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abstract

Vascular blemishes can lead to unsightly skin appearance. A neglected cause can be oedema leading to puffy eyes and promoting visibility of small blood vessels. By taking advantage of an aqueous extract from *Helichrysum italicum*, puffy eyes and visibility of spider veins could be significantly reduced in an *in-vivo* study. Data from this study and *in-vitro* investigations suggest a negative role of nitric oxide (NO) in the development of these blemishes.

Introduction

Many different parameters can be the cause of unwanted, visible skin changes. One of them is oedema, which causes tissue swelling. Oedema is the result of fluid accumulation in extracellular areas, for example in the dermis. The formation of oedemas can have different causes. Often there is an underlying general connective tissue weakness affecting both dermal structures and vascular structures. Women suffer more often from connective tissue weakness than men as they have a different dermal collagen structure [1]. Chronic oedema leads to swelling of tissues. The legs are particularly predisposed, as hydrostatic pressure is greatest here. Many people suffer from “heavy legs”, especially when they have been in an upright position for a long time. The legs feel tired, heavy and can become swollen. Chronic oedema has a negative effect on the skin: it becomes thinner and ulcers (open sores) may even develop; these are weeping wounds that heal with great difficulty. Diabetics are especially affected. This is, of course, the manifestation of a clinical condition and cannot be treated cosmetically. However, the risk of developing oedema increases with age [2]. Thus, early cosmetic support to prevent oedema can be considered a means of anti-ageing body care.

However, oedema can also occur on the face: Periorbital puffiness or puffy eyes are the result of fluid accumulation under the eyes. They are caused by insufficient lymph drainage. They make our eyes look tired and dull. It is not surprising that they can also be engendered by lack of sleep. Lymph can accumulate in the region of the bags under the eyes, especially in those who sleep on their stomach, leading to puffy eyes on waking. This swelling normally recedes in the course of the morning but can persist when individuals become older. During the ageing process, the skin becomes thinner and firmness and elasticity decrease in this delicate organ. Connective tissue weakness, smoking and alcohol intake are factors that promote the permanent appearance of bags under the eyes. An internal survey showed that 86% think puffy eyes are considered worse than wrinkles (n = 91, aged 21–70). Puffy eyes are therefore a significant comfort-reducing factor.

Another unsightly skin change is spider veins. They are dilations of fine veins just below the skin surface. It is a cosmetic issue and do not represent a disorder in the actual sense but can indicate underlying general venous insufficiency. Spider veins (telangiectasis) form preferentially on the legs and the face near the nose. They take the form of dark red to bluish veins with multiple branches. Frequently, spider veins are the result of an underlying venous reflux problem that causes blood stasis, making the vessels visible, and causing oedema in the surrounding tissue. Spider veins on the face can also be caused by sun damage [3]. The breakdown of collagen and elastin (solar elastosis) makes the veins more visible as they get closer to the skin surface. Therefore, skin ageing also plays a role in the development of spider veins on the face.

Other factors involved in spider vein formation include excessive alcohol consumption, smoking, lack of exercise, pregnancy, obesity and frequent standing or sitting causing blood stasis in the veins [4,5]. Spider veins occur more often in women than in men because they often have weaker connective tissue. It is next to impossible to completely prevent the development of spider veins, but if certain basic rules are followed the risk can be minimised. It is best to avoid sitting and standing for too long and thus advisable to move around, to stimulate the vein pump in the calves by means of foot exercises and to elevate the legs. In general, it is important to prevent blood stasis in the veins. There is as yet no tried-and-tested means of preventing the development of spider veins on the face. However, avoidance of excessive alcohol consumption certainly plays a major role here.

Extracellular fluid volume is regulated by peripheral tissue resistance and renal function, among other factors.

Nitric oxide (NO), produced by nitric oxide synthase (NOS), promotes venous dilation and varicose veins [6]. It can boost fluid accumulation in tissues by reducing systemic vascular resistance and arterial pressure and increasing vascular permeability [7,8]. A persistent increase in tissue fluid volume leads to the formation of oedema in the form of, e.g., puffy eyes on the face. It

has been demonstrated that inhibition of NOS can reduce the formation of NO-induced oedema [9].

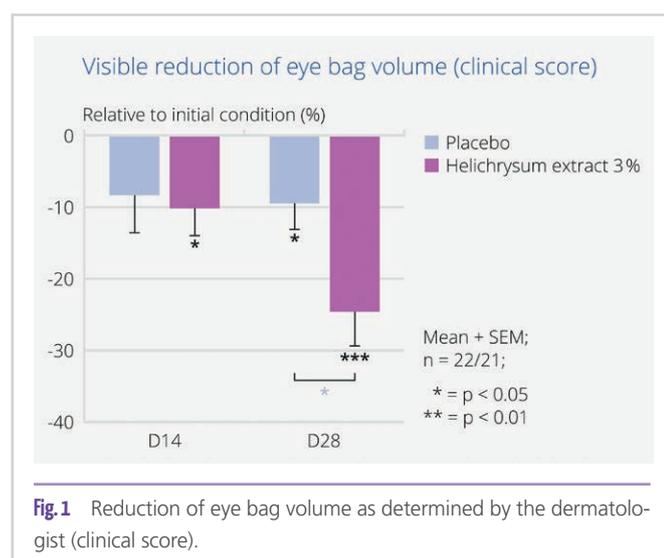
Inhibition of NOS and elimination of reactive oxygen species (ROS) have also proved effective in the prevention of sunburn [10]. In this condition, the microcirculation is greatly increased by the activity of NO. This means that inhibitors of NOS can have a soothing effect on the skin. It seems that use of these would therefore represent a general way of attenuating acute and chronic inflammatory vasodilatory responses in the skin in order to reduce redness, oedema and the visibility of spider veins as well as the sensation of “heavy legs”. Interestingly, caffeoylquinic acids, such as chlorogenic acid, and especially di-O-caffeoylquinic acids are known to inhibit NOS and to act as antioxidants [11,12].

We at RAHN-Cosmetic Actives discovered that an aqueous extract of the plant immortelle (*Helichrysum italicum* syn. *angustifolium*) is the perfect solution for the above-mentioned issues. Indeed, Helichrysum extract (PERFELINE®-FIT; INCI: Water, Propanediol, Helichrysum Angustifolium Flower Extract, Citric Acid) exhibits a direct inhibitory effect on human NOS *in-vitro*. Besides chlorogenic acid, we were able to detect three different di-O-caffeoylquinic acids in the extract. Helichrysum extract is thus the perfect fit as a body and face care agent when it comes to dealing with oedema-related cosmetic problems like puffy eyes as well as spider veins and heavy legs.

Materials and Methods

Double-blind, placebo-controlled *in-vivo* study, 43 female subjects, aged 30–65 years (average 55.0), application of cosmetic formulations for 28 days twice daily on the legs (5% active ingredient), the eyes (3% active ingredient) and to the face (1% active ingredient).

VECTRA-XT was used to investigate the effect on spider veins (photographic images). The severity of spider veins was evaluated by means of assessment by a dermatologist.



VECTRA-XT was used to investigate red structures in the face. The severity of eye bags volume was evaluated by means of assessment by a dermatologist and quantification with AEVA.

The microcirculation in the eye area was determined using laser Doppler flowmetry. All parameters were measured at days 0, 14 and 28. The immediate effects on skin microcirculation were measured 30 minutes after application of the formulations. An increase in microcirculation was provoked by heating the tissue with a self-heating probe to 42°C.

To calculate the contribution of nitric oxide release to the increase in microcirculation, fast Fourier transforms and wavelet analysis was performed [14]. For this purpose, a baseline was recorded for 8 minutes, followed by the heat stimulation and then measurement for an additional 7 minutes.

To determine the inhibitory effect of Helichrysum extract on nitric oxide synthase, human eNOS enzyme was subjected to reaction with radioactively labelled L-arginine and oxygen to produce nitric oxide and L-citrullin. The resultant amount of L-citrullin was determined by means of scintillation counting. The reaction was performed in the presence of different concentrations of the active ingredient.

Results and discussion

To investigate the efficacy of Helichrysum extract when applied to the whole face, two different types of formulations were used. One emulsion contained 1% Helichrysum extract or none (placebo). The other was a gel for the eye area containing 3% Helichrysum extract or none (placebo). This was applied as a roll-on with a metal ball applicator. One group applied verum only, the other group applied placebo only twice daily for 28 days. Application to the legs was done with an emulsion containing 5% Helichrysum extract.

After 14 and 28 days, Helichrysum extract reduced eye bag volume by 10%, which was significant in comparison with baseline (Figure 1). After 28 days, the dermatologist attested a 25% reduction in eye bag volume, significant over baseline and placebo. These effects were confirmed by AEVA measurements (not shown) and clearly visible (Figure 2).

Helichrysum extract significantly reduced red spots by 16% as measured by VECTRA-XT after 28 days (not shown). The images of the red channel clearly show a reduction of visible capillaries as well (Figure 3).

After 14 days, the basal level of skin microcirculation in the puffy eye area decreased by 10.5%, which was significant in comparison with baseline and placebo (Figure 4, left). This value remained in the same range after 28 days (7.4%). Interestingly, this effect was already achieved 30 minutes after product application (not shown). When skin was stressed (heat stimula-

tion), the resulting maximal increase in microcirculation was significantly reduced by almost 20% after 28 days application of 3% Helichrysum extract (Figure 4, middle). The effect was significant in comparison with baseline and placebo. Placebo did not reduce induced microcirculation at all. In contrast, induced microcirculation was significantly increased by more than 20% when placebo was used. It seems that the basic cosmetic formulation reduced the skin's resistance to external stressors, while supplementation with Helichrysum extract actually increased this resistance. Investigation of the nitric oxide contribution to the increase in microcirculation revealed that application of 3% Helichrysum extract significantly reduced the release of this vasodilator (Figure 4, right). The effects were visible already 30 minutes after application and remained significant in comparison with baseline and placebo after 28 days. The microcirculation results suggest that the enzyme nitric oxide synthase (NOS) was inhibited to some extent. Basal activity would involve eNOS (endothelial NOS), which is constitutively, i.e. permanently, expressed. eNOS is also responsible for additional NO release if the microcirculation is provoked [15,16]. As Helichrysum extract reduces microcirculation in stressed skin, it can function as a skin soothing agent as well.

Helichrysum extract inhibits eNOS with an IC_{50} of 0.66 % *in-vitro*. At 1%, the inhibition was 62% (not shown).

We tested a beneficial effect on spider veins on the legs as these can be affected by an increased NO content of the surrounding skin. Indeed, the visibility of spider veins on the legs was reduced significantly over baseline and placebo by 10% and 18% after 14 days and 28 days, respectively, as deduced from the clinical score (not shown). The effect was clearly visible as depicted in Figure 5.

Conclusions

PERFELINE®-FIT contains caffeoylquinic acids, which are known to inhibit nitric oxide synthase [17]. Based on this background, the effects observed in the study seems very plausible. The inhibition of NOS leads to a reduced release of NO and thus prevents excessive vasodilation and increased permeability of the

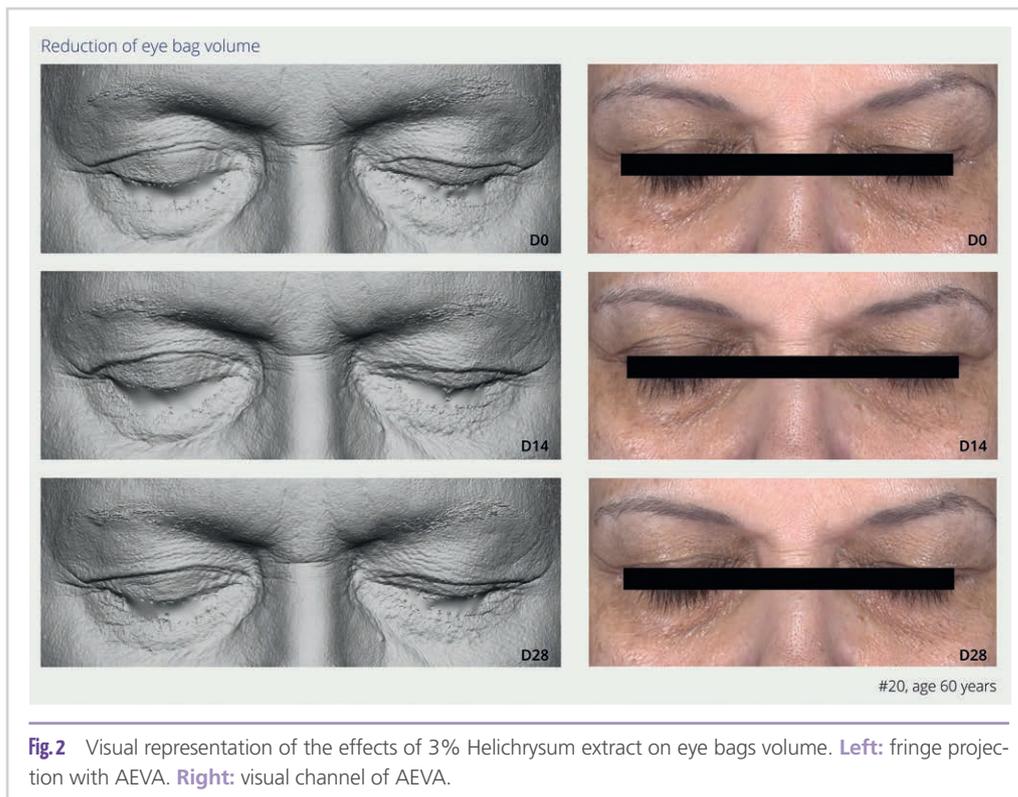


Fig.2 Visual representation of the effects of 3% Helichrysum extract on eye bags volume. **Left:** fringe projection with AEVA. **Right:** visual channel of AEVA.



Fig.3 Reduction of red spots and visible capillaries after application of 1% Helichrysum extract.

vessels. Permanent vasodilation can lead to the development of visible capillaries and spider veins as well as oedema. We have found that the extract from *Helichrysum italicum* is able to alleviate unsightly puffy eyes and the visibility of spider veins. PERFELINE®-FIT is therefore a perfect solution for taking care of the skin, whether on the face or all over the body. It is a natural cos-

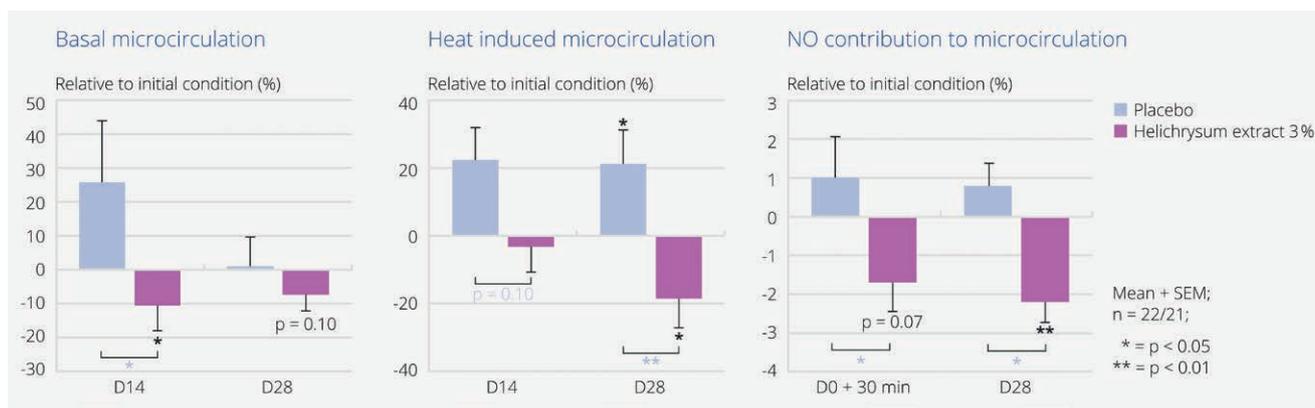


Fig. 4 Reduction in microcirculation. **Left:** Basal microcirculation. **Middle:** Heat induced microcirculation. **Right:** NO contribution to microcirculation.

metic ingredient that is mild but effective, making signs of stress and fatigue disappear for a fresh look and feel.

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Visibility of spider veins on the leg



Fig. 5 Visible reduction of spider veins after application of 5% Helichrysum extract. **Top panels:** knee area. **Bottom panels:** thigh area.

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