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Sempervivum Tectorum

Houseleek

The unusual alpine "Aloe Vera"





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1. Summary

The Latin botanical name *Sempervivum* stands for “always” or “forever” (*semper*) and “living” (*vivus*). This plant is very resistant to difficult growth conditions and keeps its leaves in summer and winter. *Sempervivum tectorum* is commonly known as “houseleek”.

The thick leaves can store water, making the plant capable to live on stony, sunny surfaces, mostly in the mountain, subalpine and alpine belts. *Sempervivum tectorum* is usually planted in the average mountain area, the Alps and foothills of the Alps on roofs and walls (which is the reason for its common name). People believe that the plant protects buildings against lightning, thunder and fire [1].

Sempervivum tectorum is used as medical herb, spice and salad. Recent medical research data present houseleek leaf extract as an antimicrobial, antinociceptive, cooling, astringent and antioxidative substance.

The Innovative glycerin houseleek leaf extract (concentration 0.1% to 1%) shows novel activities for cosmetic use. The tested houseleek leaf extract activates the Nrf2 pathway, shows an antagonistic activity against TrPV1, inhibits HIF-1 α activity, enhances glucose uptake in HaCaT keratinocytes, is a PPAR α and PPAR γ agonist, a powerful agonist of cannabinoid receptor type 1, a potent tyrosinase inhibitor and shows skin lightening effects.

Houseleek leaf extract activates cellular mechanisms which are involved in skin healing and regeneration, helps skin repair, moisturizes and refirms the skin. Additionally, it seems to be beneficial in the treatment of ageing effects, wrinkles or fine lines, sensitive and sun damaged skin. Houseleek extracts with the INCI *Sempervivum Tectorum* Extract have been used in Cosmetics (see e.g. EU 1996/335) for decades. The INCI is also known in China and Japan.

2. Classification

Family	Crassulaceae
Genus	<i>Sempervivum</i>
Species	<i>tectorum</i>



3. General Information on *Sempervivum tectorum*

3.1. Description of the houseleek



Sempervivum tectorum was first described in 1753 by Linnaeus and is a rosette-forming succulent, evergreen and perennial plant, which spreads by offsets. It is an extremely diverse plant, in particular regarding the diameter of the rosette, width, color and type of escalation of the rosette leaves.

Sempervivum tectorum in Central Europe exists also in other synonyms: *alpinum* and *schottii*. It can grow up to 15 cm tall by 50 cm wide and develops grey-green, tufted, sessile leaves, with a diameter of about 4-10 cm, which are often suffused with rose-red. In summer *Sempervivum* bears clusters of reddish-purple flowers, in multiples of 8-16, on hairy erect flat-topped stems [2, 3].

3.2. Use

Historically, houseleek (*Sempervivum tectorum* L.) leaves were used as a medicinal herb for external treatment of injuries, burns, rashes, open wounds, bee or insect stings, burns, sore nipples, corns, freckles, throat infections, uterine neuralgia, dysplasia and amenorrhea, against catarrhs of the eyelids, canker sores, fungal infections in the mouth, headaches, chapped or cracked skin, deafness, ear pain, and as a vermifuge and febrifuge. Houseleek leaves are used in tooth holes against toothache. Houseleek juice was used to treat eye infections. The plant is also sometimes used internally in the treatment of dysentery. The effectiveness of the drug has not been proven in mentioned application areas [1]. The Commission D of German BGA/BfArM mention *Sempervivum tectorum* as a treatment against nodular hardening in the skin, tongue and nipples, and additionally against warts [21].

Modern research confirmed *Sempervivum tectorum* juice for treating ear pain. The juice possessed antimicrobial activity towards clinical isolates of bacteria linked to otitis [4]. Furthermore study data mention antinociceptive, cooling, astringent effects, antioxidant activities of *Sempervivum tectorum* extracts [5, 6, 7].

Additionally, houseleek is used as a spice or salad. Leaves and young shoots can be eaten in a salad or as additive to drinking water, giving a refreshing taste, common in the Swiss canton of Grisons [1].





3.3. Content

The drug *Sempervivum minoris folium* is also known under the following synonyms: *Folia Sedi magni*, *Folia Sempervivum majoris* and *Herba sempervivi tectori*. The main component of the houseleek leaf are L-malic acid and their calcium salts. Dried leaves contain about 5.3 – 9.7% isocitric acid [1]. Polyphenol, tannin, proanthocyanidine and flavonoid contents of lyophilized houseleek leaves were determined by spectrophotometry. Numerous catechin and proanthocyanidine compounds and main flavonoids aglycone and kaempferol were identified [8]. In another study, ten flavonol glycosides and sixteen phenolic acid compounds were detected. Three kaempferol glycosides were quantified which may reduce sensitivity to painful stimuli [5].

4. Dermatological activities of houseleek extracts

4.1. Houseleek extract is an agonist of cannabinoid receptor type 1

Cannabinoid signaling is mentioned for regulating the permeability barrier and epidermal differentiation. Cannabinoid receptor type 1 in keratinocytes help to maintain epidermal barrier homeostasis and attenuate Th2-type allergic inflammatory responses [20]. The houseleek test results demonstrate its agonistic activity. A study by Ständer et al. about cannabinoid agonists mention a mast cell stabilizing function which helps against itching and inhibits histamine secretion [20]. This research indicates that houseleek leaf extract may be a powerful active ingredient to treat sensitive skin.

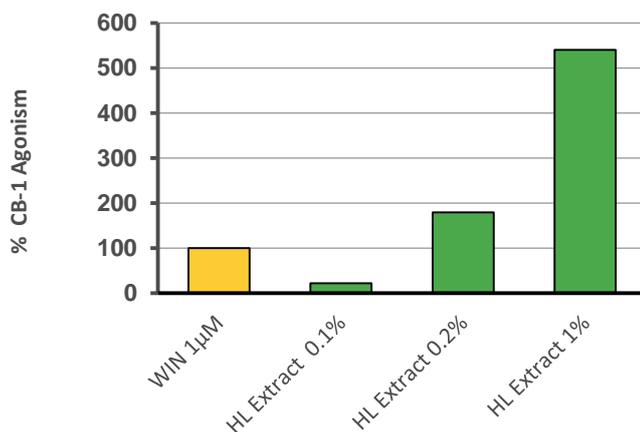


Fig.1: Houseleek leaf extract (HL Extract) showed cannabinoid receptor type 1 (CB-1) agonistic activity. WIN-55,212-2 (WIN), a cannabinoid receptor type 1 agonist, is used as positive control.





4.2. Houseleek leaf extract enhances glucose uptake in HaCaT keratinocytes

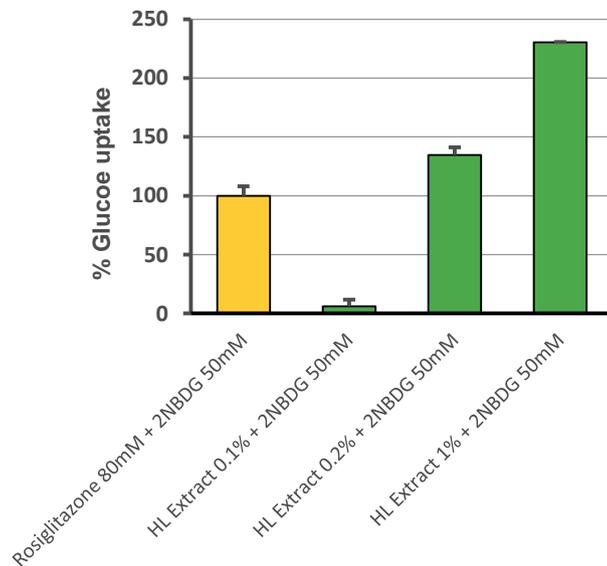


Fig.2: Houseleek leaf extract (HL Extract) showed increased glucose uptake in keratinocytes. Rosiglitazone + 2NBDG is the positive control.

Glucose plays a role in the energy metabolism of keratinocytes. It is associated with cell regeneration and renewal. Houseleek leaf extract induces glucose uptake in keratinocytes in a dose-dependent manner. Houseleek leaf extract 0.2% and 1% concentrations demonstrate a glucose stimulation. The 0.2% houseleek leaf extract concentration stimulates the glucose uptake significantly 30.4% more than positive control. The 1% houseleek leaf extract significantly increases glucose uptake up to 130.4%. This results may be useful in reversing dried, aged skin conditions to promote healthy regenerated skin.

4.3. Houseleek leaf extract is a PPAR α and PPAR γ agonist

Peroxisome proliferator-activated receptors PPAR α and PPAR γ are transcription factors that belong to the nuclear hormone receptor family. PPAR α seems to contribute to the skin barrier function, activation of β -oxidation of fatty acids, regulation of inflammation, and to play a role in cell differentiation, proliferation and skin wound healing [16, 17]. PPAR γ activates cell development (proliferation) and lipogenesis. PPAR γ is also involved in oxidative stress and wound healing [18].

Topical treatment with a PPAR α agonist had a positive effect on atopic dermatitis and stimulated sebaceous lipid production. PPAR α activators or compounds that positively regulate PPAR α gene expression may help to counteract ageing processes and can reduce the adverse effects of UVB [19].



PPAR γ agonists are known to have anti-fibrotic properties, which is characterized by inhibition of pulmonary myofibroblast differentiation and collagen production. These effects are in part induced by transforming growth factor β , leading to an activation of fibroblasts with increased collagen production and expression of cell surface receptors for growth factors [19].

Houseleek leaf extract is a PPAR α agonist which can assist in a cosmetic formulation for anti-aging, skin moisturizing, and a PPAR γ agonist which can assist for anti-wrinkle and refirming effects.

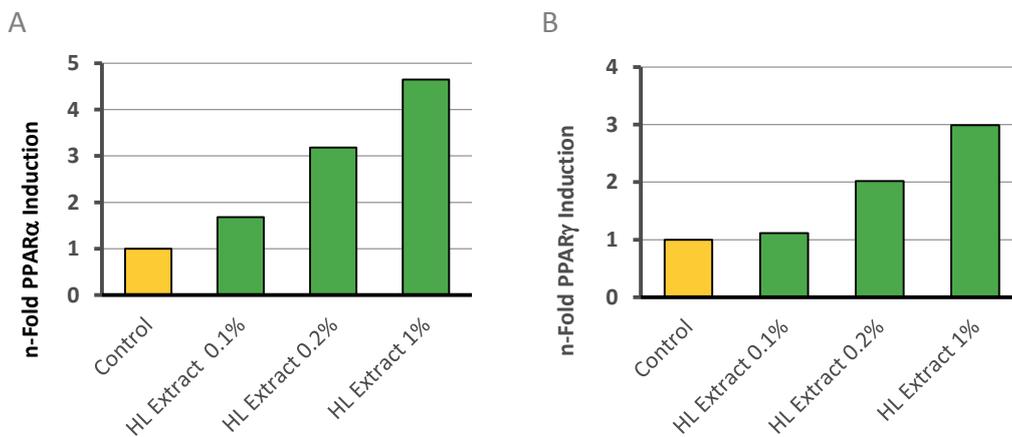


Fig.3: A) PPAR α activation. B) PPAR γ activation. Untreated skin cells (Control) are set as 1. Houseleek leaf extract (HL Extract) shows agonistic effects for PPAR α and PPAR γ in a concentration dependent manner.

4.4. Houseleek leaf extract activates the Nrf2 pathway

The transcription factor Nrf2 is known for cellular anti-oxidant defense, the activation of this transcription factor is a promising strategy to protect skin cells from environmental influences [9]. Nrf2, in keratinocytes and melanocytes, protects these cells against mutation during the keratinization and melanogenesis process. Moreover, Nrf2 involvement in wound healing and inflammation inhibition is also essential for maintaining intact and healthy skin [10].

Houseleek leaf extract stimulates the Nrf2 pathway in a concentration dependent manner. The highest effect, a 3-fold induction, is observed with 1% houseleek leaf extract. Anti-oxidative activities of houseleek leaf extract should facilitate preventing skin dryness, reducing the elastin and collagen breakdown caused by excess oxidative stress. These results indicate the potential use of houseleek leaf extract containing cosmetic formulations for anti-ageing, sun care, skin repair and moisturizing products.



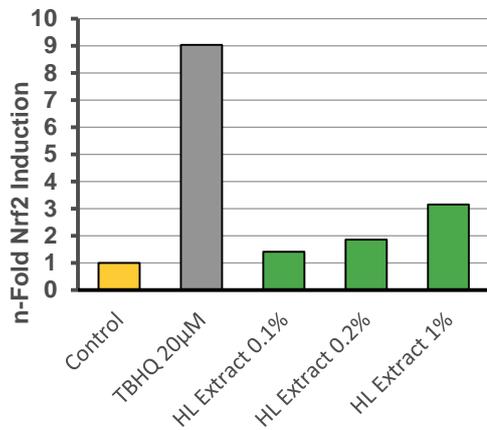
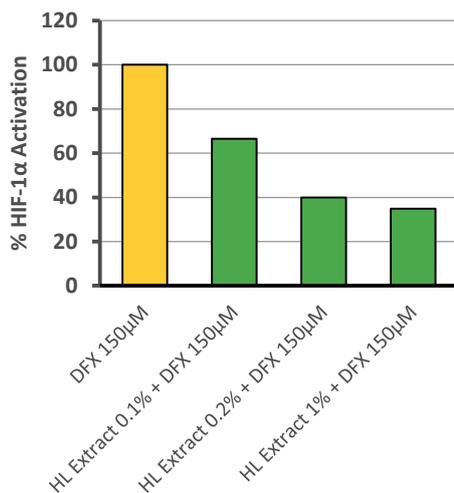


Fig.4: Houseleek leaf extract (HL Extract) slightly activated the Nrf2 pathway in HaCaT-ARE-Luc cells at the highest tested concentration. HaCaT-ARE-Luc cells were treated with HL Extract. Luciferase activity was measured in the cell lysates and results are represented as the n-fold induction over basal levels. Tert-Butylhydroquinone (TBHQ) is used as positive control. Untreated cells (Control) are set as 1.

4.5. Houseleek leaf extract inhibits HIF-1α activity

High levels of transcriptional regulator hypoxia-inducible factor 1 alpha (HIF-1α) are expressed in epidermis which could reflect its important role in local and systemic adaptation to environmental stresses. HIF-1α is an essential mediator of O₂ homeostasis and regulates cutaneous angiogenesis, it controls inflammatory and innate immune responses, modulates skin responses to sunlight by affecting the DNA repair machinery, apoptosis, and the tumorigenic processes. Increased HIF-1α lead to delayed wound healing [11, 12]. Houseleek leaf extract inhibits the DFX induced HIF-1 activation in fibroblasts and keratinocytes. HIF-1α inhibiting strategies can offer a useful addition to current treatments of inflammatory, degenerative skin states [13].

A) Fibroblasts



B) Keratinocytes

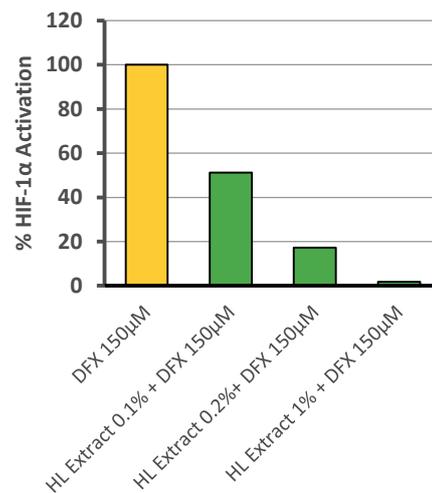


Fig.5: Houseleek leaf extract (HL-Extract) was able to inhibit DFX-induced activation HIF-α of EPO-Luc in fibroblasts (A, left) and keratinocytes (B, right) in a concentration dependent manner. Hypoximimetic desferrioxamine (DFX) was used as positive control. Fibroblasts or keratinocytes were pre-incubated with houseleek leaf extract and treated with the DFX.





4.6. Houseleek leaf extract shows an antagonistic activity against TrPV1

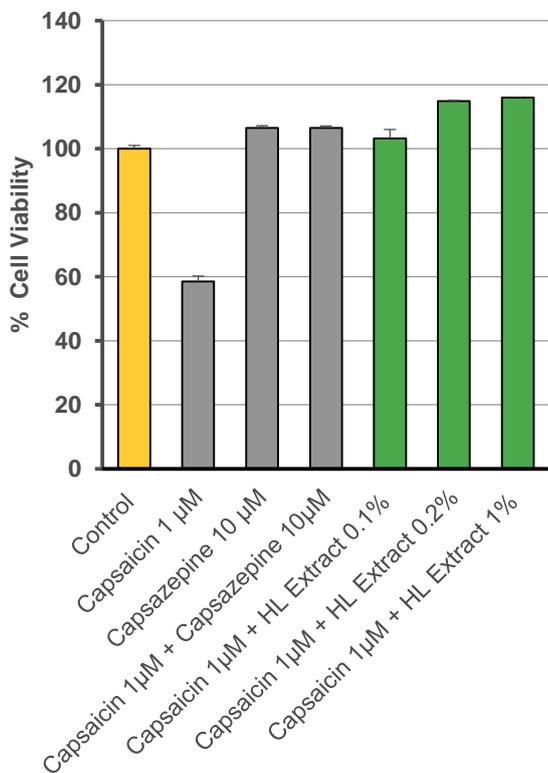


Fig.6: TrPV1 showed antagonistic activity, while houseleek leaf extract (HL Extract) did not demonstrate agonistic activity. The TrPV1 channel is activated by oxidative stress and capsaicin and it is blocked by capsazepine. Capsaicin stimulated TrPV1 and is a negative control. Capsazepine is used as the positive control of TRPV-1 antagonism. Untreated cells (Control) are set as 100%.

TRP channels are involved in cell homeostasis, survival and proliferation, endocrine and exocrine secretory processes and immune as well as inflammatory mechanisms. TRP channels are stimulated by external environmental factors like UV light, cold, heat, air pollution and chemical substances. They play a role in the recognition and physiology of sensitive skin. TrPV1, is among other stimuli activated by capsaicin [14]. TrPV1 inhibitors are described to have skin-aging prevention, wrinkle improvement and skin-whitening features, and seem to alleviate inflammation, irritation or pain [15]. This research data demonstrate antagonistic activity against TrPV1 by houseleek leaf extract treatment. The houseleek leaf extract may be beneficial in the treatment of wrinkles or fine lines, sensitive and sun damage skin.



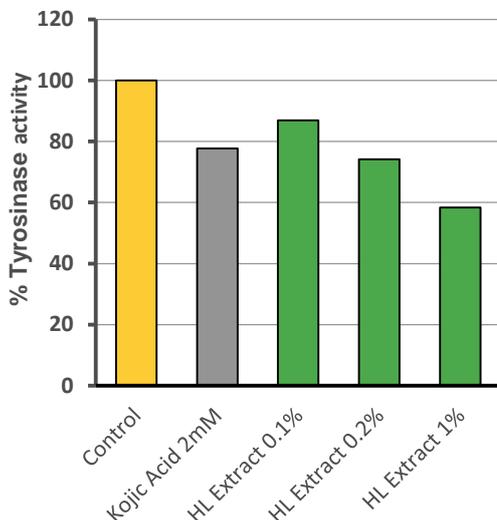


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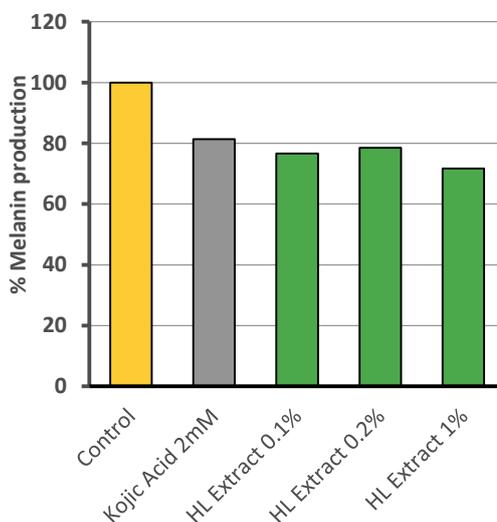
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4.7. Skin lightening effect by houseleek extract treatment



Houseleek leaf extract treatment showed an inhibitory effect on tyrosinase. The inhibitory effects were dose-dependent and higher than that of kojic acid, a well-known tyrosinase inhibitor. These results indicate that houseleek leaf extract is a potent tyrosinase inhibitor, which could be used in skin whitening products. Houseleek leaf extract could be beneficial to protect sensitive and sun exposed skin.

Fig.7: Effect of houseleek leaf extract (HL Extract) on tyrosinase activity in B16 melanoma cells. Cells were treated with houseleek leaf extract or kojic acid as a positive control. Results are represented as percentage. Untreated control cells (Control) are set to 100%.



Houseleek leaf extract inhibits melanin synthesis comparable to kojic acid. This confirms the skin-lightening abilities of houseleek leaf extract.

Fig.8: Effect of houseleek leaf extract on melanin synthesis in B16 melanoma cells. Melanin content assessment was performed as described in Methods. Briefly, cells were treated with the doses indicated of kojic acid as a positive control. Results are represented as percentage. Untreated control cells (control) are set to 100%.

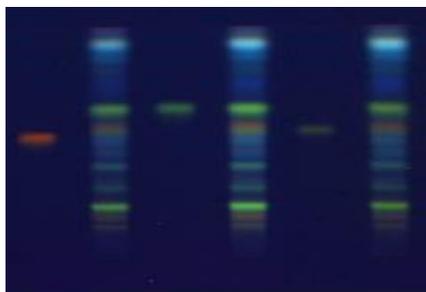


4.8. Summary dermatological activities

	Sensitive skin	Regeneration	Anti ageing	Moisturising	Sun care	Skin-lightening whitening	Collagen	Anti-wrinkle	Refriming	Skin repair	Anti cellulite	Wound healing
Cannabinoid receptor type 1	X											
Glucose uptake		X	X	X		X						
PPAR alpha agonist			X	X								X
PPAR gamma agonist			X			X	X	X				X
Transcription factor Nrf2			X	X	X				X			X
HACAT: Hypoxia-inducible factor 1 alpha				X				X			X	
Fibroblasts: Hypoxia-inducible factor 1 alpha								X			X	
TrPV1	X		prevention		X			X				
Tyrosinase inhibitor	X				X	X						
Melanin synthesis inhibitor						X						

5. Screening

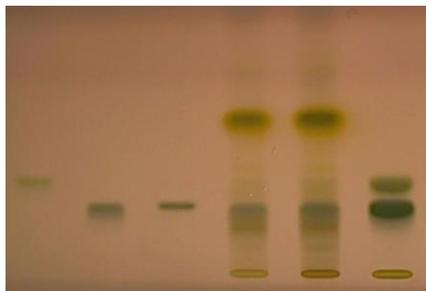
Flavonoid- „Screening“:



Track	Description
1	Hyperosid
2	Houseleek Bio Extract (CH)
3	Kaempferol-3-Glucosid
4	Houseleek Bio Extract (CH)
5	Luteolin-4-Glucosid
6	Houseleek Bio Extract (CH)

As described in section 3.3., Houseleek contains a lot of flavonoids which can be beautifully demonstrated in the HPTLC Fingerprint above. The reduction of sensation of pain is attributed to the content of Kaempferol-glycosides.

Carbohydrate-„Screening“:



Track	Description
1	Glucose
2	Fructose
3	Saccharose
4	Houseleek Bio Tincture (CH)
5	Houseleek Bio Tincture (CH) (20)
6	Aloe Vera Bio Leaf Juice Tincture

It can be demonstrated that houseleek is rich in various carbohydrates, comparable to Aloe vera leaf juice. The concentration and distribution varies, of course, but both plants offer a healthy portion of nutrients for the skin.

6. Acknowledgement

We would like to thank VivaCell Biotechnology GmbH and SimCosmetic Biotech for testing the houseleek leaf extract.

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