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Note

Commentary to the article "Human skin penetration of the major components of Australian tea tree oil applied in its pure form and as a 20% solution *in vitro*"

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Abstract

This note summarises recent studies on skin penetration of terpinen-4-ol, which is the main component of tea tree oil [S.E. Cross, M. Russell, I. Southwell, M.S. Roberts, Human skin penetration of the major components of Australian tea tree oil applied in its pure form and as a 20% solution in vitro, Eur. J. Pharm. Biopharm. doi: 10.1016/j.ejpb.2007.10.002 (in press)]. The influence of different experimental models on obtained skin penetration results is discussed.

Keywords: Skin penetration; Stratum corneum; Tea tree oil; Terpinen-4-ol

A number of drug products and cosmetics present on the market as well as an increase in the number of publications on penetration of its main components show the raising interest in the tea tree oil (TTO) that is applied on the skin in various forms. To study this process, Authors of the commented article, Cross et al. [1], used such an experimental model: Franz diffusion cells, human *epidermis* with *stratum corneum*, application as finite dose, application time to 24 h, non-occlusive and partially occlusive application conditions. Two forms of TTO were applied, namely pure (100%) essential oil and its 20% ethanolic solution. Because terpinen-4-ol is a main component of TTO (content about 40%) in this commentary I would like to focus exclusively on its skin penetration.

When pure TTO was applied in non-occlusive condition, terpinen-4-ol penetration into the acceptor fluid was about 200 μg/cm^2 after 24 h application. Change of application condition to partially occlusive caused raise in penetration by 2.5 times – to about 500 μg/cm^2 after 24 h application. Retention of terpinen-4-ol in *epidermis* with *stratum corneum* was, independently of the application conditions, a few μg/cm^2. Much lesser terpinen-4-ol penetration was noted, when TTO was applied as 20% ethanolic solution. In case of non-occlusive conditions, there was only 25 μg/cm^2 of this terpene in the acceptor fluid, while there was 0.3 μg/cm^2 retention in the *epidermis* with *stratum corneum*.

In our recent studies on *ex vivo* skin penetration and elimination of terpinen-4-ol, we have used different experimental model: that is, flow-through diffusion cells, full human skin, application as infinitive dose, occlusive application condition. Pure terpinen-4-ol (application time to 4 h for absorption study and 1 h for elimination study, elimination time to 4 h), pure TTO (application time to 8 h), pure terpinen-4-ol incorporated in concentration of 5% into grape seeds oil, carbomer hydrogel and o/w emulsion (application time to 4 h for absorption study and 1 h for elimination study, elimination time to 4 h) were applied on the skin. After application time, the skin was separated into layers using tape-stripping technique: three fractions of *stratum corneum* and *epidermis* with *dermis*.

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When pure terpinen-4-ol was applied, its absorption in *stratum corneum* after 1 h was 170 μg/cm^2, while in *epidermis* and *dermis* – 130 μg/cm^2 [2]. Extension of application time to 4 h caused increase in skin layer cumulation to 590 and 780 μg/cm^2 in *stratum corneum* and *epidermis* with *dermis*, respectively. About 35% of the terpene absorbed during 1 h was eliminated from *stratum corneum* after 4 h, while from *epidermis* and *dermis* – about 50% of terpinen-4-ol was eliminated. Eight hours application time of terpinen-4-ol in multi-co-enhancer carrier – pure TTO – caused significant increase in skin cumulation of penetrant to 910 μg/cm^2 and even to 1500 μg/cm^2 in *stratum corneum* and *epidermis* with *dermis*, respectively [3].

To avoid influence of other components of TTO on terpinen-4-ol skin penetration, we incorporated pure terpene in the concentration of 5% into dermatological vehicles: oily solution, hydrogel and o/w emulsion [4]. According to the partition coefficient rule, the greatest absorption of terpinen-4-ol in the skin layers was determined for hydrogel (175 μg/cm^2 in *stratum corneum* and 530 μg/cm^2 in *epidermis* with *dermis* after 4 h application). Significantly lower absorption of terpinen-4-ol was observed after application of oily solution and o/w emulsion – 60 μg/cm^2 in *stratum corneum* and 140 μg/cm^2 in *epidermis* with *dermis* for oily solution, and 80 μg/cm^2 in *stratum corneum* and 100 μg/cm^2 in *epidermis* with *dermis* for o/w emulsion. Desorption rate of terpinen-4-ol from the skin layers depended on its amount absorbed initially.

The same oily solution and hydrogel were applied in humans as infinite dose and in non-occlusive conditions [5]. After 1 h application of oily solution, we have determined 20 μg/cm^2 of terpinen-4-ol in *stratum corneum*, and after hydrogel application – 110 μg/cm^2 of terpene. 2 h elimination process caused decrease in terpinen-4-ol amount in *stratum corneum* to about 5 μg/cm^2 independently of the vehicle used. We have also indicated that a type of vehicle, thus amount of terpinen-4-ol absorbed in *stratum corneum*, influences the number of irritant events caused by this terpene [6].

In contrast to studies by Cross et al. [1] and by Reichling et al. [7], at any stage of our *ex vivo* experiments we have never detected terpinen-4-ol in the acceptor fluid, even though sink conditions were maintained. However, the terpene always cumulated in large or very large amounts in hydrophilic skin layers (*epidermis* with *dermis*). Therefore, it can be assumed that *dermis* served as a natural acceptor for the terpene permeating through *stratum corneum*. *Dermis* was absent in terpinen-4-ol penetration studies performed by Cross et al. [1] and Reichling et al. [7]. High cumulation of terpinen-4-ol in particular skin layers, having been proven by us after its application as infinite dose and in occlusive conditions has indicated that skin layers might have been soaked with terpene or even that microreservoirs containing terpene were formed. The process itself of terpene penetration into the skin and through the skin can be considered as strongly dependant on experimental model used (choice of membrane, its hydration resulting from application conditions, dose applied) and on the carrier for penetrating terpene. This altogether justifies the need for further studies on experimental models as well as on the terpene disposition after its application on the skin in various forms.

In summary, short time in which saturation of *stratum corneum* with terpinen-4-ol occurs, its *ex vivo* cumulation in the skin layers and diffusion into acceptor fluid prove that *in vivo* it can penetrate into the blood circulation. On the other hand, vehicle-dependent absorption and fast elimination of terpinen-4-ol from the skin layers, probably by evaporation process, can reduce possible side effects and decide about safety of TTO usage in various preparations.

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