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Anti-inflammatory / anti-oxidant activity of ingredients of sunscreen products? Implications for SPF

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Abstract

OBJECTIVE: The Sun Protection Factor (SPF) of sunscreen products is derived from testing *in vivo* their ability to prevent erythema ("sunburn"). Recently, certain articles have raised concerns that sunscreen products may actively suppress erythema via anti-inflammatory / anti-oxidant (AI/AO) activity. These articles reason that this may result in a higher labelled SPF value than that provided by the efficacy of the UVR filters alone, giving consumers a "false sense of security". On the other hand, since inflammatory processes are known to play a role in the mechanisms of photodamage / skin cancer induction and propagation, AI/AO activity may provide valuable incremental photoprotective benefit (provided that there is no interference with visible erythema). The objective of these studies, therefore, was to investigate the potential of AI/AO ingredients to suppress UVR-induced erythemal response in human skin, *in vivo*.

METHODS: *In vivo* studies with SPF30 sunscreen formulations containing a variety of AI/AO ingredients were performed according to the International Standard ISO24444:2010 method. While ISO24444:2010 requires assessment of erythema at 20 ± 4h post-irradiation, an additional assessment at 5 h post-irradiation was also used to determine potential delay in erythema development.

RESULTS: None of the formulations, containing a variety of AI/AO ingredients, influenced SPF determination in comparison to the vehicle formulation.

CONCLUSION: Our *in vivo* results demonstrate that commonly-used AI/AO ingredients, at concentrations typically used in sunscreen products, neither influence SPF value nor delay erythemal response, i.e., the measured SPF reflects the true photoprotective capacity of the product.

Résumé

OBJECTIF: Le facteur de protection solaire (SPF) des produits de protection solaire est dérivé de tests *in vivo* servant à déterminer leur capacité à prévenir un érythème (« coup de soleil »). Récemment, certains articles ont soulevé des inquiétudes en insinuant que les produits de protection solaire pourraient activement faire disparaître un érythème par le biais d'une activité anti-inflammatoire/anti-oxydante (AI/AO). Ces articles soutiennent que cela pourrait impliquer une valeur déclarée du SPF plus élevée que celle fournie par l'efficacité des filtres RUV à eux seuls, donnant ainsi une « fausse impression de sécurité » aux consommateurs. D'autre part, étant donné que les processus inflammatoires sont réputés jouer un rôle dans les mécanismes de photo-altération/d'induction et de propagation du cancer de la peau, l'activité AI/AO pourrait apporter un précieux bénéfice photo-protecteur amplifié (à condition qu'il n'y ait aucune interférence avec un érythème visible). L'objectif de ces études était, par conséquent, d'étudier le potentiel des ingrédients contribuant à l'activité AI/AO à faire disparaître la réponse érythémateuse induite par les RUV dans la peau humaine, *in vivo*.

MÉTHODES: Des études *in vivo* avec des formules de produits solaires à SPF30 contenant une variété d'ingrédients contribuant à l'activité AI/AO ont été effectuées conformément à la méthode correspondant à la norme internationale ISO24444:2010. Bien que l'ISO24444:2010 nécessite l'évaluation de l'érythème à 20 _ 4 heures post-irradiation, une évaluation supplémentaire à 5 heures post-irradiation a également été utilisée pour déterminer l'éventuel délai d'apparition d'un érythème.

RÉSULTATS: Aucune des formules, contenant une variété d'ingrédients contribuant à l'activité AI/AO, n'a influencé la détermination du SPF par comparaison à la formule véhicule.

CONCLUSION: Nos résultats *in vivo* démontrent que les ingrédients contribuant à l'activité AI/AO fréquemment utilisés, aux concentrations généralement utilisées dans les produits de protection solaire, n'influencent pas la valeur du SPF, pas plus qu'ils ne retardent la réponse érythémateuse, autrement dit, le SPF mesuré reflète la véritable capacité photo-protectrice du produit.

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Introduction

Exposure of human skin to ultraviolet radiation (UVR) leads to a myriad of acute and chronic effects. The most prominent acute effects include erythema, pigmentation and immunosuppression, while the most prominent chronic effects comprise photocarcinogenesis and photoageing. All these effects are caused by alterations on a molecular or cellular level, including DNA damage, formation of reactive oxygen species (ROS) and inflammatory mediators, melanogenesis and apoptosis [1–3].

With continued year-on-year increases in skin cancer rates [4], dermatologists strongly recommend the use of sunscreens to help protect against solar UVR [5].

The level of protection against erythema ("sunburn") provided by sunscreen products is expressed as the Sun Protection Factor (SPF). The derived SPF value represents the ratio of the dose of solar-simulated UVR required to induce erythema with and without sunscreen (applied *in vivo* to the skin of human volunteers [2]. In Europe, Canada, Australia and Japan, SPF is determined using the *in vivo* International Standard method ISO24444:2010 [6].

By definition, sunscreens can never be 100% effective in preventing solar UVR transmission. Even with an SPF50 product, 2% of incident erythemally-effective solar UVR is still transmitted through the product layer, into the skin. Following UVR exposure, acute activation of inflammatory pathways, as well as low-level chronic inflammation, are believed to play a crucial role in premature skin ageing and skin cancer development [7–9]. In this context, (non-UVR-absorbing) anti-oxidant and anti-inflammatory (AI/AO) ingredients integrated into sunscreen products have been shown to exert beneficial effects in skin photoprotection [10–13].

Concerns have been raised recently, however, regarding the accuracy of the labelled SPF on sunscreen products which contain AI/AO ingredients such as bisabolol, allantoin or 18β-Glycyrrhetinic acid [14–16]. This is because visible erythema is the endpoint in human *in vivo* SPF determination (ISO24444:2010) and AI/AO ingredients could, at least theoretically, moderate this response after irradiation (thus resulting in sunscreens containing these substances bearing a higher SPF than that justified by the formulated sunscreen filters). Some have also raised concerns that sunscreen filters themselves, in particular salicylates, may have inherent AI/AO activity [17]. Others have commented that, if these concerns were valid, consumers could wrongly assume adequate UVR protection [18].

Recently, other authors reported no significant difference in the measured SPF of sunscreen products with or without AI/AO ingredients [19,20].

To further investigate the impact of AI/AO ingredients on measured SPF values, we performed two *in vivo* studies using the ISO24444(2010) protocol. SPF30 sunscreen products were tested containing a variety of AI/AO ingredients (Tocopheryl Acetate, Glycyrrhetinic Acid, Panthenol or Glycyrrhiza Inflata Root Extract). A control SPF30 sunscreen (containing no AI/AO ingredients) was also tested.

Material and methods

Sunscreen products

Sunscreen formulations (oil-in-water [O/W] emulsion; expected SPF30) containing various AI/AO ingredients were prepared for the study. In Study I, formulations were used containing no AI/AO ingredients (vehicle control) or 1.0% Tocopheryl Acetate, 0.1% Glycyrrhetinic Acid, or 5.0% Panthenol, respectively. For study II, a formulation (O/W emulsion) containing no AI/AO ingredients (vehicle control) or the AI/AO ingredient Glycyrrhiza Inflata Root Extract (0.025%) were used. All formulations were the same except for the AI/AO ingredients and all contained the same concentration of the UVR filters homosalate, ethylhexyl salicylate, titanium dioxide, butyl methoxydibenzoylmethane and octocrylene.

In vivo determination of sun protection factor

The two SPF studies were performed according to the international standard protocol ISO24444:2010. While ISO24444:2010 requires a visual determination of skin erythema at 20 ± 4h after irradiation, an additional reading at 5h after irradiation was also implemented. The standard formulation P2 was included as a reference SPF product in both studies. The test institute was informed that the expected SPF value of the test products was in the range of SPF30–40.

The studies were executed at a certified contract research laboratory. In both studies, 10 subjects with Fitzpatrick skin types I, II and III were enrolled (Table I) into and completed the SPF test (ITA° value range of 30–64 in Study I and 29–59 in Study II; the age range of subjects was 30–64 years in Study I and 29–59 in Study II).

Study execution, data analysis and reporting were performed in line with Good Clinical Practice principles and the requirements of the Declaration of Helsinki. Test subjects were informed about the study, its objectives, probable benefits, potential risks, rights and responsibilities. Informed Consent was obtained in writing from each subject.

Statistics

Statistical analysis was performed using SAS-Institute®JMP.Pro 14 software®.

A paired (within-subject) analysis was performed for each time point (5 h and 24 h). Normality was probed using a Shapiro and Wilk's *W*-Test. Where a normal data distribution was found, data were analysed using a Student's *t*-test (with a mean comparison to 0). Where a non-normal data distribution was found, a Wilcoxon Signed Rank test was used instead.

Results and discussion

In Study I, a W/O emulsion sunscreen product was used as the vehicle control and the SPF of this formulation was determined as 31.5 ± 6.5 at 20 ± 4 h after irradiation (Table II) with a 95% confidence interval (CI) of 26.8–36.2 (CoV 14.8%). The identical vehicle formulated with either 1.0% Tocopheryl Acetate, 0.1% Glycyrrhetinic acid or 5.0% Panthenol returned tested SPF values of 30.7 ± 6.0, 34.1 ± 4.3 or 33.1 ± 5.5, respectively (Table II).

In Study II, the W/O emulsion sunscreen used as the vehicle control returned a tested SPF of 32.4 ± 5.0 with a 95% CI of 28.8–36 (CoV 11.0%). The identical vehicle formulated with 0.025% Glycyrrhiza Inflata Root Extract returned a tested SPF value of 30.1 ± 4.1.

When the SPF was determined at 5 h after irradiation, most subjects did not show any measurable erythema reaction. While this led to an increase in the 95% CI, however, no influence of the AI/AO ingredients was evident.

Table I Test panel demographics

	Study I	Study II
Test subjects	10	10
Age: mean/range	30–64	18–69
Gender: male/female	4/6	2/8
Skin phototype: I, II, III	2, 4, 4,	1, 3, 6
ITA° range, min - max	30–64	29–59

Table II SPF determination 20 ± 4 h post-irradiation

Formulation	*n*	Mean	SD	95% CI		CI (%)
				Lower limit	Upper limit	
Vehicle (Study I)	10	31.5	6.5	26.9	36.1	14.8
+1.0% tocopheryl acetate	10	30.7	6.0	26.4	35.0	14.1
+0.1% glycyrrhetinic acid	10	34.1	4.3	31.0	37.2	9.1
+5.0% panthenol	10	33.1	5.5	29.2	37.0	11.9
Standard P2	10	15.1	2.4	13.3	16.9	11.5
Vehicle (Study II)	10	32.4	5.0	28.8	36.0	11.0
+0.025 licorice	10	30.1	4.6	26.8	33.4	10.9
Standard P2	10	14.8	2.6	12.9	16.7	12.5

n, number of subjects with visible erythema.

In both Study I and Study II, variation of SPF values at 20 ± 4 h after irradiation was within the accepted range for SPF determination (CoV ≤ 17%) and the standard P2 returned the expected values (in Study I, the SPF of P2 was 15.1 and the CoV was 11.5%; in Study II the SPF was 14.8 and the CoV was 12.5 (Table III)). The W Test revealed a non-normal distribution of data for Vehicle + 1% tocopheryl acetate and Vehicle + 5% panthenol and, therefore, a Wilcoxon Signed Rank test was used (Table IV). The *W* Test revealed a normal distribution of data for Vehicle + 0.1% glycyrrhetinic acid and Vehicle + 0.025% licorice and, therefore, a Student's *T*-test was used (Table IV). For all products, the addition of AI/AO ingredients had no influence on determined SPF values.

Table III SPF determination 5 h post-irradiation

Formulation	n	Mean	SD	95% CI		CI (%)
				Lower limit	Upper limit	
Vehicle (Study I)	4	39.5	9.5	24.4	54.6	38.4
+1.0% tocopheryl acetate	4	38.1	8.2	25.1	51.1	34.0
+0.1% glycyrrhetinic acid	4	38.2	6.7	27.5	48.9	27.8
+5.0% panthenol	2	28.8	4.6	−12.5	70.1	143.6
Standard P2	6	16.4	3.7	12.8	16.9	23.6
Vehicle (Study II)	7	29.5	4.6	25.2	33.8	14.5
+0.025 licorice	7	29.8	3.5	26.6	33.0	10.8
Standard P2	10	15.3	3.5	12.8	17.9	16.4

n, number of subjects with visible erythema

These results are in line with those of Werner *et al.* [20], who studied the influence of bisabolol and D-panthenol (each up to 1.0%) on determined *in vivo* SPF in two different sunscreen formulations where, once again, no significant influence of these AI/AO ingredients on SPF values was measured in this study. The authors also applied the same formulations as an Après Sun treatment, where test subjects' skin was first irradiated and then treated immediately and again at 6, 12 and 24 h after irradiation. Once again, there was no influence of the formulations containing these AI/AO ingredients on UVR-induced erythema when compared to the base formula without the inclusion of AI/AO technology.

This latter experimental approach to assess potential moderation of erythemal response because of anti-inflammatory activity independent of UVR-attenuation (that is, the application of topical formulations after irradiation), was first used by Staton and Feng in the study of the putative anti-inflammatory efficacy of an SPF100 sunscreen formulation [21]. Although this formulation did not contain recognized AI/AO ingredients, Sayre *et al.* [17] had previously expressed concerns that UVR filters (especially salicylates) may possess AI/AO activity and may, therefore, moderate the generation of erythema in irradiated skin (especially when formulated at high concentrations up to 39%). In light of vigorous ensuing debate [22,23], Staton and Feng [19] were the first to test Sayre's hypothesis. In their study, they found no evidence for AI/AO activity because of the inclusion of high concentrations of certain UVR filters in a SPF100 product. Moreover, the authors added 1% hydrocortisone to the standard formulation P2 (nominal SPF16). Even the addition of this potent anti-inflammatory corticosteroid did not significantly change erythemal response. While a small change in measured a* value was recorded instrumentally (0.48–1.1 units), this change was not visible to the naked eye and did not influence SPF determination.

The concerns expressed by Couteau *et al.* [15] that AI/AO ingredients might delay erythema and, thus, mislead consumers into protracted sun exposure was addressed in our studies by the inclusion of an additional erythema reading at 5 h post-irradiation. Paired statistical analysis showed, once again, that there was no detectable influence of AI/AO ingredients on measured erythema (Table V). The only difference to the standard measurement

Table IV Paired analysis for 24 h

	Shapiro–Wilk's *P*-value	Difference Average	Difference SEM	Student's *P*-value	Wilcoxon's *P*-value	*n*	Conclusion
Vehicle (Study I)							
+1.0% tocopheryl acetate	0.0027	−0.7400	1.5447	0.6433	0.7500	10	NS
+0.1% glycyrrhetinic acid	0.1877	2.6300	1.2886	0.0716	0.1094	10	NS
+5.0% panthenol	0.0223	1.6600	1.7788	0.3751	0.5781	10	NS
Vehicle (StudyII)							
+0.025 licorice	0.8765	−2.3500	1.9952	0.2691	0.2031	10	NS

Table V Paired analysis for 5 h

	Shapiro–Wilk's *P*-value	Difference Average	Difference SEM	Student's *P*-value	Wilcoxon's *P*-value	*n*	Conclusion
Vehicle (Study I)							
+1.0% tocopheryl acetate	0.4666	2.5000	4.5347	0.6368	1.0000	3	NS
+0.1% glycyrrhetinic acid	0.7262	−0.1000	2.8000	0.9748	1.0000	3	NS
+5.0% panthenol	-	-	-	-	-	1	-
Vehicle (Study II)							
+0.025 licorice	0.1603	1.5500	2.3717	0.5423	0.7500	6	NS

Shapiro-Wilk's *P*-value (null hypothesis: the distribution is Normal) – Normal if *P*-value >0.0500.
Difference average – Product SPF minus Vehicle SPF per volunteer.
Difference SEM – Difference Standard Error of Mean.
Student's *P*-value (null hypothesis: the mean = 0) – No significant difference if *P*-value >0.050.
Wilcoxon's *P*-value (null hypothesis: number of positive differences = number of negative differences) – Normal if *P*-value > 0.050.
n – Number of available differences (SPF both evaluated for product and vehicle).
Conclusion (NS = No Significant, based on Student if Normal and Wilcoxon if not) – Note: in case of no Normal distribution if the conclusions of Wilcoxon and Student match, the Student's *P*-value can be used.

according to the ISO24444:2010 protocol (reading of erythema at 20 ± 4 h post-irradiation) was an increase in confidence interval, because of the lack of erythema on test sites in many subjects at 5 h after irradiation. This absence of erythema at 5 h reflects the expected variability of erythema induction in the general population. Notwithstanding this observation, no effect for the addition of AI/AO could be detected.

AI/AO ingredients are used in many sunscreen products and our data (on file) demonstrate that they are welcomed by consumers. The main function of these ingredients is to provide additional technical benefit (for example, moderation of chronic skin damage because of low-level pro-oxidative and pro-inflammatory stress, demonstrated by various authors for various ingredients; 7, 11, 12, 13).

AI/AO mechanisms are considered to help reduce the risk of non-melanoma skin cancer and, therefore, inclusion of ingredients with this mode of efficacy in sun care products may be beneficial in protection against chronic skin damage because of solar UVR exposure [8,10]. In this present study, we have demonstrated that the tested AI/AO ingredients have no effect on measured *in vivo* SPF values. The main reason for under-performance of sunscreen products in-use is mis-use by many consumers. For example, sunscreens are not always applied at the correct dosage, are often not applied homogeneously and re-application is often not performed as recommended [24,25].

The scope of this paper was solely to investigate the influence of AI/AO on the early development of erythema because the first 24 h after irradiation are crucial in the determination of sunscreen *in vivo* SPF. Because sunscreens are re-applied frequently and erythema persists for more than 24 h, however, additional studies could be performed to explore the effects of AI/AO on skin change resulting from sub-erythemal UVR exposure.

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References

1. Young, A.R. Acute effects of UVR on human eyes and skin. *Prog Biophys Mol Biol.* **92**, 80–85 (2006).
2. Young, A.R., Claveau, J. and Rossi, A.B. Ultraviolet radiation and the skin: Photobiology and sunscreen photoprotection. *J Am Acad Dermatol.* **76**(3S1), S100–S109 (2017).
3. Matsumura, Y. and Ananthaswamy, H.N. Short-term and long-term cellular and molecular events following UV irradiation of skin: implications for molecular medicine. *Expert Rev Mol Med.* **4**, 1–22 (2002).
4. Robinson, K. Sun Exposure, Sun Protection, and Vitamin D. *JAMA* **294**, 1541–1543 (2005).
5. Hughes, M.C., Williams, G.M., Baker, P. and Green, A.C. Sunscreen and prevention of skin aging: a randomized trial. *Ann Intern Med* **158**, 781–790 (2013).
6. Technical Committee ISO/TC 217, Cosmetics. ISO 24444: 2010. Cosmetics - sun protection test methods - in vivo determination of the sun protection factor (SPF). Geneva, Switzerland: International Organization for Standardization; 2010.
7. Pillai, S., Oresajo, C. and Hayward, J. Ultraviolet radiation and skin aging: roles of reactive oxygen species, inflammation and protease activation, and strategies for prevention of inflammation-induced matrix degradation – a review. *Int. J. Cosmet. Sci.* **27**, 17–34 (2005).
8. Maru, G.B., Gandhi, K., Ramchandani, A. and Kumar, G. The role of inflammation in skin cancer. In: *Inflammation and Cancer* (Aggarwal, B.B., Sung, B. and Gupta, S.C. eds.), pp. 427–469. Springer, Basel (2014).
9. Haywood, R., Wardman, P., Sanders, R. and Linge, C. Sunscreens inadequately protect against ultraviolet-A-induced free radicals in skin: implications for skin aging and melanoma? *J Invest Dermatol.* **121**, 862–868 (2003).
10. Afaq, F. and Katiyar, S.K. Polyphenols: Skin Photoprotection and Inhibition of Photocarcinogenesis. *Mini Rev Med Chem.* **11**, 1200–1215 (2011).
11. Lin, J.Y., Selim, M.A., Shea, C.R., et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. *J Am Acad Dermatol.* **48**, 866–874 (2003).

12. Lin, J.Y., Tournas, J.A., Burch, J.A., Monteiro-Riviere, N.A. and Zielinski, J. Topical isoflavones provide effective photoprotection to skin. *Photodermatol Photoimmunol Photomed.* **24**, 61–66 (2008).
13. Nichols, J.A. and Katiyar, S.K. Skin photoprotection by natural polyphenols: Anti-inflammatory, anti-oxidant and DNA repair mechanisms. *Arch Dermatol Res.* **302**, 71–83 (2010).
14. Couteau, C., Chauvet, C., Paparis, E. and Coiffard, L.J. Influence of certain ingredients on the SPF determined in vivo. *Arch Dermatol Res* **304**, 817–821 (2012).
15. Couteau, C., Chauvet, C., Paparis, E. and Coiffard, L.J. UV filters, ingredients with a recognized anti-inflammatory effect. *PLoS ONE* **7**, e46187 (2012).
16. Frikeche, J., Couteau, C., Roussakis, C. and Coiffard, L.J. Research on the immunosuppressive activity of ingredients contained in sunscreens. *Arch Dermatol Res.* **307**, 211–218 (2015).
17. Sayre, R. Sun-protection factor confounded by anti-inflammatory activity of sunscreen agents? *J Am Acad Dermatol.* **69**, 481 (2013).
18. Haydar, K. and Burkhart, C.G. Sunscreen regulations and use of anti-inflammatory agents in sunscreens. *Dermatol Online J.* **19** (7), 18969 (2013).
19. Staton, J. and Feng, H. Anti-inflammatory effects of sunscreens – wonder or science? *Sci Beauty* **4**, 57–61 (2015).
20. Werner, M., Herling, M., Garbe, B., Theek, C., Tronnier, H., Heinrich, U. and Braun, N. Determination of the Influence of the Antiphlogistic Ingredients Panthenol and Bisabolol on the SPF Value in vivo. *Skin Pharmacol Physiol.* **30**, 284–291 (2017).
21. Ou-Yang, H., Stanfield, J., Cole, C., Appa, Y. and Rigel, D. High-SPF sunscreens (SPF≥70) may provide ultraviolet protection above minimal recommended levels by adequately compensating for lower sunscreen user application amounts. *J Am Acad Dermatol.* **67**, 1220–7 (2012).
22. Ou-Yang, H., Stanfield, J., Cole, C., Appa, Y. and Rigel, D. High sun-protection factor sunscreens (≥70) may provide ultraviolet protection above minimal recommended levels by adequately compensating for lower sunscreen user application amounts. *J Am Acad Dermatol.* **69**, 481–3 (2013).
23. Lim, H.W. and Wang, S.Q. What is the significance of anti-inflammatory activity of UV filters in sunscreens? *J Am Acad Dermatol.* **69**, 483 (2013).
24. Jovanovic, Z., Schornstein, T., Sutor, A., Neufang, G. and Hagens, R. Conventional sunscreen application does not lead to sufficient body coverage. *Int J Cosmet Sci.* **39**(5), 550–5 (2017).
25. Pissavini, M. and Diffey, B. The likelihood of sunburn in sunscreen users is disproportionate to the SPF. *Photodermatol Photoimmunol Photomed.* **29**, 111–5 (2013).