Macedonian pharmaceutical bulletin, 69 (Suppl 1) 243 - 244 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.119
Short communication

In vitro transdermal delivery and skin metabolism of salidroside from *Rhodiola rosea* extract

Jindra Valentová[1*], Andrea Baránková[1], Desana Matušová[2]

[1]*Department Chemical Theory of Drugs, Faculty of Pharmacy, Comenius University Bratislava, Odbojárov 10, 832 32 Slovakia*
[2]*Department Chemical Theory of Drugs, Faculty of Pharmacy, Comenius University Bratislava, Odbojárov 10, 832 32 Slovakia*

Introduction

Salidroside (SAL), a phenylpropanoid glycoside extracted from the root of *Rhodiola rosea*, is known for its pharmacological properties such as antioxidation, anti-inflammation, neuroprotective, anti-cancer, and cardioprotective properties (Ching et al., 2015; Zhao et al., 2021). Salidroside is effective in suppressing solar ultraviolet-induced skin inflammation (Wu et al., 2016) and prevents skin carcinogenesis (Kong and Xu, 2016).

The hydrophilicity of SAL leads to poor skin permeability, therefore different liposomal nanocarriers for SAL were tested (Zhang, 2015). To improve the SAL transdermal delivery, the transdermal patches containing the dry extract from *Rhodiola rosea* were formulated. The patch adhesion and dissolution of SAL were tested. The most promising formulations were matrix systems containing two different combinations: gelatine with chitosan or pectin with polyethylene oxide (Haršányová et al., 2018). Based on previous results, the aim of our work was the evaluation of transdermal permeation of SAL from *Rhodiola rosea* extract

Materials and methods

The dry extract of *Rhodiola rosea* was manufactured by the company Calendula (Slovakia) for drug dosage preparation, including transdermal patches.

The transdermal permeation experiment was performed using the Franz diffusion cells with a volume of 5.6 mL and the area of skin available for diffusion was 1.5 cm^2. The porcine skin was used as a diffusion membrane. The donor vehicles contained: salidroside (0.1 %) in PBS solution; suspension of 600 mg dry extracts of *Rhodiola rosea* in water. The acceptor phase containing saline with phosphate buffer (pH 7.4) was constantly stirred and the temperature was maintained at 32 °C.

HPLC method was developed for salidroside detection in the acceptor phase. Analysis was performed on the C18 column Poroshell 120 EC (50 x 4.6 mm, 2.7 μm) with mobile phase consisting of (A) methanol with 0.1% of formic acid, 1mM of ammonium formate and (B) water with 0.1% of formic acid, and 1 mM of ammonium formate. Salidroside was separated using gradient elution; the retention time was 8.3 min.

The MS detection of isolated salidroside and its metabolite was performed by HRMS system Orbitrap-XL mass spectrometer. The dry *Rhodiola rosea* extracts 1 and 2 contained 22% and 5 % of salidroside, respectively.

Results and discussion

During the preliminary study of the transdermal permeation of 0.1% of salidroside in phosphate buffer solution through pig skin, salidroside was detected in the acceptor phase after 5 hours of the experiment. After 24 h, salidroside was not present in the acceptor liquid and a new peak appeared on the chromatogram, which had the same UV spectrum as salidroside but the retention time was shifted.

We concluded that it may be a metabolic transformation of salidroside itself. The HRMS analysis confirmed salidroside (Mr^{neg-1} 299.0956) in the acceptor phase after 5 hours and the structure of aglycone tyrosol

*jindra.valentova@uniba.sk

(Mr neg-1 137.0956) was confirmed in the acceptor phase after 24 hours (Fig. 1).

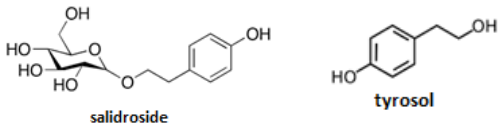

Fig.1. Structure of salidroside and its detected metabolite

The chemical stability of the salidroside was proven under experimental conditions, therefore the influence of the skin on metabolic hydrolysis of salidroside was tested. Pieces of pig skin were placed in a solution of salidroside in PBS and incubated for 24 hours. The solution was analyzed at different time periods. It was confirmed that salidroside was present in the solution for 5 hours, consequently, the metabolite concentration increased, and salidroside was transformed completely into tyrosol within 24 hours.

The metabolic hydrolysis of salidroside also occurred upon transdermal permeation of suspension of *Rhodiola rosea* extract through porcine skin. The permeation profile of salidroside is presented in Fig. 2. The values of cumulative permeated amount are average from 6 samples. The salidroside molecule permeated for 5 h, later salidroside was hydrolyzed, and after 7 h permeation both salidroside and its metabolite were detected. After a long time period, only tyrosol permeated through the skin. Based on the results we can assume the occurrence of enzymatic hydrolysis of salidroside during transdermal delivery.

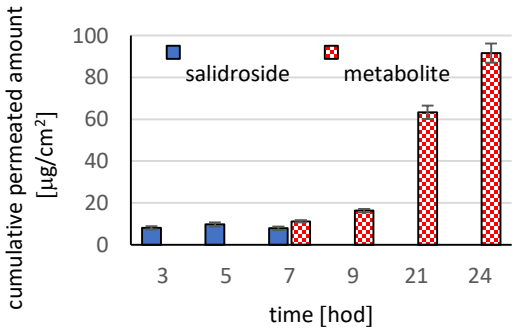

Fig. 2. Permeation profile of salidroside and its metabolite from *Rhodiola rosea* extracts through porcine skin.

Enzymatic activity is localized in special cell types in the skin. Enzymes that have been identified in the Stratum corneum include lipases, proteases, phosphatases, sulfatases, and glycosidases (Baron, 2011). Enzymatic hydrolysis in the skin is used for many drugs to prepare lipophilic prodrug forms that are converted into active compounds in the skin (Imai, 2016). The metabolism of salidroside has been not described yet

Conclusion

Transdermal permeation and metabolism of salidroside through porcine skin were evaluated. Results confirmed the hydrolysis of glycosidic bond in salidroside and the formation of tyrosol metabolite, which should be taken into account in the formulation of transdermal patches containing salidroside and other natural glycosides. This is of importance when considering the evaluation of the therapeutic potential of salidroside in skin inflammation and skin cancer.

Acknowledgments: The work was supported by grant Vega 1/0145/20

References

Chiang, H. M., Chen, H. C., Wu, C. S., Wu, P. Y., & Wen, K. C., 2015. Rhodiola plants: Chemistry and biological activity. J. Food Drug Anal. 23, 359-369. https://doi.org/10.1016/j.jfda.2015.04.007

Zhao, C. C., Wu, X. Y., Yi, H., Chen, R., Fan, G., 2021. The therapeutic effects and mechanisms of salidroside on cardiovascular and metabolic diseases: An updated review. Chem. Biodivers. 18, e2100033. https://doi.org/10.1002/cbdv.202100033

Wu D., Yuan P., Ke C., Xiong H., Chen J., Guo J., Lu M., Ding Y., Fan X., Duan Q., Shi F., Zhu F., 2016. Salidroside suppresses solar ultraviolet-induced skin inflammation by targeting cyclooxygenase-2. Oncotarget. 7, 25971-25982. https:// doi: 10.18632/ oncotarget.8300

Sun, A. Q., Ju, X. L., 2021. Advances in research on anticancer properties of salidroside. Chin. J. Integr. Med., 27, 153-160. https://doi.org/10.1007/s11655-020-3190-8

Zhang, Y., Zhang, K., Wu, Z., Guo, T., Ye, B., Lu, M., Zhao , Zhu CH., Feng, N. 2015. Evaluation of transdermal salidroside delivery using niosomes via in vitro cellular uptake. Int. J. Pharm., 478, 138-146.http://dx.doi.org/10.1016/j.ijpharm.2014.11.018

Haršányová, T., Bauerová, K., Matušová, D., 2018. Matrix adhesive system containing plant extract. Monatsh. Chem. 149, 883-885. hhttps://doi.org/10.1007/ s00706-017-2139x

Baron, J.M., Merk, H.F., 2001 Drug metabolism in the skin. Curr. Opin. Allergy Clin. Immunol. 1, 287-291. doi: 10.1097/01.all.0000011028.08297.b3

Imai, T., Ariyoshi, S., Ohura, K., Sawada, T., & Nakada, Y., 2016. Expression of carboxylesterase isozymes and their role in the behavior of a fexofenadine prodrug in rat skin. J. Pharm. Sci. 2016, 105, 714-721. doi: 10.1002/jps.24648.