ACTIVE BEAUTY

Silybidiol™

The CBD challenger against urban pollution

Skin guard / Detox -Destress

Givaudan

Human by nature

Focus on the product

Exposome, OxInflammation and pre-ageing

The perception of skin care protection and ageing has recently shifted to a more positive and resilient approach called "pre-ageing."[1] This emphasizes taking care of ourselves and embracing our individual beauty, focusing more on prevention and overall well-being, recognising the connection between emotional well-being and skin conditions leading to healthy longevity.

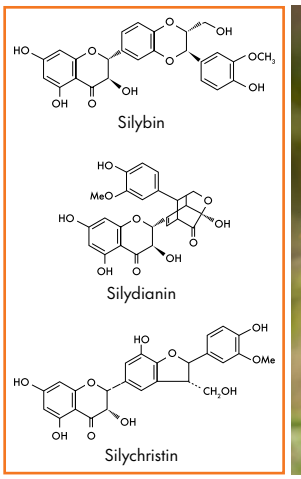
In this regard, the exposome represents the ensemble of extrinsic aggressors to our skin, specifically challenging skin health and longevity. UV radiation and pollution are its two major contributors, leading to the disruption of the delicate OxInflammation balance, the fragile interconnection of two key biological pathways. Furthermore, they have a potentially cumulative detrimental effect on our skin health, and even on our emotional balance.

The superpower of traditional medicinal plants: Milk thistle

At the heart of Silybidiol™ lies the incredible power of milk thistle and its key components silybin, silydianin and silychristin, a phytocomplex known as silymarin. For centuries, milk thistle (*Silybum marianum*) has been revered in traditional medicine for its numerous health benefits. Extracted from its fruits, silymarin is a flavonoid complex renowned for its exceptional antioxidant, detox and anti-inflammatory properties. Silybidiol™ reveals the new power of silymarin.

When applied topically, it effectively combats oxidative stress caused by environmental factors like pollution and UV radiation, which can accelerate ageing and damage the skin and its healthy longevity.

Silybidiol™ has been proven to efficiently protect our skin from the exposome challenge by activating the cannabinoids receptor pathways and protecting the delicate crosstalk at the base of the OxInflammation balance.



Silybidiol™

Silybidiol™ as CBD alternative on OxInflammation balance and well-being

The exposome components (pollution and UV) have an additive and detrimental action on skin health by interacting with the AhR (Aryl Hydrocarbon Receptor), which triggers inflammation and the production of ROS (Reactive Oxygen Species). These two pathways are closely connected and represent the fragile OxInflammation balance. Disrupting this crosstalk leads to dull and uneven skin tone.

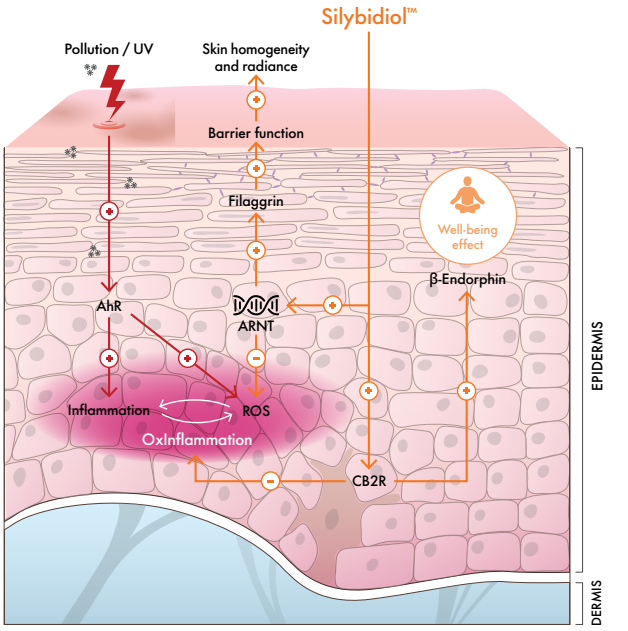
Silybidiol™ **acts as a CB2 agonist:**

- Reducing inflammation.
- Boosting the production of beta endorphins, well-being peptides.

At the same time, Silybidiol™ **promotes functional cellular crosstalk:**

- Stimulating phase 2 cellular oxidative and detox defenses (Nrf2↑).
- Promoting an enhanced skin barrier function (FLG↑).

These benefits promote a healthy OxInflammation balance, resulting in an ameliorated skin tone and well-being, all thanks to Silybidiol™.



[1] Jimenez, In Cosmetics Marketing Trends, 2021

Biological activity

Silybidiol™ is active on the cannabinoids pathways

1. Activation of CB2R in cellular functional assay (*in vitro*)

The activation of CB2R by the benchmark Cannabidiol (CBD) or Silybidiol™ has been evaluated on Human CB2R (cannabinoid type 2 receptor, type GPCRi).

The activation of CB2R was evaluated by the measurement of cAMP (CB2R response) by TR-FRET luminescent methodology.

Compound	EC50* (µg/mL)
Silybidiol™	76 µg/mL calculated as pure molecule
CBD	55.4 µg/mL

*Effective concentration activating 50% of the receptors

Results: Silybidiol™ has shown a similar agonist effect on CB2R compared to CBD.

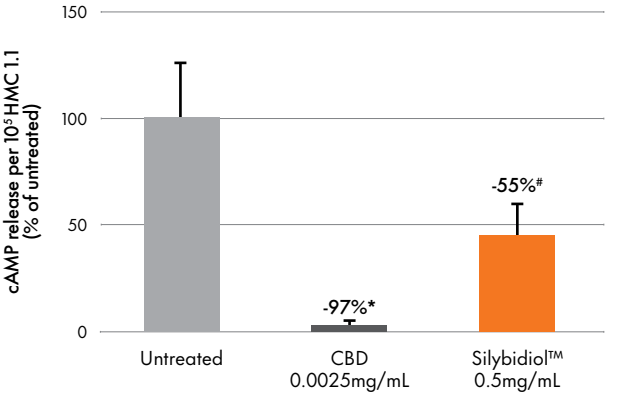
2. Activation of CB2R in mast cells (*in vitro*)

The CB2 receptor is present in keratinocytes and mast cells, where it is involved in the regulation of skin barrier function and homeostasis. Mast cells were treated with the benchmark CBD (0.0025mg/mL) or Silybidiol™ (0.05 mg/mL).

cAMP release was evaluated by ELISA method as a measurement of CB2R activation: when CB2R is activated, it inhibits adenylate cyclase enzyme thus reducing the conversion of ATP in cAMP.

Results: Both Silybidiol™ and CBD activate the CB2R present in the mast cells, as demonstrated by the lower release of cAMP.

Activation of CB2R



Mann-Whitney test: #p<0.1, *p<0.05

3. Release of beta-endorphin (*in vitro*)

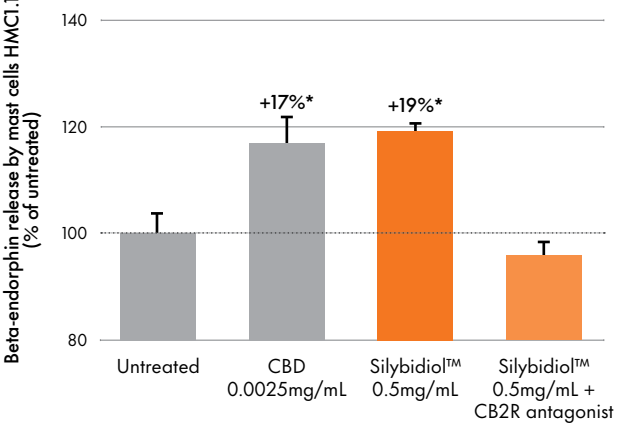
The activation of the CB2 receptor is one of the known pathways of beta-endorphins release. Mastocytes have been treated for 16 hours with the benchmark CBD (0.0025mg/mL) or Silybidiol™ (0.05 mg/mL). Other mastocytes have been treated with a CB2R antagonist (SR1 44528) before to be treated with Silybidiol™ for 16 hours.

Beta-endorphin release has been evaluated by ELISA methodology.

Results: Silybidiol™ increased beta endorphin release by 19%* via the CB2R pathway, equivalent to CBD, suggesting a similar potential effect in well-being boosting.

The activation on the CBD2 pathway was demonstrated by the different activation in presence of the CB2 antagonist.

Release of beta-endorphin



Mann-Whitney test: *p<0.05

Biological activity

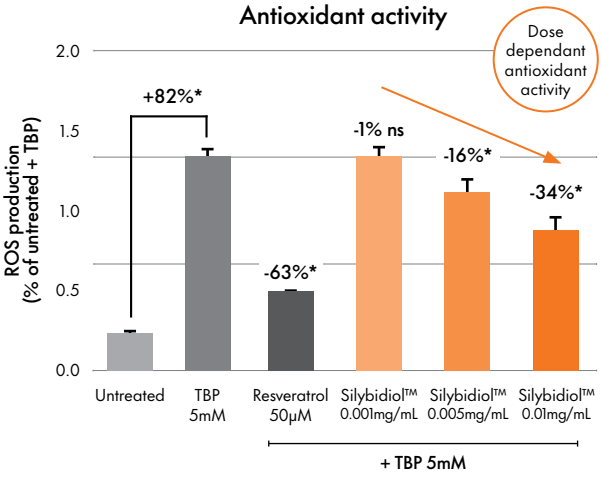
1. Antioxidant activity (*in vitro*)

Reactive Oxygen Species (ROS) formation and antioxidant defenses are part of the OxInflammation crosstalk.

Normal human keratinocytes (NHEK) were pre-treated with Silybidiol™ from 0.001 to 0.01 mg/mL for 24h (resveratrol at 50µM as positive control); a chemical stress was then induced with TBP 5mM to trigger ROS production (24h).

Oxidative stress was measured by the fluorescent detection of intracellular ROS using DCFH-DA probe.

Results: Silybidiol™ **reduced the formation of ROS** in a dose dependent manner, up to -34%* (at 0.01mg/mL).

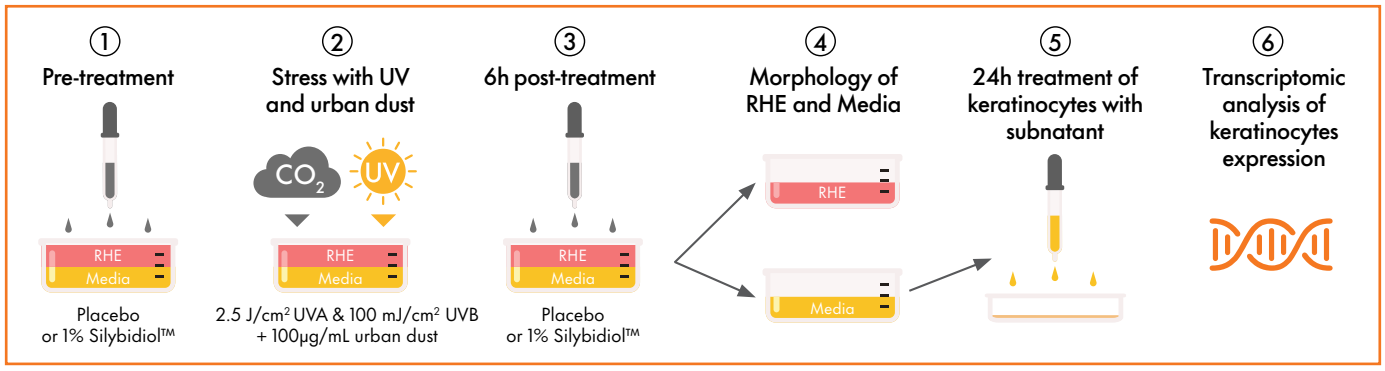


Mann-Whitney test: *p<0.05, ns: not significant

2. Silybidiol™ restores the OxInflammation balance

Maintaining the crosstalk balance, the way different biological pathways influence one another, is key to skin health. Reconstructed Human Epidermis (RHE) was pretreated with a formula* containing Silybidiol™ at 1% (24h) or a placebo, then submitted to the damaging action of the exposome (UV + urban dust).

After the following experimental procedure was applied (see figure below), epidermis has been observed and morphological modifications were evaluated. At the same time, the culture media of the epidermis has been used to treat keratinocytes, and their gene expression evaluated by a transcriptomic analysis.



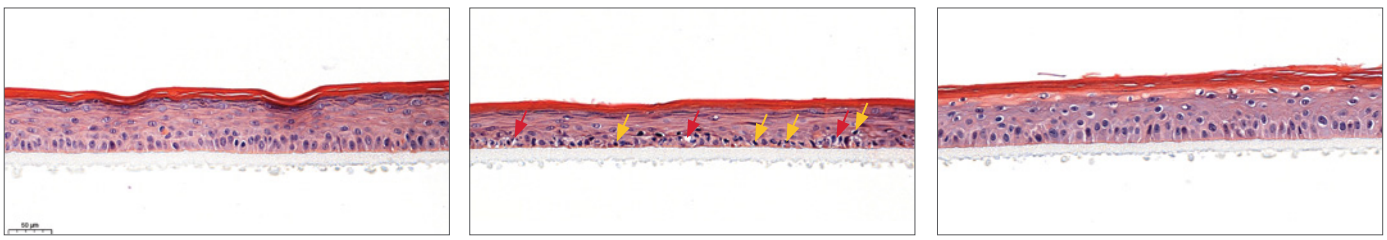
*INCI formula: Aqua/Water, Cetyl Alcohol, Glyceryl Stearate, Peg-75 Stearate, Ceteth-20, Steareth-20, Isodecyl Neopentanoate, Pentylene Glycol, Phenoxyethanol

2.1 Silybidiol™ protects the cells crosstalk (RHE)

a. Reduction of inflammation

Silybidiol™ at 1% has induced a **strong decrease of two morphological signs of skin damage**, evaluated by hematoxylin staining:

- Formation of pycnotic nuclei (irreversible condensation of chromatin and the nucleus, occurring as a sign of apoptosis).
- Spongiosis (morphological indication of inflammation).



Untreated | Exposome: UVA/B - Dust | Exposome + Silybidiol™ 1%

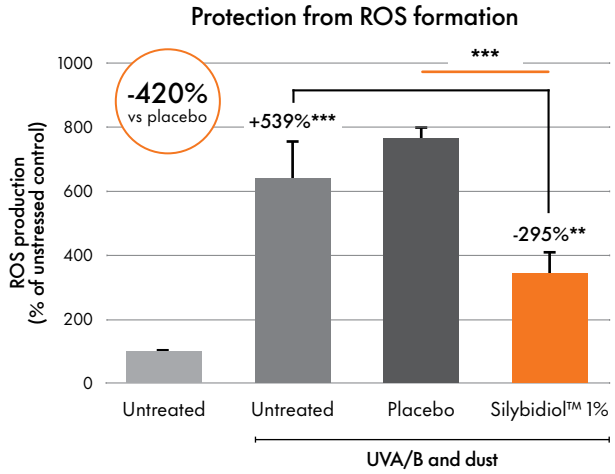
Spongiosis — Pycnotic nuclei

Biological activity

b. Antioxidant activity by ROS inhibition

ROS production was quantified by fluorescence DCFH-DA after 6h.

Results: Silybidiol™ at 1% reduced the formation of ROS by -295%**, suggesting a protective activity from exposome-induced damage in reconstructed epidermis.

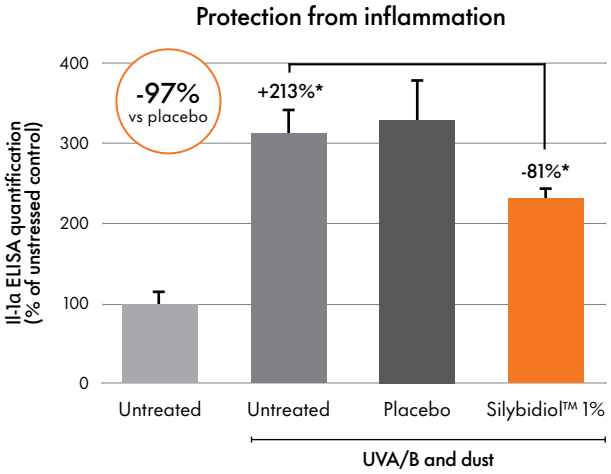


Mann-Whitney test: **p<0.01, ***p<0.001

c. Soothing activity by reduction of pro-inflammatory markers

The release of the pro-inflammatory marker IL-1a was quantified by ELISA methodology after 6h.

Results: Silybidiol™ at 1% reduced the release of IL-1a by 81%*, indicating a protective activity from exposome-induced inflammation in reconstructed epidermis.



Mann-Whitney test: *p<0.05

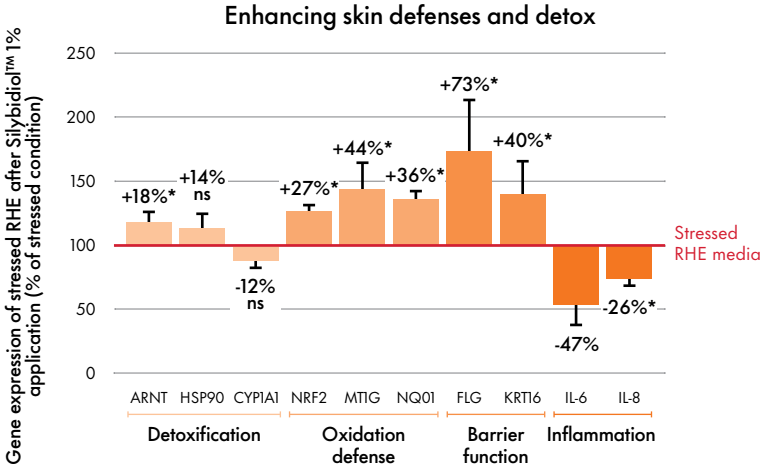
2.2 Transcriptomic analysis: how are epidermis and dermis interconnected?

The media of the RHE was used as the conditioned media for keratinocytes, a transcriptomic analysis by RT-qPCR method was performed on gene expression with a focus on AhR and NRF2 pathways, the main regulation mechanisms of cells protective responses to environmental stress.

Results: Silybidiol™ has activated the crosstalk that led to the overexpression of genes:

- Activating the detox processes (ARNT vs exposome).
- Endogenous antioxidant systems (MT1G, NQO1).
- Boosting the skin barrier function (FLG, KRT16).
- Reducing inflammation (IL-6, IL-8).

Silybidiol™ **enhanced the oxidative stress defence of the cells**, improved the **barrier function** related mechanisms and has shown a **strong anti-inflammatory** effect.



Mann-Whitney U test: *p<0.05, #p≤0.1, ns: not significant

Efficacy

Silybidiol™ improves skin tone homogeneity and radiance better than CBD

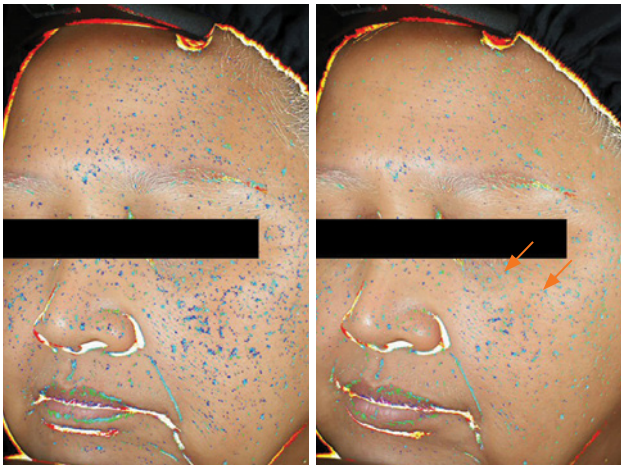
A panel of 68 women aged from 45 to 75 years old selected for their dull complexion and uneven skin tone according to the CLBT scale[2] was divided in 3 groups.

Group 1 (23 volunteers) applied a cream containing Silybidiol™ at 1%, group 2 (23 volunteers) applied a cream containing CBD at 0.02% and group 3 (22 volunteers) applied the placebo cream twice a day during 56 days. The test was conducted in Thailand, where volunteers were exposed to UV and urban dust.

The skin tone homogeneity and radiance were evaluated by Visia CR2.3®, darker blue marks indicate less contrasted skin colour dishomogeneity, light blue marks indicate stronger dischromia*.

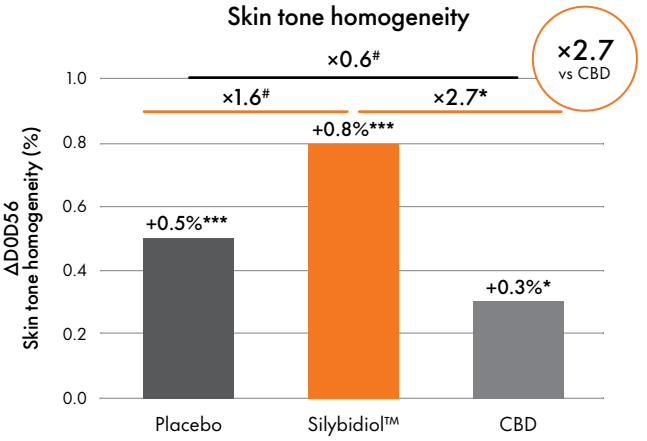
Results: Silybidiol™ **significantly improves skin tone homogeneity** both versus placebo and positive benchmark CBD (x2.7 vs CBD) and **skin radiance** versus CBD by x1.6. The skin colour and tone is much more even.

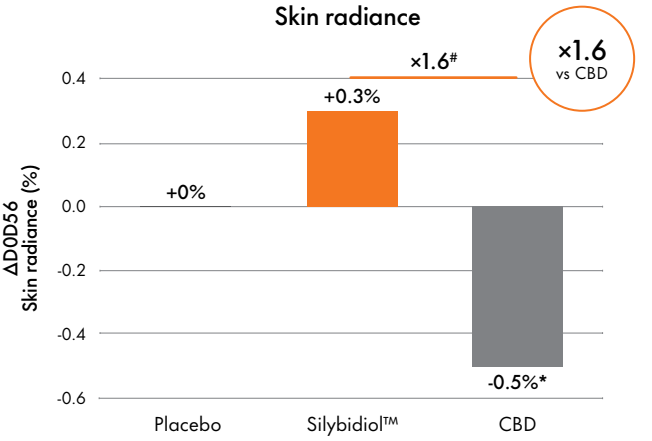
Representative pictures of volunteers using Silybidiol™ at 1%



D0 D56

*heterogeneity is indicated by blue spots: light blue representing the highest contrast to dark blue representing the lowest contrast.



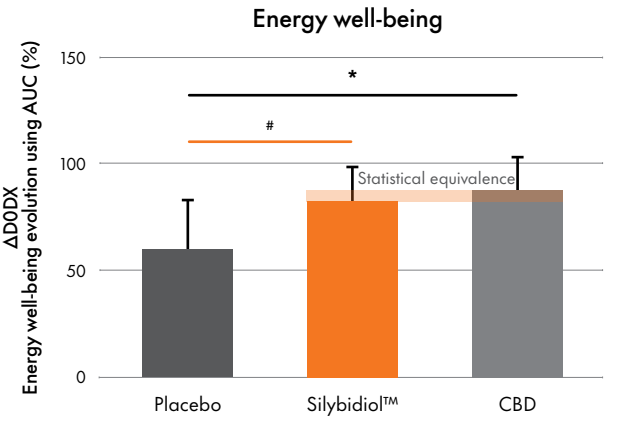


Wilcoxon test vs. D0, Mann-Whitney test vs. placebo: #p<0.1 #, *p< 0.05, ***p<0.001

Silybidiol™ enhances well-being as good as CBD

The same panel completed a self assessment wellness questionnaire (W-BQ) and the parameter related to energy was evaluated.

Results: Silybidiol™ **significantly improves energy well-being, triggering a positive mood dynamic**, in a similar manner than CBD.



Mann-Whitney test : #p<0.1, *p< 0.05, ns: not significant

2. CLBT scale: Color, Luminosity, Brightness, Transparency

Summary

Technical information

INCI:	Silybum Marianum Fruit Extract
Origin:	Green Fractionation
Preservation:	None
Appearance:	Yellowish powder
Solubility:	Soluble in pentylene glycol at 60°C
Dosage:	Up to 1%
Processing:	In solution, add the premix at the end of the formula. In cream, disperse Silybidiol™ in pentylene glycol (ratio 1:5) at 45°C and add it just after the emulsion at 60°C.

Claims

Claims:	CBD alternative, protects from exposome, boosts well-being, antioxidant, anti-inflammatory, skin tone evening, counteracting dull skin, boosting radiance, antipollution.
Applications:	Protection from exposome, day creams, CC creams and foundation, primers, skin radiance, skin homogeneity serums.

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