Comment on "Anti-aging effects of ingenol mebutate for patients with actinic keratosis" and phenol-croton oil peelings

To the Editor: We have read with interest the article by Kim et al,[1] which discusses the cosmetic benefits of ingenol mebutate. Essential phytochemical insights are presented in this letter to link such treatment with an established dermatologic resurfacing procedure for chronic photodamage, the phenol-croton oil peel.[2]

Croton tiglium (Euphorbiaceae) oil has been used in Western medicine since the 1800s[3] and in Eastern medicine for millennia. In the 1920s, phorbol esters, a class of toxic diterpenes, were discovered in croton oil[4] and were later found in other species of the genera *Croton*, *Sapium*, and *Euphorbia*.[5] In the 1960s the medical technique of mixing drops of croton oil with phenol was developed to create a deep chemical peel for treatment of extremely photodamaged facial skin, with long-lasting impressive results.[2] Croton oil is a rich natural matrix of phorbol esters that have the same general structure yet vary in their composition by ester bonding to hydroxyl groups.[6] (Fig 1, *A-C*). For example, the extremely potent phorbol 12—myristate 13—acetate (Fig 1, *C*) has 2 esters on a tigliane skeleton. Phorbol 12—myristate 13—acetate rapidly triggers numerous biochemical functions in cells, the most notorious of which are related to the strong membrane activation of protein kinase C isoforms.[7] Ingenol mebutate (Fig 1, *D*) is a diterpenoid ester isolated from the *Euphorbia peplus* (Euphorbiaceae), which has one ester on an ingenane skeleton. It shares enzymatic targets with croton oil phorbol esters on account of structural similarities (Fig 1, *C* and *D*). Phenol-croton oil peels have the potential to eradicate mutated keratinocyte clones by causing cytotoxic necrosis in the epidermis and papillary and reticular dermis and by resetting the basal layer from deep-seated follicular stem cells, which are naturally protected from ultraviolet light. This topical procedure also promotes an appealing dermal effect by producing a neocollagenesis band and erasing elastosis.[2]

Compared with the phenol-croton oil chemical peel, ingenol mebutate peels have mild antiaging effects even at concentrations of 0.05% (Figs 2 and 3). One hypothesis for this difference in efficacy is the fact that in this commercial presentation, ingenol mebutate might be unable to reach the reticular dermis. Conversely, phorbol esters penetrate far deeper during chemical peels that also contain phenol as an adjuvant agent. Nevertheless, these secondary effects, although mild, are important motivators for endurance of the typical downtime period of such treatment.

Thus, it is possible that ingenane diterpenoid esters from family Euphorbiaceae, such as ingenol mebutate, have an effect on photoaging by similar mechanisms of the phorbol esters present in classic peeling preparations containing croton oil. Clinical trials exploring the plausibility of this possibility with a higher concentration are yet to be performed, as are clinical trials to evaluate safety and long-term efficacy of phenol-croton oil peels for the treatment of actinic keratoses and actinic cheilitis.

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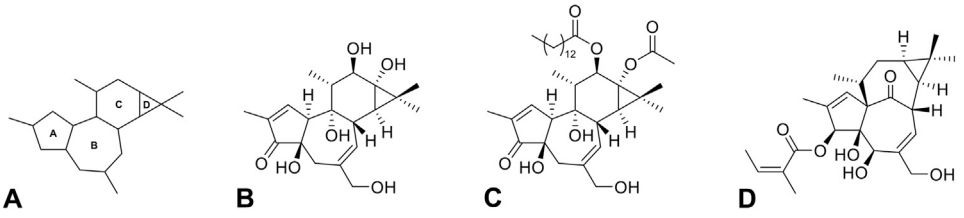

Fig 1. **A**, Tigliane, the carbon framework of phorbol and the phorbol esters, contains 4 rings designated A, B, C, and D. **B**, Phorbol, the parent diterpene of phorbol esters, contains 5 hydroxyl groups. **C**, Phorbol 12—myristate 13—acetate. **D**, Structure of ingenol mebutate.

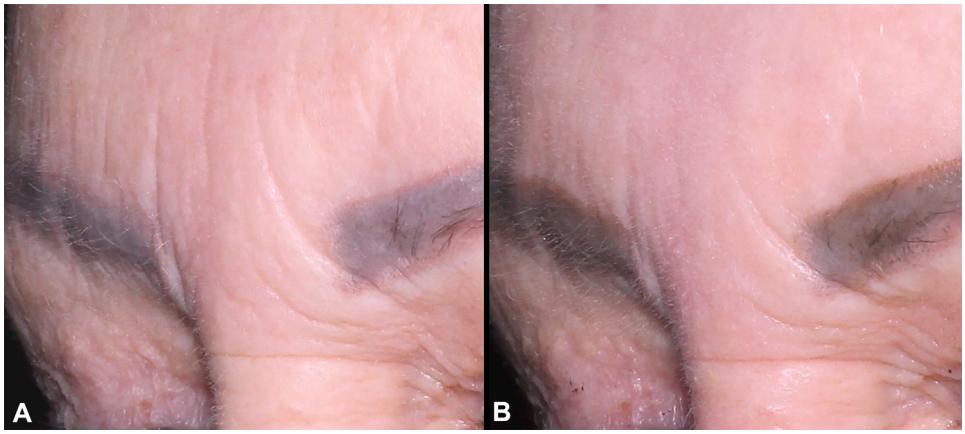

Fig 2. Photoaging treatment with a segmental Picato peel. Close-up of before (**A**) and 3 months after (**B**) a 0.05% ingenol mebutate chemical peel performed on a patient with cardiac contraindications for a standard phenol-croton oil peel. The peel was performed on 2 consecutive days; it was applied over the lower forehead, glabella, and eyelids, showing modest effects compared with the usual results of a deep chemical peel such as Hetter 0.4% croton oil in 35% phenol.

Fig 3. Photoaging treatment with a segmental Picato peel. Frontal view before (**A**) and during the downtime period, on the fourth postoperative day, showing brisk erythema and yellow-brown crusts (**B**) There was involution of the edema and less exudate than on the previous day. After 3 months, pigmentation and shallow wrinkles improved, reflecting injury at the level of the papillary dermis, as in a medium-depth peel (**C**). The patient was wearing mascara and had a touch-up of the eyebrow's permanent makeup 1 month after the procedure.

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