論文 EyesOn

01

The Science of Skin Longevity: Fasting-mimicking Plant Biotechnology Redefining Glass Skin

Ò. Expósito, M. Buchholz, V. Vidal, A. Gallego, S. Ruiz, P. Riera, D. Luna, M. Mas, M. Gibert, L. Cano, S. Laplana, T. Ruiz, R. Ferreira, A. Guirado

Vytrus Biotech harnesses this principle through a novel cosmetic approach: the fasting-mimicking strategy. This innovation supports the emerging concept of skin longevity, which moves beyond conventional anti-aging by targeting biological aging itself – striving to maintain both skin function and aesthetic quality over time.

Scientific studies on intermittent fasting and caloric restriction have revealed the modulation of key cellular longevity pathways, including reduced insulin/IGF-1 signaling, enhanced autophagy and DNA repair, diminished chronic inflammation, and sustained telomere integrity [1-5].

Applying these insights to skincare, Vytrus introduces a fasting-mimicking paradigm that activates similar protective and regenerative mechanisms in skin cells – ushering in a new era of dermocosmetic innovation focused on sustained skin health and rejuvenation (Tab. 1).

■Tab. 1 Comparison between the effects of fasting and metformin on ageing markers.

Aging Process	Fasting-Induced Effect
Oxidative Stress & Inflammation	Reduces ROS levels & inflammation, preserving skin health.
Senescence (Cellular Aging)	Prevents premature aging by removing damaged cells.
Mitochondrial Dysfunction	Enhances mitochondrial function for sustained energy production.
Loss of Collagen & Elastin	Stimulates fibroblast activity, maintaining skin structure.
Pigment Accumulation (Lipofuscin & Melanin)	Reduces cellular waste buildup for an even skin tone.
Telomere Shortening	Protects telomeres, extending cellular lifespan.

Plant-Inspired Resilience: Crafting a Fasting-Mimicking Secretome for the Skin

Building on the growing scientific understanding of fasting's systemic benefits, Vytrus Biotech has pioneered an innovative approach that translates these biological insights into dermocosmetic application. The result is Clarivine™, a next-generation biotechnological active designed to replicate the cellular responses associated with fasting – directly within the skin.

This strategy leverages nature's adaptive intelligence, aiming not only to visibly enhance skin luminosity and resilience but also to stimulate deep-rooted mechanisms of cellular renewal and longevity. Clarivine™ acts at the intersection of aesthetic performance and biological function, targeting key markers of skin health and age-related decline.

Clarivine™ is derived from *Vitis vinifera* stem cells – a long-lived, perennial species known for its regenerative potential and metabolic adaptability. Under rigorously controlled conditions, these plant cells are cultivated in a nutrient-restricted environment that simulates intermittent fasting. This controlled deprivation elicits a hormetic response: a positive biological adaptation to mild stress that activates survival programs and initiates the production of a fasting-induced secretome. This complex bioactive matrix is enriched in longevity-supporting molecules such as resveratrol, biopeptides, and signaling compounds, all naturally encapsulated in plant exosomes for enhanced delivery and effectiveness (Fig. 1).

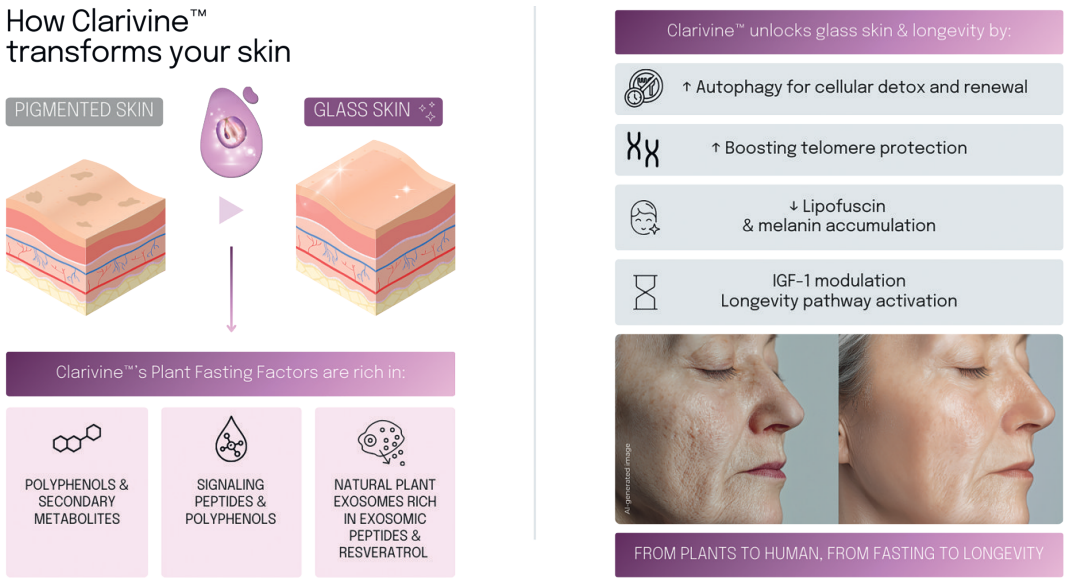
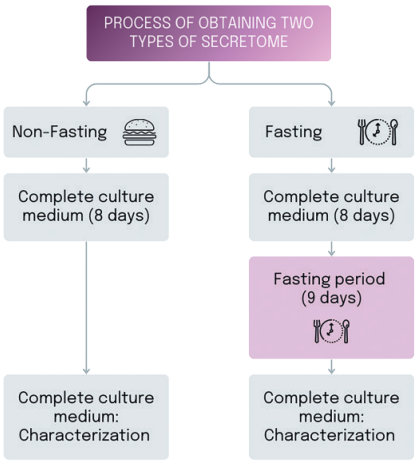


Fig. 1 Bioactive profile of *Vitis vinifera* fasting-mimicking secretome

■Tab. 2 **Fasting-induced changes in *Vitis vinifera* secretome. Comparison of key compound production and metabolic markers**



	Non-Fasting Secretome	Fasting Secretome	Change %
Antioxidant capacity (%)	27.14	48.63	+21.5%
Resveratrol (mg/L)	2.25	4.05	+80%
Polyphenols (mg/L)	226.46	673.78	+197%
Peptides (mg/L)	491.18	1158.63	+136%
Proteins (mg/L)	128.67	79.80	-45%
Total sugars (g/L)	14.90	13.74	-8%

As part of this development, Vytrus Biotech implemented a specialized protocol where *Vitis vinifera* stem cells undergo metabolic conditioning under fasting-like conditions. This process stimulates the cells to shift into a resource-conserving mode, initiating recycling mechanisms and activating longevity pathways – mimicking the physiological effects observed in caloric restriction models [6) 7)].

To validate this approach, a comparative metabolic profiling was performed between secretomes from fasted versus non-fasted cultures. Key metrics included the levels of peptides, proteins, sugars, polyphenols, and resveratrol, as well as their overall antioxidant potential (Tab. 2).

The analysis confirmed that the fasting condition significantly enhanced the antioxidant profile of the secretome, with notable increases in polyphenols (especially resveratrol) and peptide content. Resveratrol, in particular, has been well documented for its dual role as an antioxidant and a modulator of key cellular processes tied to longevity, calorie restriction, and inflammation management [8-11)].

Clarivine™'s unique value lies in the rich composition of its secretome, characterized by four main bioactive pillars:

- Polyphenol-rich matrix: the fasting-triggered secretome features a robust concentration of antioxidant polyphenols, including resveratrol. These compounds are critical for neutralizing oxidative stress, supporting cellular longevity, and preserving skin integrity over time [17)].
- Abundance of plant-derived peptides: naturally secreted signaling peptides and proteins

play essential roles in cellular communication and skin renewal. These molecules aid in maintaining epidermal balance, enhancing regeneration, and reinforcing the skin barrier.

- High-density natural exosomes: the bioprocess yields an exceptionally concentrated population of plant-derived nanovesicles – measured in the range of millions per milliliter. These exosomes protect and transport the bioactive compounds, facilitating precise delivery and improved absorption by skin cells.
- Exosomic resveratrol a breakthrough innovation by vytrus, this form of resveratrol is naturally encapsulated within plant exosomes during the fasting-mimicking process. It serves as a potent cellular modulator, activating longevity pathways and enhancing bioavailability – amplifying its regenerative and protective effects within the skin.

Collectively, these findings underscore how strategic nutrient deprivation can reprogram plant cell metabolism to yield a highly potent bioactive profile. Among the resulting compounds, resveratrol emerges as a cornerstone ingredient – not only due to its antioxidant strength but also for its role in cellular signaling, promoting pathways that enhance skin vitality, regeneration, and long-term resilience.

Biological Activity (*in vitro* Assays)

A comprehensive series of *in vitro* studies was conducted to validate how Clarivine™'s Plant Fasting Factors enhance resource optimization and modulate longevity-related biomarkers.

Human dermal fibroblasts (HDFs) and senescent melanocytes were subcultured for two months under different conditions: control, with a known hypoglycemic agent (C+; metformin), and Clarivine™ at different concentrations (0.65% and 2.5%). Key findings underscore the biomimetic potential of Clarivine™ to induce metabolic optimization and regeneration in skin cells by means of the activation of the following longevity pathways:

- **IGF-1 modulation:** Treatment with Clarivine™ led to a significant modulation in IGF-1 secretion in HDF cultures, indicating a metabolic shift that mirrors caloric restriction [12-14]. While a modulation of up to 60% in IGF-1 levels was observed, this result suggests a potential downstream activation of FOXO pathways, which are known to regulate DNA repair, oxidative stress resistance, and longevity-associated gene expression [15) 16)].
- **Autophagy activation:** The conversion of LC3-I to LC3-II, a widely accepted marker for autophagic flux, was significantly increased upon Clarivine™ exposure comparable to hypoglucemic effects of metformin (C+) (Fig. 2).
- **Telomere protection:** Extended culture studies in HDFs revealed stabilization of telomere length in Clarivine™ treated cells, suggesting a protective role against replicative senescence.
- **Protection against senescence:** Enhances cellular recycling, reducing senescence markers like SA-β-galactosidase (Fig. 3).

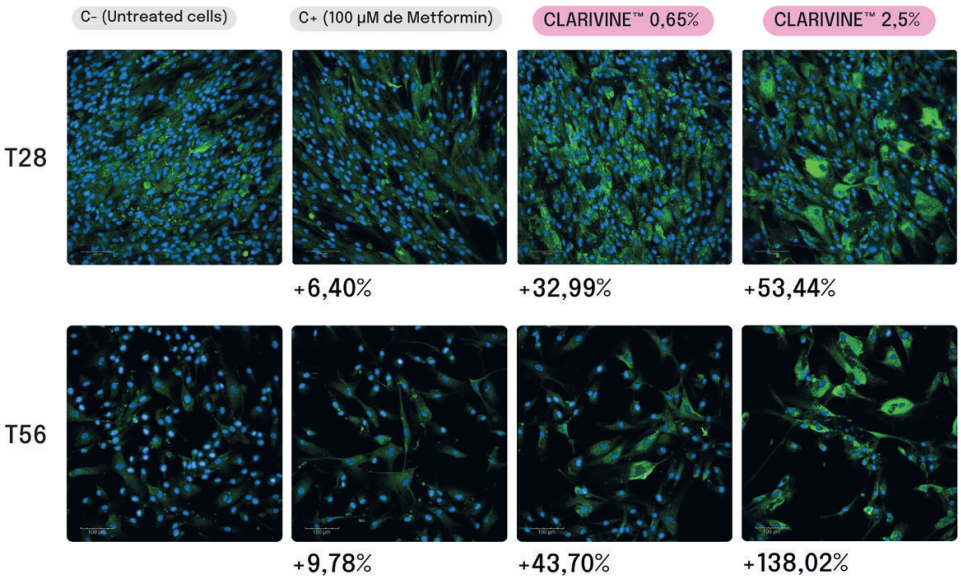


Fig. 2 Autophagic activity measured by LC3 immunodetection in HDF.

P4 = 4 weeks, P8 = 8 weeks

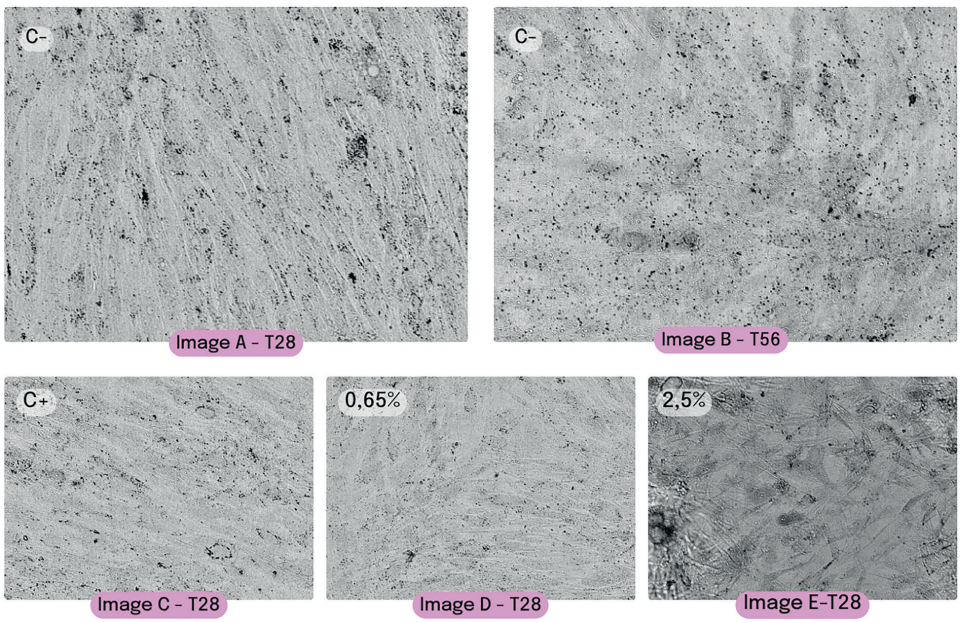


Fig. 3 Optical microscopy images reveal that Clarivine™ significantly decreases SA-β-galactosidase activity – a key marker of cellular senescence – compared to the untreated control.

- A marked **reduction of intracellular ageing pigments lipofuscin** (34%) in fibroblasts **and melanin** content (29%) was demonstrated in senescent melanocyte models.

Clinical Evaluation(*in vivo* Assays)

To confirm the biological findings in human subjects, Clarivine™ underwent clinical validation through three randomized, double-blind, placebo-controlled studies in multi-ethnic panels composed of both Caucasian and Asian volunteers with signs of photoageing, uneven pigmentation, dehydration, and fine lines.

In *in vivo* 1 and *in vivo* 2, a formulation containing Clarivine™ was applied twice daily over 28 to 56 days. Key endpoints were assessed to proof the fasting-mimicking and glass skin effect as well as well-ageing benefits in short term demonstrated in *in vivo* 3.

In vivo 1: The fasting-mimicking effect (Caucasian panel)

Clinical studies demonstrate that Clarivine™ delivers visible and measurable improvements similar to those observed in fasting in Caucasian volunteer panel (Fig. 5 and 6) demonstrating Clarivine™'s dual action: visible aesthetic benefits and deeper cellular renewal. By reducing oxidative stress and skin surface roughness (Fig. 4) and promoting cellular recycling mechanisms, Clarivine™ enhances long-term skin resilience and vitality. This contributes to a more even tone, healthier appearance, and improved radiance. Furthermore, a significant reduction in the skin melanin index was ob-

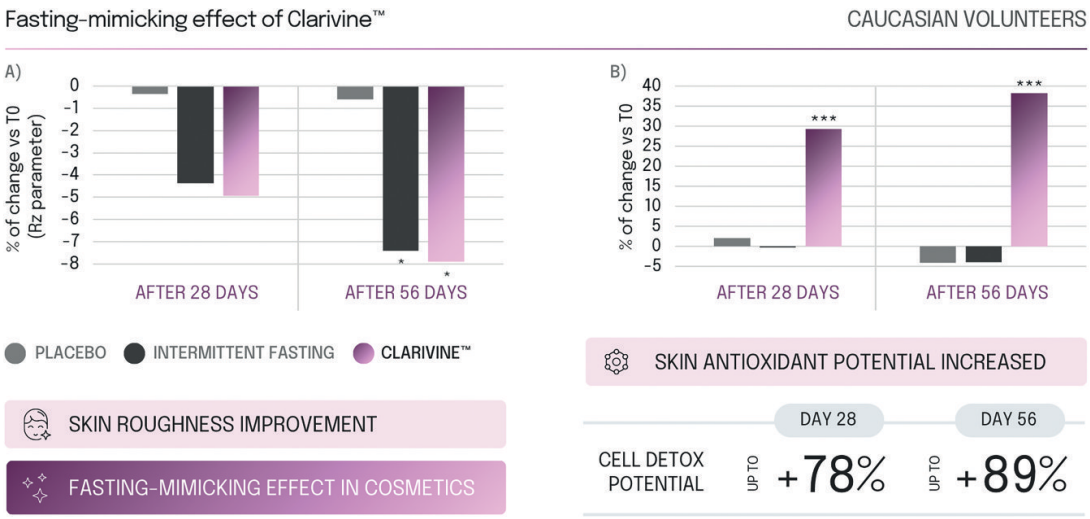


Fig. 4 (A) Skin profilometry (Rz parameter) to assess Clarivine™ progressive results on skin roughness higher than fasting . (B) Skin antioxidant potential was assessed in the first skin layers.

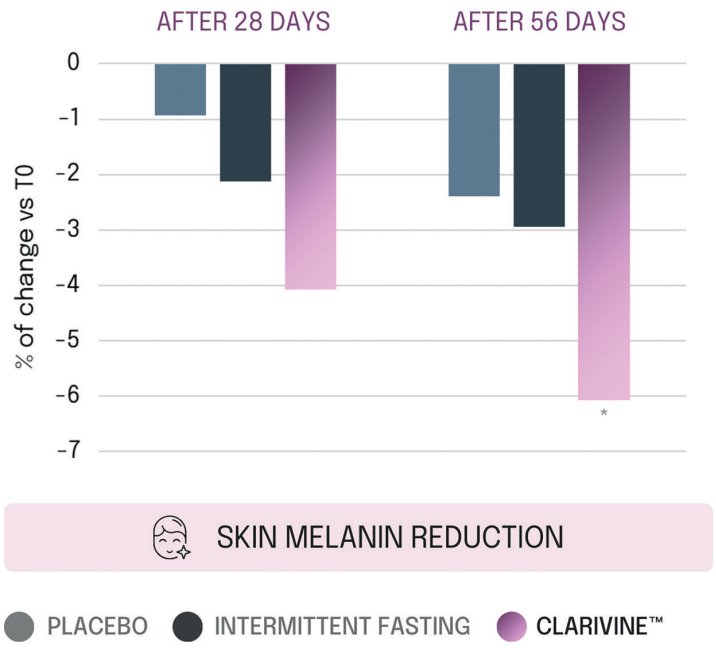


Fig. 5 **Clarivine™ effectively reduces both global and dark spot pigmentation, delivering results comparable to those of fasting interventions.**

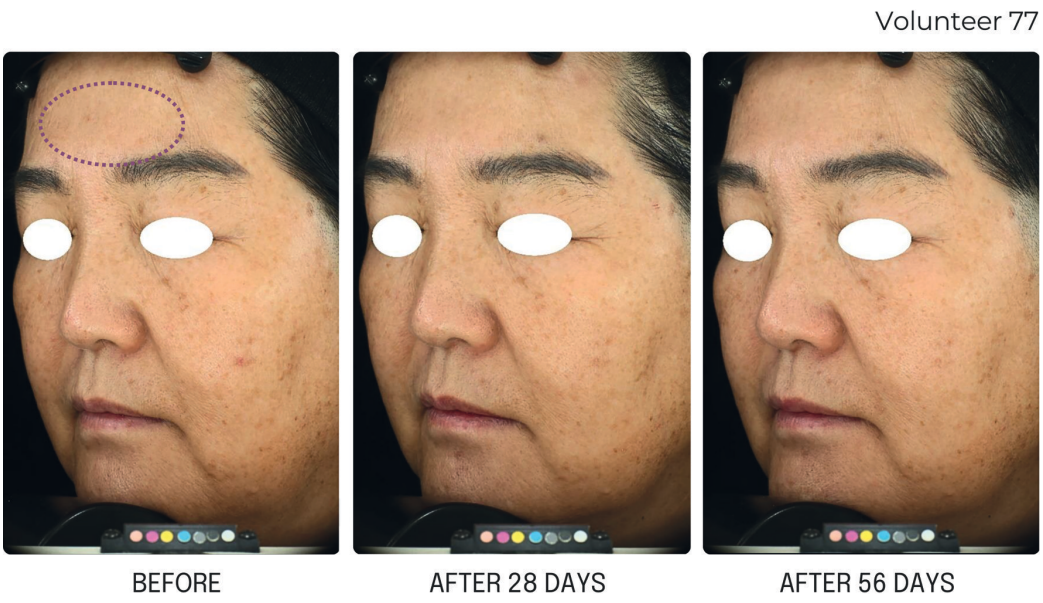


Fig. 6 **After the application of Clarivine™ , the skin appears less yellowish due to a reduction in lipofuscin, the pigment associated with ageing.**

served – 27% at day 28 and 28.9% at day 56, demonstrating its effective depigmenting action and contribution to a more uniform complexion (Fig. 5).

In vivo 2: Radiance, pigmentation and texture improvement (Asian panel)

The clinical evaluation of Clarivine™ in the Asian panel demonstrates significant improvements across key markers of skin quality. The active ingredient notably enhanced skin radiance, with increases up to 70.5% at 28 days and up to 96.5% at 56 days, indicating a strong brightening effect. In parallel, skin melanin content was reduced down to 14.4% at day 28 and 23% by day 56, reflecting a measurable depigmenting action. Furthermore, skin roughness decreased down to 29.5% at day 28, and maintained a reduction of 33.9% at day 56, supporting its role in improving skin texture and surface smoothness. Collectively, these results confirm Clarivine™'s efficacy in promoting a more luminous, even-toned, and refined skin appearance over time.

In vivo 3: Well-ageing benefits in the short term (Caucasian panel)

Clarivine™ showed visible results within 14 days in terms of moisturization and anti-aging effects. Skin hydration increased significantly, up to 48.1% at day 14 and up to 67.8% at day 28, indicating rapid and sustained improvement in the skin's moisture retention capacity. These results contribute to a visibly healthier, more supple, and luminous complexion – hallmarks of the Glass Skin ideal. In parallel, wrinkle depth was reduced to 27.4% at day 14 and down to 36.1% at day 28, confirming Clarivine™'s effectiveness in improving skin smoothness and minimizing signs of aging within a short application period (Fig. 7).

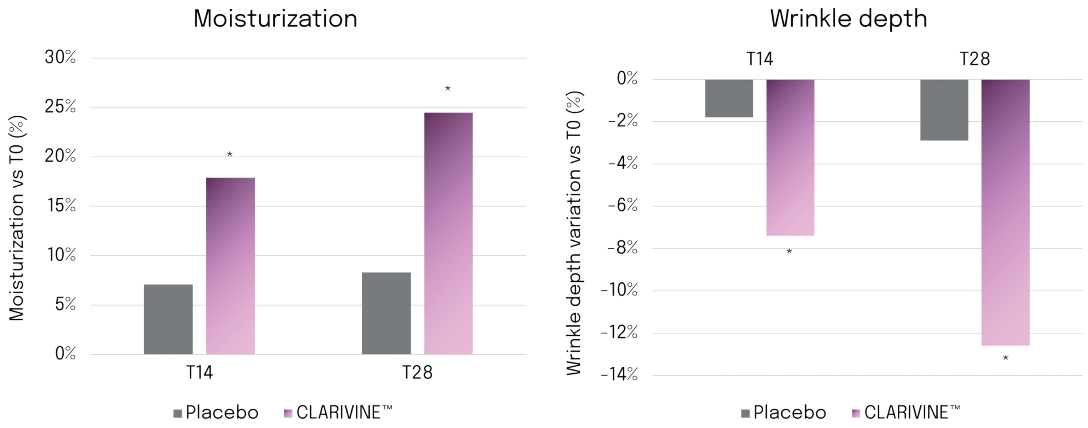


Fig. 7 Clarivine™ boosts and maintains skin hydration while reducing wrinkle depth, contributing to healthier, more supple and radiant skin, a perfect Glass Skin

Conclusion

Clarivine™ is a 100% natural active, paptented technology, obtained from *Vitis vinifera* stem cells and developed through sustainable plant biotechnology. It is designed to promote skin longevity while delivering the smooth, translucent radiance characteristic of the glass skin ideal. This plant-based biotechnological ingredient is COSMOS-certified, China-compliant, Halal-approved, and microbiota-friendly – offering a clean, inclusive profile for global skincare innovation.

Through a carefully designed nutrient restriction protocol, the plant cells undergo a mild stress response (hormesis), stimulating the production of a uniquely potent secretome. This metabolically enhanced complex is rich in Plant Fasting Factors such as resveratrol and skin-signaling peptides, which are naturally encapsulated in plant-derived exosomes to maximize bioavailability and targeted cellular communication.

Acting as a true fasting-mimetic at the cellular level, the ingredient reactivates essential longevity mechanisms including autophagy, oxidative stress protection, and telomere maintenance. It also reduces lipofuscin accumulation – the hallmark pigment of cellular aging – and lowers melanin levels, helping restore clarity and uniformity to the skin. Clinical trials on both Asian and Caucasian skin types demonstrate significant improvements in skin glow, moisture retention, evenness, pigmentation reduction, and wrinkle smoothing.

Combining immediate visual results with deep regenerative potential, this active represents a new generation of high-performance cosmetic biotechnology. It offers a robust tool for formulators focused on well-ageing, brightening, and skin revitalization – perfectly aligned with today's demand for results-driven, health-conscious, and sustainable skincare solutions.

References :

1) *Longo VD, Di Tano M, Mattson MP, Guidi N.* (2021). Intermittent and periodic fasting, longevityand disease. Nat Aging. 2021 Jan;1(1): 47-59. doi: 10.1038/s43587-020-00013-3. Epub 2021 Jan 14.PMID: 35310455; PMCID: PMC8932957.

2) *Maduro, Ana T. BSca,b; Luís, Carla MScb,c; Soares, Raquel PhDb,c,*. (2021) Ageing, cellular senescence and the impact of diet: an overview. Porto Biomedical Journal 6(1): p e120, January/February 2021. | DOI: 10.1097/j.pbj.0000000000000120

3) *Park, D., Jeong, H., Lee, M. N., Koh, A., Kwon, O., Yang, Y. R., Ryu, S. H.* (2016). Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. Scientific reports, 6(1), 21772.

4) *Różanowska MB.* (2023). Lipofuscin, Its Origin, Properties, and Contribution to RetinalFluorescence as a Potential Biomarker of Oxidative Damage to the Retina. Antioxidants (Basel). 2023 Dec 13;12(12):2111. doi: 10.3390/antiox12122111. PMID: 38136230; PMCID: PMC10740933.

5) *Yin Z, Klionsky DJ.* (2022). Intermittent time-restricted feeding promotes longevity through circadian autophagy. Autophagy. 2022 Mar;18(3):471-472. doi: 10.1080/15548627.2022.2039524. Epub 2022 Feb 27. PMID: 35220894; PMCID: PMC9037462.

6) *Ramakrishna, A., Ravishankar, G.A.* (2011). Influence of abiotic stress signals on secondarymetabolites in plants. Plant Signal Behav. 6(11), 1720-173

7) *Calabrese, E., Hayes, A. W., Pressman, P., Kapoor, R., Dhawan, G., Calabrese, V., & Agathokleous,E.* (2023). Polyamines and hormesis: making sense of a dose response dichotomy. Chemico-Biological Interactions, 110748.

8) *Baur JA, Sinclair DA* (2006). Therapeutic potential of resveratrol: the *in vivo* evidence. Nat RevDrug Discov. 2006 Jun;5(6): 493-506. doi: 10.1038/nrd2060. Epub 2006 May 26. PMID: 16732220.

9) *Cantó C, Auwerx J* (2009). Caloric restriction, SIRT1 and longevity. Trends Endocrinol Metab.2009 Sep;20(7): 325-31. doi: 10.1016/j.tem.2009.03.008. Epub 2009 Aug 25. PMID: 19713122; PMCID:PMC3627124.

10) *Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J* (2021). Anti-Inflammatory Action and Mechanisms of Resveratrol. Molecules. 2021 Jan 5;26(1): 229. doi: 10.3390/molecules 26010229. PMID: 33466247; PMCID: PMC7796143.

11) *Zhou DD, Luo M, Huang SY, Saimaiti A, Shang A, Gan RY, Li HB* (2021). Effects and Mechanisms of Resveratrol on Aging and Age-Related Diseases. Oxid Med Cell Longev. 2021 Jul 11;2021:9932218. doi: 10.1155/2021/9932218. PMID: 34336123; PMCID: PMC8289612.

12) *Jamal Rahmani, et.al.* (2019). The influence of fasting and energy restricting diets on IGF-1 levelsin humans: A systematic review and meta-analysis, Ageing Research Reviews, Volume 53,2019,100910, ISSN 1568-1637.

13) *Van Heemst D* (2010). Insulin, IGF-1 and longevity. Aging Dis. 2010 Oct;1(2): 147-57. Epub 2010Aug 26. PMID: 22396862; PMCID: PMC3295030.

14) *Vitale G, Pellegrino G, Vollery M, Hofland LJ.* (2019). ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective. Front Endocrinol(Lausanne). 2019 Feb 1;10:27. doi: 10.3389/fendo.2019.00027. PMID: 30774624; PMCID: PMC6367275.

15) *Du, S., Zheng, H.* (2021). Role of FoxO transcription factors in aging and age-related metabolicand neurodegenerative diseases. Cell Biosci 11, 188 (2021). https://doi.org/10.1186/s13578-021-00700-7

16) *Chakravarti D, LaBella KA, DePinho RA* (2021). Telomeres: history, health, and hallmarks of aging. Cell. 2021 Jan 21;184(2): 306-322. doi: 10.1016/j.cell.2020.12.028. Epub 2021 Jan 14. PMID: 33450206; PMCID: PMC8081271.

17) *Domingos, S., Fino, J., Cardoso, V. et al.* (2016). Shared and divergent pathways for flowerabscission are triggered by gibberellic acid and carbon starvation in seedless *Vitis vinifera* L.BMC Plant Biol 16, 38 (2016). https://doi.org/10.1186/s12870-016-0722-7

Authors : Òscar Expósito, Monika Buchholz, Victoria Vidal, Ana Gallego, Sandra Ruiz, Pau Riera, Daniel Luna, Maria Mas, Marta Gibert, Laura Cano, Sara Laplana, Tarik Ruiz, Raquel Ferreira, Alejandro Guirado
Vytrus Biotech S.A. Barcelona (Spain)