RATIONALE FOR THE USE OF CAFFEINE IN THE GEL FOR CORRECTION OF AGE-RELATED CHANGES IN THE PERIORBITAL ZONE

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Introduction. Gel forms of therapeutic and cosmetic skin care products for different skin areas are becoming increasingly common due to their light texture, the ability to combine a large number of active pharmaceutical ingredients (APIs) of different nature, and high consumer properties. Literature data and analysis of the pharmaceutical market of products in this area indicate the expediency of the complex use of APIs that have anti-edematous, antioxidant, moisturizing, capillary strengthening, muscle relaxant effects and the ability to inhibit the action of free radicals. In previous studies conducted at the Department of Pharmacy Drug Technology, we substantiated the use of acetyltetrapepide-5 in a gel for the periorbital area. However, the desire to create a comprehensive care product prompted us to continue research on other APIs that we consider necessary to include in the gel.

Caffeine is a well-known purine alkaloid that is used not only as a component of tonic drinks, but also as an active ingredient in medicinal and cosmetic products due to its wide range of effects. Due to the high biological activity of caffeine and its ability to penetrate the epidermal barrier, there are currently a large number of topical caffeine-based products aimed at solving problems ranging from cellulite to alopecia [1].

Objective of the study. To screen the literature sources on the effect of caffeine on the physiological processes of the skin and to confirm its potential for the development of a domestic therapeutic and cosmetic gel.

Materials and methods. The research methods included a comprehensive analysis of scientific literature, empirical research, theoretical generalization of the data obtained and their logical analysis.

Results and discussion. Caffeine is 1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione, a purine derivative, an alkaloid found in coffee seeds (1-2 %), tea leaves (2 %), and kola nuts [2]. It exhibits powerful antioxidant and anti-edematous properties; protects cells from carcinogenesis caused by UV radiation and photoaging, prevents excessive accumulation of fat in cells [3].

The mechanism of lymphatic drainage action of caffeine is explained by its ability to tone blood vessels, increase blood microcirculation in the skin, which leads to the removal of excess fluid and thus reduces swelling and inflammation. Caffeine strengthens the structure of cell membranes, retaining moisture in the upper layers of the skin. Due to its antioxidant properties, the ability to deactivate free radicals, caffeine protects the skin from ultraviolet radiation, which leads to the destruction of collagen and accelerated aging with the appearance of premature wrinkles and sagging skin.

The lipolytic effect of this alkaloid is explained by the inhibition of phosphodiesterase activity, which results in the stimulation of fat breakdown during lipolysis [1].

For the use of caffeine in cosmetic products, one of the important factors is the ability to penetrate the skin. It has been established that the maximum rate of caffeine absorption through human skin is 2.24 ± 1.43 μg/cm2/h, and the peak absorption is reached 100 minutes after topical application in vivo [11, 12].

Anti-carcinogenic properties. Numerous scientific studies have shown that caffeine is a pro-apoptotic agent that counteracts cancer processes caused by UV radiation [4, 5, 6]. Thus, topical application of caffeine to the dorsal skin of mice that had been previously exposed to UV radiation for 20 weeks led to increased apoptosis in foci of basal epidermal hyperplasia (probably precancerous lesions), but not in areas with diffuse hyperplasia. Oral administration of green tea (6 mg of dry matter per 1 ml) or caffeine (0.4 mg/ml) as the only source of water during UV irradiation, which was performed twice a week for 20 weeks, reduced the formation of mutant areas by about 40%. The administration of green tea (6 mg dry matter per 1 ml) orally or daily topical application of caffeine (6.2 μmol) 5 times a week after the completion of UV irradiation accelerated the disappearance of mutant p53-positive areas and increased the degree of their elimination. This study showed that the chemopreventive effect of caffeine or green tea may occur due to the pro-apoptotic effect mainly on early precancerous lesions [7].

Subsequent studies have confirmed that topical application of caffeine (dissolved in acetone at 1-2% by weight by volume) to the skin of mice after UV irradiation helps to remove DNA-damaged keratinocytes and can partially reduce photodamage and photocarcinogenesis [8].

Another study in 2016 showed that the use of caffeine in solution protected mouse skin from UV-induced photoaging by downregulating matrix metalloproteinases, which are known to be responsible for collagen breakdown [9]. A study of the antioxidant properties of caffeine in 2019 showed that the combination of this alkaloid with sunscreens increased in vivo protection against UV exposure by about 25% [10].

Anti-edematous properties. According to scientific studies using computed tomography, it was found that caffeine can change the microcirculation of blood vessels. Oral administration of the alkaloid in a dose of 250 mg leads to a 30% increase in blood flow in the brain. It has also been found that a lower dose of caffeine (100 milligrams) has a positive effect on blood microcirculation in the vessels of the human fundus [13, 14].

A study of the effectiveness of an anti-cellulite preparation containing a 7% caffeine solution showed that the use of this product led to a decrease in lipodystrophy and improved thigh microcirculation in all women who participated in the study [15].

In addition, clinical trials of cosmetic forms such as patches and gels containing the active ingredient caffeine have shown its ability to reduce swelling due to its vasoconstrictor effect and lighten dark skin under the eyes [16,17].

Safety of caffeine in cosmetics. A study of the effect of caffeine and hyaluronic acid on collagen biosynthesis in human skin fibroblasts showed that caffeine can inhibit this process by blocking β1-integrin and insulin-like growth factor receptors. However, the results of the study show that the use of caffeine in a concentration of

up to 3% is considered safe, non-toxic, and easily penetrates human skin and does not damage liver cells [18, 19].

Physical properties. Caffeine is moderately soluble in water (1:60), readily soluble in boiling water (1:2), and slightly soluble in ethanol and ether (1:100) [2]. The introduction of this active ingredient into the gel composition increases its permeability through the epidermal barrier [29].

Conclusions. The scientific literature on the effect of caffeine on the physiological processes of the skin was analyzed. It was found that the introduction of caffeine into the composition of the gel for the periorbital zone will help reduce edema by increasing microcirculation, protect the skin from photoaging due to the antioxidant properties of caffeine and help reduce hyperpigmentation. The high potential of caffeine for the development of a domestic medical and cosmetic gel for comprehensive skin care has been confirmed.

References:

1. Herman A, Herman AP. Caffeine's mechanisms of action and its cosmetic use Skin Pharmacol Physiol. 2013;26:8–14
2. Від субстанції до ліків: Навчальний посібник/ П.А. Безугий, В.В. Болотов, І.С. Гриценко, С.М. Дроговоз, О.В. Зайченко, І.А. Зупанець, Б.А. Самура, Е.В. Супрун, В.П. Черних, Л.О. Шемчук; Під ред. В.П. Черних. - Харків: Вид-во НФаУ: Золоті сторінки, 2005. - 1244 с.
3. Oh CC, Koh WP. Reply to: “Coffee and skin-Considerations beyond the caffeine perspective” J Am Acad Dermatol. 2020;82(2):e65–e66 doi: 10.1016/j.jaad.2019.10.021
4. Conney AH, Lu YP, Lou YR, Kawasumi M, Nghiem P. Mechanisms of caffeine-induced inhibition of UVB carcinogenesis Front Oncol. 2013;3:144
5. Heffernan TP, Kawasumi M, Blasina A, Anderes K, Conney AH, Nghiem P. ATR-Chk1 pathway inhibition promotes apoptosis after UV treatment in primary human keratinocytes: Potential basis for the UV protective effects of caffeine J Invest Dermatol. 2009;129:1805–15
6. Lu YP, Lou YR, Peng QY, Xie JG, Nghiem P, Conney AH. Effect of caffeine on the ATR/Chk1 pathway in the epidermis of UVB-irradiated mice Cancer Res. 2008;68:2523–9
7. Lu YP, Lou YR, Liao J, Xie JG, Peng QY, Yang CS, et al Administration of green tea or caffeine enhances the disappearance of UVB-induced patches of mutant p53 positive epidermal cells in SKH-1 mice Carcinogenesis. 2005;26:1465–72
8. Koo SW, Hirakawa S, Fujii S, Kawasumi M, Nghiem P. Protection from photodamage by topical application of caffeine after ultraviolet irradiation Br J Dermatol. 2007;156:957–64
9. Choi HS, Park ED, Park Y, Han SH, Hong KB, Suh HJ. Topical application of spent coffee ground extracts protects skin from ultraviolet B-induced photoaging in hairless mice Photochem Photobiol Sci. 2016;15:779–90

10. Rosado C, Tokunaga VK, Sauce R, de Oliveira CA, Sarruf FD, Parise-Filho R, et al Another reason for using caffeine in dermocosmetics: sunscreen adjuvant Front Physiol. 2019;10:519
11. van de Sandt JJ, van Burgsteden JA, Cage S, Ca rm ich ae l PL , Di ck I , Ke nyo n S, Kor int h G , Larese F, Limasset JC, Maas WJ, Montomoli L, Nielsen JB, Payan JP, Robinson E, Sar-torelli P, Schaller KH, Wilkinson SC, Wil-liams FM: In vitro predictions of skin ab-sorption of caffeine, testosterone, and ben-zoic acid: a multi-centre comparison study. Regul Toxicol Pharmacol 2002; 39: 271–281
12. Zesch A, Schaefer H, Stuttgen G: The quan-titative distribution of percutaneously ap-plied caffeine in the human skin. Arch Der-matol Res 1979; 266: 277–283
13. Came ron OG, Modell JG, Ha riharan M : Caf-feine and human cerebral blood flow: a posi-tron emission tomography study. Life Sci 1990 ; 47: 1141–1146
14. Okuno T, Sugiyama T, Tominaga M, Kojima S, I keda T: Effec ts of ca ffeine on microci rcu-lation of the human ocular fundus. Jpn J Ophthalmol 2002; 46: 170–176
15. Lupi O, Semenovitch IJ, Treu C, Bottino D, Bouskela E: Evaluation of the effects of caf-feine in the microcirculation and edema on thighs and buttocks using the orthogonal polarization spectral imaging and clinica l parameters. J Cosmet Dermatol 2007; 6: 102–107.
16. Ahmadraji F, Shatalebi MA. Evaluation of the clinical efficacy and safety of an eye counter pad containing caffeine and vitamin K in emulsified Emu oil base Adv Biomed Res. 2015;4:10
17. Amnuaikit T, Maneenuan D, Boonme P. Evaluation of caffeine gels on physicochemical characteristics and in vivo efficacy in reducing puffy eyes J App Pharm Sci. 2011;1:56–9
18. Donejko M, Przylipiak A, Rysiak E, Głuszuk K, Surażyński A. Influence of caffeine and hyaluronic acid on collagen biosynthesis in human skin fibroblasts Drug Des Devel Ther. 2014;8:1923–8
19. Gajewska, M., Paini, A., Benito, J. S., Burton, J., Worth, A., Urani, C., & Schramm, K. W., 2015. In vitro-to-in vivo correlation of the skin penetration, liver clearance and hepatotoxicity of caffeine. Food and Chemical Toxicology, 75, pp. 39-49.