

ORIGINAL ARTICLE

Effects of a standardized olive (*Olea Europea*) fruit extract on healthy skin aging parameters

Effetti di un estratto di oliva standardizzato (*Olea Europea*) sui parametri di invecchiamento fisiologico della cute

Stefano TOGNI ¹, Giada MARAMALDI ¹*, Antonella RIVA ¹,
Ambra CORTI ², Gianni BELCARO ³, Maria R. CESARONE ³

¹Indena S.p.A, Milan, Italy; ²Polistudium SRL, Milan, Italy; ³IRVINE3 Vascular Lab, Department of Medical Science, Chieti-Pescara University, Pescara, Italy

*Corresponding author: Giada Maramaldi, Indena S.p.A, Milan, Italy. E-mail: giada.maramaldi@indena.com

Abstract - Riassunto

BACKGROUND: Opextan® (Indena, S.p.A., Milan, Italy) is a non-caloric standardized extract of the fruit of *Olea europea*, which contains high concentrations of polyphenols and the phytonutrient verbascoside. These molecules exert a potent antioxidant activity, thus playing an important role in skin health.

METHODS: In this registry study, we enrolled 67 healthy women who freely chose to receive Opextan® 300 mg daily or no specific skin oral treatment for 4 weeks. Multiple biochemical and physiological properties of the skin were assessed at baseline and after 2 and 4 weeks of treatment, including water and oil content, number of exfoliating cells, transcutaneous oxygen and carbon dioxide tension, surface hydration, and nutritional and thermoregulatory blood flow.

RESULTS: Women treated with Opextan® benefited from a progressive increase in the water and oil content of the skin, improvement in skin hydration, reduction in the number of exfoliating cells, increase in O₂ tension and decrease in CO₂ tension, and improvement in skin thermoregulatory and nutritive flux. The results were superior to those observed in the control group. Moreover, some preliminary analyses have shown a beneficial effect of Opextan® on blood lipid metabolism. In addition, in a smaller study conducted on ten subjects undergoing the histamine prick test, we observed that Opextan® treatment lead to a smaller lesion and fastest recovery time.

CONCLUSIONS: Overall, these results suggest that Opextan®, administered orally, is a “healthy aging” supplement, as it promotes healthy skin aging, it improves the recovery capacity of the skin and exerts some possible beneficial effects on cardiovascular risk factors.

(Cite this article as: Togni S, Maramaldi G, Riva A, Corti A, Belcaro G, Cesarone MR. Effects of a standardized olive (*Olea europea*) fruit extract on healthy skin aging parameters. *Esperienze Dermatol* 2019;21:6-10. DOI: 10.23736/S1128-9155.19.00479-5)

KEY WORDS: Skin; Cosmetics; Dietary supplements; Healthy aging; Olea; Beauty.

OBIETTIVO: Opextan® (Indena, S.p.A., Milano, Italia) è un estratto non calorico standardizzato di *Olea europea*, che contiene alte concentrazioni di polifenoli e il fitonutriente verbascoside. Queste molecole esercitano una potente azione antiossidante, svolgendo quindi un ruolo importante a livello cutaneo.

METODI: In questo studio abbiamo arruolato 67 volontarie sane, che hanno deciso liberamente di assumere Opextan® 300 mg al giorno o nessun trattamento orale specifico per la pelle per un periodo di 4 settimane. Al basale e dopo 2 e 4 settimane di trattamento sono state valutate diverse proprietà biochimiche e fisiologiche della pelle, tra cui contenuto di acqua e olio, grado di esfoliazione, tensione transcutanea di ossigeno e anidride carbonica, idratazione superficiale, flusso nutrizionale e termoregolatore.

RISULTATI: Le donne trattate con Opextan® hanno beneficiato di un progressivo aumento nel contenuto di acqua e olio della pelle, aumento dell'idratazione cutanea, riduzione dell'esfoliazione, aumento della tensione di O₂ e diminuzione della tensione di CO₂ e miglioramento della termoregolazione e del flusso nutritivo cutaneo. I risultati sono stati superiori a quelli osservati nel gruppo di controllo. Alcune analisi preliminari hanno inoltre evidenziato un effetto benefico di Opextan® sul metabolismo dei lipidi nel sangue. Inoltre, in uno studio ancillare limitato a dieci soggetti sottoposti al test dell'istamina, abbiamo osservato che il trattamento con Opextan® porta a sviluppare una lesione più piccola e a tempi di recupero più rapidi.

CONCLUSIONI: Nel complesso, questi risultati suggeriscono che Opextan®, somministrato per via orale, è un integratore che promuove un “invecchiamento sano”, in quanto favorisce un sano invecchiamento cutaneo, migliora la capacità di recupero della pelle e ha un possibile effetto benefico su alcuni fattori di rischio cardiovascolare.

Human skin, like any other organ, is subject to aging, a process that leads to a progressive loss of both functional and esthetic features. In aging skin, cell replacement is gradually reduced, leading to impairment of the skin barrier function, delay in immune response and wound healing, altered thermoregulation, and decrease in sweat and sebum production. All these degenerative changes translate into clearly distinguishable alterations of skin appearance, such as the formation of wrinkles, changes in skin texture, laxity and dyspigmentation.¹

Skin aging is the result of both intrinsic genetic factors and exposure to external agents, such as UV radiation, smoking, wind and chemical agents.² Solar UV exposure is one of the main factors associated with extrinsic skin damage, as it appears to generate reactive oxygen species (ROS), which contribute to lipid peroxidation, damage to DNA, lipid and cellular proteins, sunburn reactions, photo-toxicity, photo-allergy and photo-aging.³⁻⁵ Most recently, even visible light with the highest energy (namely “blue light”), whose main source is sunlight but to which we are also exposed indoors by means of technological devices, such as monitors, tablets and smartphones, has also been recognized as an additional agent of extrinsic aging.⁶

Many natural ingredients have been discovered to exert an antioxidant effect that may be beneficial in reducing ROS formation and damages caused by oxidation. These nutrients can be both topically applied or provided as oral supplementation.⁷

One of the most widely recognized antioxidant present in nature is olive oil, an ingredient known for its healing and nutritional properties and recommended in most diets for its healthy aging effect. For example, higher levels of consumption of olive oil have been associated with decreased mortality and reduction in cancer and coronary heart disease.⁸

Opextan® (Indena, S.p.A., Milan, Italy) is a non-caloric standardized extract of the fruit of *Olea Europea*, which contains high concentrations (>10%) of polyphenols (hydroxytyrosol, tyrosol and isoacteoside),⁹ in addition to the phytonutrient verbascoside (>2%), one of the most potent antioxidants derived from the olive tree.¹⁰ *In-vitro* and *in-vivo* studies have shown that verbascoside exerts a strong antioxidant activity and contributes to the protection of the skin from UV radiation, reducing wrinkle formation and damage to the epidermal permeability barrier.¹¹ In clinical studies, Opextan® has also proven to support skin health by protecting the skin from UV-induced damage and by exerting a remarkable lipid peroxidation inhibition both when applied topically and when administered orally.¹¹⁻¹³ Moreover, an *in-vitro* study suggests that Opextan® may contribute to healthy blood sugar level metabolism, which can play a very important role in skin health.¹⁴

In this registry, we evaluated the effects of Opextan®

administered orally on skin health of healthy women, focusing especially on the biochemical and physiological properties of the skin.

Materials and methods

Healthy women were enrolled in the registry and either chose to be assigned to the treatment group receiving Opextan® 300 mg standardized extract daily (150 mg capsules, two capsules a day) for 4 weeks or to the control group with no specific skin oral treatment.

All the participants underwent the following evaluations: measurement of water and oil content in the stratum corneum (by Moisture Monitor EP-Hydr8), number of exfoliating cells, transcutaneous oxygen tension (pO₂) and carbon dioxide tension (pCO₂), skin surface hydration, nutritional and thermoregulatory skin blood flow by Laser Doppler flux. All the measurements were performed at baseline and repeated after 2 and 4 weeks of treatment.

The status of the skin was also assessed by subjective parameters: all the subjects were asked to rate the radiance of the skin and the cutaneous touch sensation on an analogue scale from 0 to 5. The results were compared with the control group of untreated women.

The registry study was approved by the local Ethics Committee and all the patients signed an informed consent before enrollment.

Statistical analysis

All data were analyzed by descriptive statistics only, due to the pilot nature of the registry. The ANOVA test with Bonferroni correction was used to evaluate differences in subjective measures between the Opextan® and control group both at baseline and after 4 weeks of treatment.

Results

Overall, 67 women were enrolled in the registry; 34 women were treated with Opextan® whereas 33 were included in the control group. Participants mean age was 45.5±3.6 years old for women in the Opextan® group and 44.8±4.2 for those in the control group.

Among the subjects treated with Opextan®, we observed a progressive increase in the water and oil content, respectively, after 2 and 4 weeks of treatment (Figure 1). Moreover, the number of exfoliating cells, which is an index of fast degrading skin, was progressively reduced from 3.23 at baseline to -3.3 after 2 weeks and to -3.89 after 4 weeks.

The transcutaneous O₂ and CO₂ monitoring revealed a progressive increase in O₂ tension, and a continuous decrease in pCO₂ tension, thus suggesting an improvement in cutaneous perfusion and skin nutrition during treatment with Opextan® (Figure 2). Moreover, global skin

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

Togni

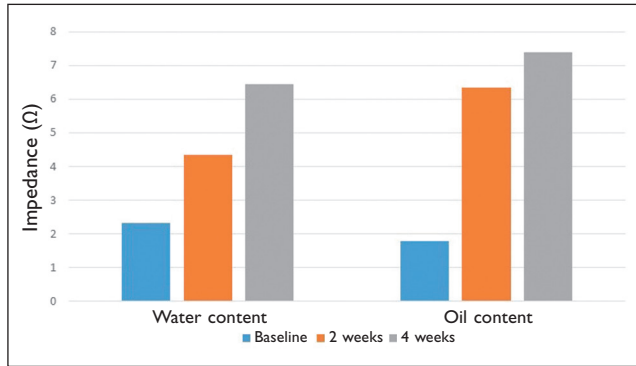


Figure 1.—Variation in skin elements in women treated with Opextan®.

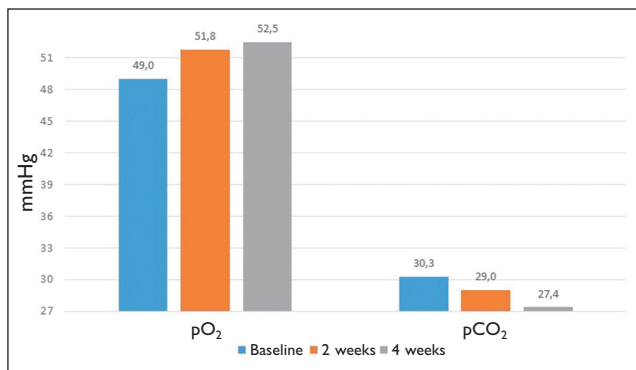


Figure 2.—Variation in oxygen tension (pO₂) and carbon dioxide (pCO₂) tension in women treated with Opextan®.

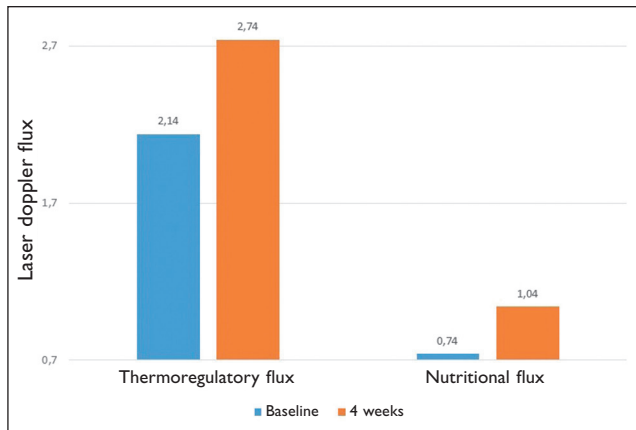


Figure 3.—Variation in thermoregulatory and nutritional flux in women treated with Opextan®.

hydration improved with Opextan®, increasing from 36.5% at baseline to 37.7% after 2 weeks and to 41.8% after 4 weeks of treatment.

Last, the laser Doppler measurement highlighted an increase both in the skin thermoregulatory flux and the nutritive flux after 4 weeks of treatment with Opextan® compared with baseline (Figure 3).

Table I.—Subjective assessment score (0-5).

	Baseline	4 weeks
Skin radiance		
Opextan®	2.36±0.44	4.1±0.13*
Control	2.37±0.40	2.40±0.22
Skin touch sensation		
Opextan®	2.32±0.20	4.32±0.12*
Control	2.33±0.20	3.20±0.20
*P<0.05 (ANOVA).		

As summarized in Table I, women treated with Opextan® also reported a significant improvement in subjective evaluation of skin radiance and cutaneous touch sensation after 4 weeks of treatment compared with baseline. The results registered in the treated group were superior to those observed in the control group.

No side effects or intolerance signs were registered among women treated with Opextan®.

Discussion

Overall, the results of this registry study suggest that Opextan®, administered as an oral supplement, has a beneficial effect on the skin, improving skin health and promoting healthy skin aging in women.

Proper hydration and adequate oil content are critical factors for a healthy skin, as both parameters provide the skin with a smooth texture and natural pigmentation, which are important features for cosmetic appearance. Moreover, on a functional point of view, both elements play a central role in protecting and preserving skin integrity, maintaining the skin barrier function and creating a filter against the external environment.¹⁵ As shown by our study, Opextan® treatment leads to an increase in skin water and oil content, therefore contributing to the protection of the skin and counteracting skin dryness observed in some of the participants. Of note, dry skin is a well-known result of oxidative stress in lipid rich tissues;¹⁶ the antioxidant effect of the polyphenols and verbascoside contained in Opextan®, which have been shown to reduce lipid peroxidation, may contribute to the amelioration of skin moisture.¹²

In addition, as shown in our study, Opextan® seems to reduce the number of exfoliating cells, therefore suggesting a decrease in the processes of skin degradation.¹⁷

Another important element that impacts on skin health is represented by skin nutritional microcirculation, which contributes to regulating tissue perfusion, fluid homeostasis, delivery of oxygen and nutrients and thermoregulation.¹⁸ Skin oxygen flux provides cells with raw material and energy for cell activation and vitality. Actually, accord-

ing to a recent study, an increase in oxygen flux and cell vitality seem to be associated with improved skin elasticity, one of the main parameters whose reduction is related to wrinkle formation and skin aging.¹⁹

In our study, the results of the transcutaneous pO₂/pCO₂ analysis and the laser Doppler flux tests have shown that Opextan® exerts a beneficial effect on skin circulation, increasing the thermoregulatory and nutritional flux and the oxygen flux, and therefore improving skin nutrition and perfusion.

Of note, the blood flow and the ability of the skin to use and retain oxygen is known to progressively decrease with aging, with a reduction of 40% between the ages of 20 and 70 years.²⁰ The reduction in oxygen content in the skin layer may result in more wrinkles, fine lines and dull-looking skin. Our study suggests that the improvement in oxygen, thermoregulation and nutritional flux provided by Opextan® may reduce the loss in microcirculation observed in aging skin, thus limiting the cosmetic deterioration associated with impaired microcirculation.

Furthermore, the results of Opextan® treatment seem to be appreciated by women, who subjectively reported an improvement in skin radiance and cutaneous touch feeling after 4 weeks of use. Moreover, Opextan® was perfectly tolerable and no side effects or adverse reactions have been observed during the course of the study.

Notably, an additional pilot study was carried out with the same supplement in ten subjects who underwent the histamine model test. The tests consist of a prick (a mi-

cro-injection) of histamine on the skin, which induces the formation of a temporary lesion (wheal) that lasts for 30-60 minutes. The wheal formation is caused by a sudden increase in local permeability that prompts skin reactivity.²¹ The ten subjects treated with Opextan® and submitted to the histamine prick test showed a smaller wheal size, a lower maximal flux and a faster disappearance of the wheal compared with untreated subjects, thus suggesting a faster ability of the skin to recover from induced skin damage. Finally, based on some preliminary analysis on the effects of Opextan® on blood lipid metabolism, the oral supplementation of this olive fruit extract seems to improve HDL cholesterol and triglycerides profile in otherwise healthy women, with a possibly positive impact on subject's cardiovascular risk (manuscript in preparation).

Conclusions

Even though these data are limited to a small number of subjects, the whole of the represented data — displaying a more comprehensive elaboration of skin health — actually suggests that Opextan® may qualify as a more global “healthier aging” supplement. Indeed, Opextan® has been shown not only to impact on the signs of skin aging, but also on the recovery capacity of the skin (histamine prick test), and to additionally ameliorate some parameters of aging linked to cardiovascular risk, such as HDL and triglycerides profile.

References

1. Wiegand C, Raschke C, Elsner P. Skin Aging: A Brief Summary of Characteristic Changes. In: Farage M., Miller K., Maibach H, editors. Textbook of Aging Skin. Berlin, Heidelberg: Springer; 2015.
2. Gendler EC. Topical treatment of the aging face. *Dermatol Clin* 1997;15:561–7.
3. Dalle Carbonare M, Pathak MA. Skin photosensitizing agents and the role of reactive oxygen species in photoaging. *J Photochem Photobiol B* 1992;14:105–24.
4. Yamamoto Y. Role of active oxygen species and antioxidants in photoaging. *J Dermatol Sci* 2001;27(Suppl 1):S1–4.
5. Harman D. Origin and evolution of the free radical theory of aging: a brief personal history, 1954–2009. *Biogerontology* 2009;10:773–81.
6. Mizutani T, Sumida H, Sagawa Y, Okano Y, Masaki H. Carbonylated proteins exposed to UVA and to blue light generate reactive oxygen species through a type I photosensitizing reaction. *J Dermatol Sci* 2016;84:314–21.
7. Rona C, Vailati F, Berardesca E. The cosmetic treatment of wrinkles. *J Cosmet Dermatol* 2004;3:26–34.
8. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348:2599–608.
9. Yokota T. Anti-oxidative effect of several polyphenols derived from olive fruits and its application for cosmetics and supplements. Presented at: The 57th Society Cosmetic Chemists Japan Research Conference, 25 November 2005. 33.
10. Obied HK, Prenzler PD, Konczak I, Rehman AU, Robards K. Chemistry and bioactivity of olive biophenols in some antioxidant and antiproliferative in vitro bioassays. *Chem Res Toxicol* 2009;22:227–34.
11. Maramaldi G, Artaria C, Ikemoto T, Haratake A. Estratto standardizzato di frutti di *Olea europaea*. *Integr Nutr* 2006;9:23–9.
12. Maramaldi G, Artaria C. Estratto standardizzato di frutti di *Olea europaea* - Antiossidante e Antiaging. *Cosmetic Technology* 2006;9:9–13.
13. Togni S, Maramaldi G, Conte C, Milano E, Giacomelli L. Photoprotective and antioxidant effects of a standardised olive (*Olea europaea*) extract in healthy volunteers. *Esperienze Dermatol* 2015;17:143–8.
14. Suzuki K, Uchiwa H, Ikemoto T, Yamakado M. Effect of Olive Polyphenol Dry Extract on Glucose Metabolism in Subjects with Hypertension. *Off J of Japan Soc of Ningen Dock* 2011;25:825–83.
15. Dayan N. *Skin Aging Handbook*. New York: William Andrew Inc.; 2008.
16. Girotti AW. Lipid hydroperoxide generation, turnover, and effector action in biological systems. *J Lipid Res* 1998;39:1529–42.
17. Brysk MM, Rajaraman S. Cohesion and desquamation of epidermal stratum corneum. *Prog Histochem Cytochem* 1992;25:1–53.
18. Bentov I, Reed MJ. The effect of aging on the cutaneous microvasculature. *Microvasc Res* 2015;100:25–31.

Togni

19. He Y, Zhu J, Li L, Dong Z, Zhu W, Meng H. Research on the relationship between the skin biophysical parameters versus wrinkles of 36–49 years old Beijing female. *Asian J Beauty Cosmetol* 2018;16:93–102.

20. Tsuchida Y. The effect of aging and arteriosclerosis on human skin blood flow. *J Dermatol Sci* 1993;5:175–81.

21. Malling HJ. Skin prick testing and the use of histamine references. *Allergy* 1984;39:596–601.

Conflicts of interest.—Stefano Togni, Giada Maramaldi and Antonella Riva are Indena employees.

Acknowledgements.—Editorial assistance for the preparation of this manuscript has been provided by Luca Giacomelli, PhD and Aashni Shah, on behalf of Polistudium srl.

Manuscript accepted: April 17, 2019. - Manuscript received: February 8, 2019.