

**Reply to: “Comment on ‘Anti-aging effects of ingenol mebutate for patients with actinic keratosis’ and phenol-croton oil peelings”**



We are pleased that Wambier et al<sup>1</sup> have provided additional commentary on our article linking phenol-croton oil peel to the application of topical ingenol mebutate, as both share similar essential phytochemical structures. As mentioned by Wambier et al, phenol-croton oil, which has chemical structures and enzymatic targets similar to those of ingenol mebutate, can eradicate mutated keratinocytes and reset follicular stem cells into basal layer cells. This process, which induces the remodeling and promotes collagen formation in the dermis, is fundamentally consistent with our notion of the antiaging mechanism of ingenol mebutate. Furthermore, in another study,<sup>2</sup> we observed that the application of ingenol mebutate resulted in decreased expression of apoptosis-related molecules such as p53 and BCL2, apoptosis regulator and increased expression of erythroid differentiation regulator 1, implying that ingenol mebutate modulates cell apoptosis and apoptosis-associated factors. As ingenol mebutate and the phorbol ester contained in croton oil share a similar structure, it would be effectively helpful to consider an evaluation of apoptosis-related factors when performing a clinical study of phenol-croton oil peels for the treatment of actinic keratosis and actinic cheilitis.

After reviewing the article by Wambier et al on the phenol peel,<sup>3</sup> we were fascinated by the persisting effect of phenol on pigmentation, as well as by its dramatic renovation against wrinkles, because unlike ingenol mebutate, phorbol esters (which contain phenol as an adjuvant agent) can reach the reticular dermis. Such deeper penetration into the dermis during chemical peels may result in both long-lasting and rejuvenating effects for chronically photo-damaged facial skin. However, in the case of an

Asian with a darker skin tone (Fitzpatrick skin types of III or IV), phenol peels might induce hypertrophic scar and postinflammatory hyperpigmentation.<sup>3,4</sup> Therefore, to prevent postinflammatory hyperpigmentation in Asian patients, careful attention should be paid to the doctor's instructions before, during, and after the procedure.

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**REFERENCES**

1. Wambier CG, Lee KC, Bertolini TM, et al. Comment on “Anti-aging effects of ingenol mebutate for patients 1 with actinic keratosis” and phenol-croton oil peelings. *J Am Acad Dermatol.* 2019;80(6):e185-e186.
2. Woo YR, Lim JH, Jeong SW, et al. Analysis of apoptosis-associated molecules erythroid differentiation regulator 1, bcl-2 and p53 in actinic keratosis after treatment with ingenol mebutate. *Exp Dermatol.* 2017;26:1012-1017.
3. Wambier CG, Lee KC, Soon SL, et al. Advanced chemical peels: phenol-croton oil peel. *J Am Acad Dermatol.* doi: <https://doi.org/10.1016/j.jaad.2018.11.060>.
4. Lee KC, Wambier CG, Soon SL, et al. Basic chemical peeling-superficial and medium-depth peels. *J Am Acad Dermatol.* doi: <https://doi.org/10.1016/j.jaad.2018.10.079>.

<https://doi.org/10.1016/j.jaad.2019.01.064>