degree of the severity of the venous disease: Venous Disability Score (VDS); Venous Segmental Disease Score (VSDS); Venous Clinical Severity Score (VCSS) (Marinović Kulišić, 2016).

The VCSS consist of ten descriptors (pain or other discomfort, varicose veins, venous edema, skin pigmentation, inflammation, induration, active ulcer number, active ulcer duration, active ulcer size, use of compression therapy) graded from 0 (no symptoms/disease) to 3 (highest degree of the symptoms/disease) (Vasquez et al., 2010).

The purpose of this work was testing of clinical performance of Bioapifit® wound care ointment composed of honey, glycerin, herbal macerates of the astringent plants, beeswax and three essential oils for the treatment of 112 active venous ulcers.

## 2. Patient and Method

### 2.1. Study Design

The study was conducted at the following locations: FINDRI GUŠTEK HEALTHCARE INSTITUTION, Ninska 5a, Sesvete, Croatia and FAMILY MEDICINE CLINIC, Vilima Korajca 19 Zagreb, Croatia. The investigator recruited the patients based on their medical history, following the predefined inclusion and exclusion criteria. The study protocol was approved by the Ethics Committee of Findri Gustek Health Care Center with EudraCT number 2019- 001379-35.

50 patients (35 females and 15 males) ranging from 57 to 77 years with total of 112 active ulcers and the total surface area of all ulcers of 572.5 $cm^2$ were included. All the participants signed informed consent and completed the questioner.

The patients were treated 60 days with the product. The ointment was applied on the previously cleaned wound twice a day by nurse and covered with bandage during the whole course of the study. At each changing of the bandages each wound was cleaned from the slough. Clinical evaluation of the patients before and following the therapy was done by Venous Clinical Severity Score (VCSS) tool consisting of ten descriptors each graded from 0 (no symptoms/disease) to 3 (worse possible symptoms/disease).

### 2.2. Description of investigational product

Bioapifit® wound care ointment is homogeneous, greasy, viscous mass of characteristic herbal odor and olive green color with pH of 4.43±0.13. It consists of the following ingredients: honey (certified organic), beeswax (*Cera flava*), glycerol, the macerates of the plant species: *Plantago major* L., *Achilea millefolium* L., *Quercus robur* L., *Salvia officinalis* L., *Olea europaea* L., *Polygonum aviculare* L., *Symphytum officinale* L., *Calendula officinalis* L., *Matricaria chamomilla* L., essential oils: Australian tea tree (*Melaleuca alternifolia* (Maiden & Betche, Cheel), thyme (*Thymus vulgaris* L. ct. thymol), oregano (*Origanum vulgare* L.).

### 2.3. Statistical analysis

For statistical evaluation Statistica 11.0 software package was employed. The description of the treated population was done by basic statistics and frequency tables. Statistical significance was set to $p<0.05$ in all the tests performed. The differences in the mean values of each parameter prior and after the therapy as well as different treatment periods were assessed by Newman-Keuls test. The influence of the predictor variables on the dependent variable was tested by Multiple regression method and General regression model (Oreščanin, 2016).

## 3. Results

### 3.1. Description of the population

The study included 35 females and 15 males. The number of childbirth ranged from 1 to 4 with majority of them (16 of 35) having two childbirth. 75% of the participants had previous leg injuries and 24% of them suffer from deep venous thrombosis. 82% of the participants had prevailing sedentary lifestyle or occupation with inadequate physical activity. Among the participants 68% of them are smokers. Family history of venous disease was present in 80% of the participants and phlebitis in 12% of them.

The basic statistical parameters for age and body mass index expressed separately for males and females as well as total population is presented in Table 1. The female population ranged from 57 to 77 years (67.97±4.97) and males from 61 to 77 years (67.60±4.81). Both female and male participants were overweighed with BMI ranging from 26.30 to 44.80 mg/m$^2$ (33.80±4.61 mg/m$^2$) and males from 28.70 to 42.90 mg/m$^2$ (36.10±4.93 mg/m$^2$). T-test showed no significant difference between males and females regarding age or BMI.

**Table 1.** The basic statistical parameters for age and body mass index separately for males and females as well as total population.

| Gender | Age | | | Body mass index | | |
|---|---|---|---|---|---|---|
| | $\bar{X}$±SD | Min. | Max. | $\bar{X}$±SD | Min. | Max. |
| Female | 67.97±4.97 | 57.00 | 77.00 | 33.80±4.61 | 26.30 | 44.80 |
| Male | 67.60±4.81 | 61.00 | 77.00 | 36.10±4.93 | 28.70 | 42.90 |
| All | 67.86±4.88 | 57.00 | 77.00 | 34.49±4.77 | 26.30 | 44.80 |

*X-mean value; SD-standard deviation*

The results of multiple regression analysis showed very good, statistically significant correlation between VCSS score and selected predictor variables ($R=76.7$; $p<0.0000$). The variables with the highest, statistically significant contributions to the VCSS score were BMI ($p<0.0027$), family history ($p<0.043$) and age ($p<0.047$).

The results were completely in agreement with those obtained by General regression model expressed as Pareto chart of t-values (Figure 1) which identified BMI, family

history and age as statistically significant contributors to the total VCSS score.

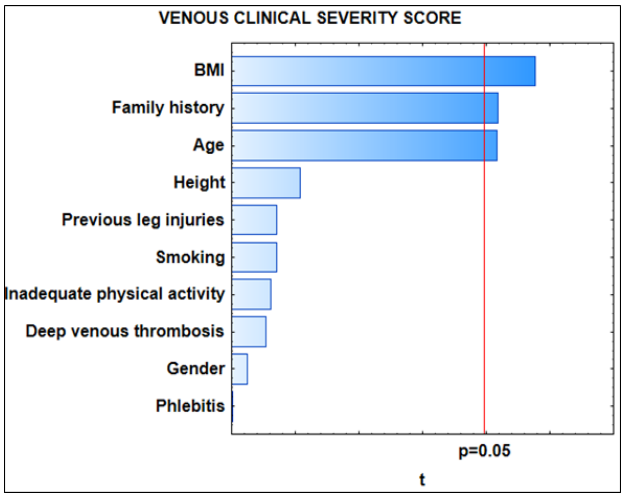


**Figure 1.** Pareto chart of t-values testing for the influence of predictor variable onto venous clinical severity score before the treatment

### 3.2. Treatment efficiency

The results of the assessment of venous ulcers according to the venous clinical severity score (VCSS) following the treatment with Bioapifit® wound care ointment were presented in Table 2 and Figure 2. Prior to the therapy the mean value and standard deviation of the total VCSS score was 25.03 ± 4.37 and 25.53 ± 3.36 for females and males, respectively (Table 2, Figure 2).

The number of active ulcers ranged from 1 to 4 and their surface area from 1.6 to 28.1 $cm^2$ (10.94±9.26 $cm^2$) for females and from 1.60 to 29.20 $cm^2$ (12.65 ± 10.85 $cm^2$) for males. There was no significant difference between males and females in all descriptors and the total VCSS score or surface area of the ulcers at baseline.

**Table 2.** Mean values and standard deviations for each descriptor and total value of venous clinical severity score for male (M) and female (F) population at baseline (B) and following 60 days of the treatment (F) with Bioapifit® wound care ointment

| Descriptor | F-B | F-F | M-B | M-F |
|---|---|---|---|---|
| **Pain** | 3.00±0.00 | 0.54±0.51* | 3.00±0.00 | 0.73±0.46* |
| **Varicose veins** | 2.54±0.51 | 1.17±0.45* | 2.73±0.46 | 1.27±0.59* |
| **Venous edema** | 2.57±0.50 | 0.46±0.51* | 2.87±0.35 | 0.60±0.51* |
| **Skin pigmentation** | 2.77±0.43 | 1.31±0.47* | 3.00±0.00 | 1.33±0.49* |
| **Inflammation** | 2.57±0.50 | 0.26±0.44* | 2.73±0.46 | 0.33±0.49* |
| **Induration** | 2.63±0.49 | 0.63±0.60* | 2.67±0.49 | 0.87±0.35* |
| **Active ulcer number** | 2.09±0.78 | 0.37±0.49* | 2.00±0.76 | 0.33±0.49* |
| **Active ulcer duration** | 2.20±0.76 | 0.74±1.15* | 2.07±0.70 | 0.33±0.49* |
| **Active ulcer size** | 2.29±0.67 | 0.37±0.49* | 2.27±0.59 | 0.33±0.49* |
| **Use of compression therapy** | 2.37±0.69 | 0.40±0.55* | 2.20±0.56 | 0.33±0.49* |
| **VCSS-total score** | 25.03±4.37 | 6.26±4.59 | 25.53±3.36 | 6.47±3.72* |

Following the 60 days of tropical treatment with Bioapifit® wound care ointment all descriptors of the VCSS score decreased significantly. The mean value and standard deviation of the total VCSS score was 6.26 ± 4.0 and 6.47 ± 3.9 for females and males, respectively (Table 2, Figure 2). The total number of active ulcers decreased from 112 to 17 and the total surface area of all ulcers from 572.5 $cm^2$ to 7.6 $cm^2$. The mean value and standard deviation for active ulcers surface area following the therapy was 0.13 ± 0.21 $cm^2$ for females and 0.19 ± 0.29 $cm^2$ for males.

### 4. Discussion and Conclusion

Two months of the topical treatment with Bioapifit® wound care ointment resulted in

reduction of total VCSS score for app. 75%, complete closure of 84.8% of the venous ulcers and reduction in the ulcer's total surface area for 98.7% with the mean healing time of 37.2 days.

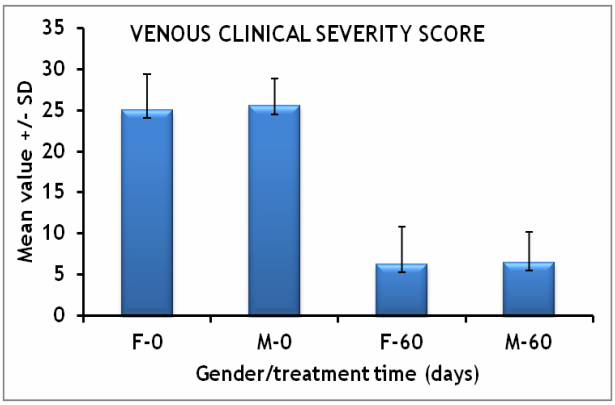


**Figure 2.** Mean values and standard deviations for total value of venous clinical severity score for male (M) and female (F) population prior and following 60 days of the treatment with Bioapifit® wound care ointment.

Since venous ulcers are wounds that are very difficult to heal, obtained results could be attributed to the selection of the ingredients with pH adjusting, osmotic, moisturizing, astringent and coating effect. Among them, honey was identified as most important ingredient of the ointment which thanks to its low pH value (4.16) creating an acidic wound micro-environment necessary for healing process. Debridement of slough and necrotic tissue through autolytic debridement was also present. Moreover, honey absorbed wound exudates due to high osmotic effect/high sugar content and created the environment with low water activity that all together supported wound closure and in the same time prevented pathogens growth. Previous studies connected antimicrobial activity of honey against the pathogens causing invasive wound infections including methicillin- resistant *Staphylococcus aureus* (MRSA) either to the production of hydrogen-peroxide by glucose oxidize enzyme or non-peroxide antimicrobial activity which could be connected to low pH value, osmotic effect of sugar, the presence of polyphenols and flavonoides, carbohydrate and its break-down Maillard products, aromatic acids, 10-HAD defensin-1 protein, 1,2-dicarbonyl compound methylglyoxal and bacillomycin F antibiotic like polypeptide (Lusby et al., 2002; Simon et al., 2009; Al-Waili et al., 2011).

It was confirmed that topical application of honey (directly or in the form of various types of wound dressing had very beneficial effects on wound healing. The treatment of pressure ulcers with honey alginate (Vandamme et al., 2003) resulted with rapid and complete wounds healing, reduced inflammation and deodorizing effect. Subrahmanyam et al., 2001 reported significantly faster wound healing in the patients treated with honey dressing compared to those treated with silver sulphadiazine. Moreover, completely sterile wounds were obtained in 90% of honey treated patients. It was reported that pH of the wound has critical influence on its healing potential since the wounds with pH higher than 8 showed no reduction in size (Gethin et al., 2008). Alam et al. (2014) summarized beneficial effects of honey for the treatment of diabetic wounds that were mostly connected to its antimicrobial activity, low pH value, hydrogen peroxide activity that all together stimulated wound closure. Debridement of slough and necrotic tissue through autolytic debridement and minimizing wound odor was another important mechanism (Alam et al., 2014).

A significant improvement of venous ulcer wound healing was observed following the treatment with the honey-based dressing (Alcaraz and Kelly, 2002). Mohamed et al. (2014) reported complete wound closure amputation wound after four weeks continuous treatment with natural honey. The treatment of foot ulcers with natural honey once a day resulted in complete wound closure within three weeks with no contractures or scars (Mohamed et al., 2015). The treatment of the patients with neuropathic diabetic foot ulcers with manuka

honey impregnated dressings (Kamaratos et al., 2014) resulted in complete healing after 31±4 days while in app. 78% of the patients wound became sterile following one week of the treatment which was in agreement with the results obtained in the current study.

Researchers confirmed beneficial effect of the astringent plants rich in soluble tannins in the treatment of open wounds (Abascal and Yarnell, 2005; Odukoya et al., 2007) which could be explained by surface coagulation of the proteins resulting in the shrinking of the wound as well as by forming the protective coating over damaged tissue. For that purpose oil macerates of the plants with strong astringent properties *Plantago major* L.*, Achilea millefolium* L.*, Quercus robur* L., *Salvia officinalis* L.*, Olea europaea* L., *Polygonum aviculare* L., *Symphytum officinale* L., were included in the product formulation. Moreover, the macerates of marigold flowers (*Calendula officinalis* L.) and chamomile flowers (*Matricaria chamomilla* L.) were used due to its soothing and calming effect to the wounded skin (Oreščanin, 2016).

Additionally, herbal macerate was used in the formulation due to its low pH and coating effect. Moreover, the macerate created the environment with no water activity which was unsupportive for pathogens growth and replication.

Glycerol was used in the formulation in order to provide enough moisture content of the wound necessary for the healing process. Beeswax was employed not only because of its emulsifying and thickening effect but also for wound isolation and protection from the microbial infection due to its excellent coating effect (Oreščanin, 2016). Essential oils served as natural preservatives and wound malodor correctors.

## Conflict of Interest

The authors declared that they have no conflict of interest.

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