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Promotion of dermal permeation of bioactive compounds using a microneedle device †

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Abstract: Several natural bioactive compounds are described for their beneficial effects to skin. Nevertheless, for some compounds, dermal absorption is a challenge demanding new methods to enhance skin penetration. In this work, pre-treatment with microneedle device was tested to promote the permeation of caffeine and epicatechin through *ex vivo* pig skin. The results indicated that the microneedle pre-treatment increased the permeation of both compounds at a similar range. Compared to untreated skin, more than 20% higher amounts of caffeine and epicatechin crossed the treated skin. The data support the application of microneedle systems to promote dermal delivery of bioactive compounds.

Keywords: Bioactive compounds; caffeine, epicatechin; skin permeation; microneedles.

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1. Introduction

The skin is the largest organ of the human body and the skin beneficial effects of bioactive compounds such as those found in green tea are reported [1], either by oral or topical administration [2,3]. Catechins are a group of compounds found in green tea and recognized for their antioxidant effects. In fact, a previous randomized clinical trial, where a beverage of green tea providing 1402 mg of total catechins per day was administered, reported skin protection against UV and skin quality enhancement [4]. Topical and oral administration of other natural compounds is also being investigated as skin and systemic protective strategy [5]. Nevertheless, topical application is not a simple strategy and chemical characteristics of compounds can influence skin permeation, such as hydrophobicity [6]. In the case of catechins, skin absorption represents a challenge with different studies investigating the use of drug delivery systems [7–10]. Similarly, the skin permeation of caffeine is also reported as difficult mainly due to its hydrophilic nature, and a microneedle hydrogel was described to increase the transdermal penetration [11]. Indeed, microneedle devices are gaining interest in the last years presenting technical advantages when compared to other delivery systems. One of these advantages corresponds to the disruption of the superficial skin layers, enabling a deeper penetration of the compounds but without associated pain [12,13]. As reviewed by Waghule and colleagues (2019), the possibilities are numerous with the different types of microneedles, different types of applications, and several approved products [13]. In the case of solid microneedles they can be applied in the patch form or as a roller device. The last one with the advantage of having the highest number of pores, which helps the permeation of compounds through the skin [14]. In this work, we aimed to investigate the effect of a

solid microneedle device on the dermal permeation of caffeine and epicatechin, using pig skin as a model mounted on Franz diffusion cells.

2. Materials and Methods

2.1. Reagents and Materials

Caffeine and epicatechin were obtained, respectively, from Fluka Chemical Co. (cat. no. 405218, purity ≥99%) and Sigma-Aldrich (E1753, ≥99%). The microneedle device was from Bloom Beauty (200 micro-meter), obtained from a cosmetical store, and pig skin was obtained from a local butcher.

2.2. Skin permeation experiments

Portions of pig skin were obtained from the outer part of the ear and mounted on static diffusion Franz cells between the donor and receptor compartment. The pre-treatment with the microneedles was performed before montage. Caffeine and epicatechin were applied in the donor compartment either in saline or in acetone vehicle, respectively. An infinite dose was applied in the case of caffeine and in the case of epicatechin the dose applied was 98.3 μg/cm^2. During the experiments, Franz cells were kept at 32 °C with an agitation of 600 rpm. Samples were collected from the receptor compartment at predefined times for quantification of the compounds.

2.3. Quantification of the bioactive compounds

For both caffeine and epicatechin, UV-Vis spectra were gathered in a Varian Cary 50 spectrophotometer to obtain the maximum absorption wavelength for each compound. The resulting spectra showed the maximum absorption wavelength is 273 and 268 nm for caffeine and epicatechin, respectively (data not shown). Onwards the different samples collected from skin permeation experiments were quantified based on calibration curves previously obtained at these wavelengths with the corresponding standards. Epicatechin was also quantified by the Folin-Ciocalteu assay that measures the phenol content, as described in [10]. For this method, control blank permeation experiments were carried out with untreated skin and application of the acetone vehicle without epicatechin.

3. Results and Discussion

3.1. Effect of microneedle pre-treatment on the permeation of caffeine through pig skin

The quantities of caffeine that permeated skin in normal and pre-treatment conditions, after 2h, are represented in Figure 1. The pre-treatment promoted a 26 ± 6% increase in the amount permeated compared to untreated skin.

3.2. Effect of microneedle pre-treatment on the permeation of epicatechin through pig skin

In the case of epicatechin, after 4h permeation, the microneedle pre-treatment promoted an increase superior to 20% in the amount measured by UV spectrometry in the Franz cells' receptors (Figure 2.a). This increment in the skin permeation of epicatechin was also detected by the Folin-Ciocalteu assay (Figure 2.b).

Overall, our results show that microneedle applications increase the permeation of natural bioactive compounds. This is in accordance with other studies where solid microneedle rollers increased skin permeability of therapeutic compounds [15,16].

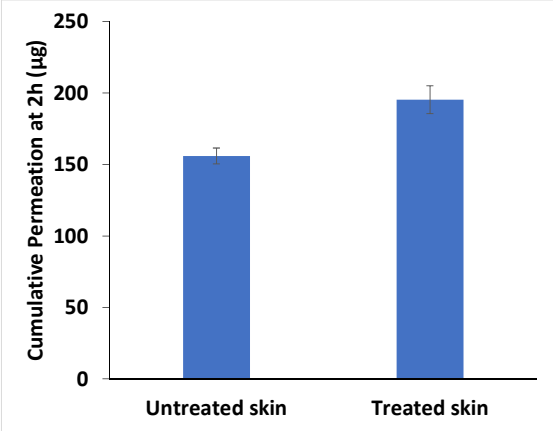
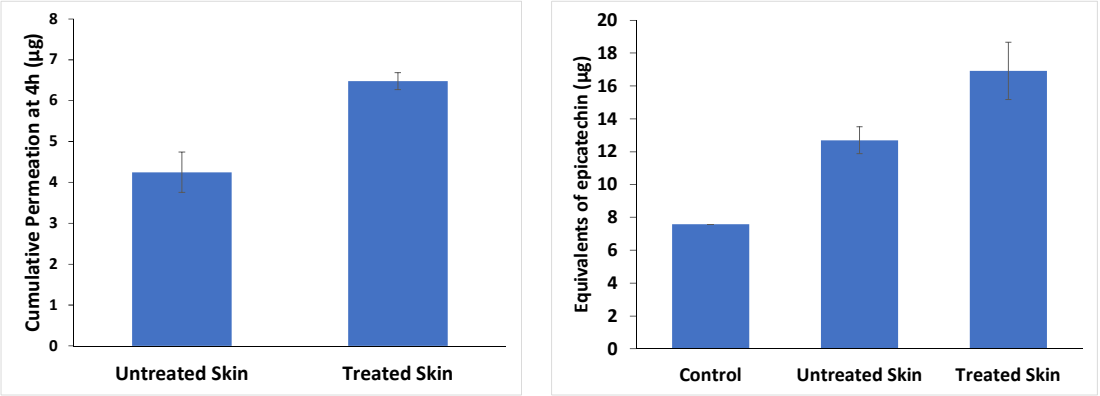


Figure 1. Quantity of caffeine that permeated *ex vivo* pig skin after 2h in normal conditions and after microneedle pre-treatment. Caffeine quantification using UV absorption at 273 nm (n=2).



(**a**) (**b**)

Figure 2. Quantity of epicatechin that permeated *ex vivo* pig skin after 4h in normal conditions and after microneedle pre-treatment (n=2): (a) epicatechin quantification using UV absorption at 268 nm; (b) phenol content quantification using the Foli-Ciocalteu assay.

4. Conclusion

This work shows that the pre-treatment of skin with a microneedle device can be used to enhance the skin penetration of caffeine and epicatechin. Thus, it encourages further research on the application of solid microneedles to promote the transdermal delivery of natural compounds with pharmacological interest.

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