Rhodiola rosea L. modulates inflammatory processes in a CRH-activated BV2 model: targeting microglia with adaptogens.

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Introduction *Rhodiola rosea* L. has been used for years in the traditional medicine of several countries as an adaptogen drug, able to preserve homeostasis in response to stress stimuli. A recent systematic review suggested evidence for the use of *R. rosea* for enhancing physical performance and certain mental health conditions, by alleviating mental fatigue [1]. Corticotropin releasing hormone (CRH) and corticosterone are strictly related to physical and psychological stress [2]. *R. rosea* was recently found to decrease the stress-induced CRH and peripheral corticosterone levels, suggesting that modulation of the hypothalamus-pituitary-adrenal axis is necessary for the adaptogenic activity [3]. Increasing evidence suggests the involvement of neuroinflammation in response to CRH [4] with a crucial role of microglia in the stress-related symptoms.

Aim of the study This study aims to investigate the possible modulation of molecular inflammatory processes elicited by a standardized *Rhodiola rosea* L. ethanolic extract in an *in vitro* neuroinflammatory model of CRH-stimulated BV2 microglial cells.

Methods BV2 cells were stimulated with CRH 100 nM at different time points, and then the changes induced by CRH on microglial activation were evaluated, focusing on cytokines production, activation of intracellular inflammatory pathways NF-κB nuclear translocation, and heat shock protein 70 (Hsp70) expression. The adaptogenic activity of *R. rosea* was found to be concentration-dependent and to vary depending on the extract used [5]. Thus, in this work, we used a standardized pharmaceutical-grade *R. rosea* extract containing 2.7% m/m rosavin and 1% m/m salidroside.

Results We found that *R. rosea* extract 20 µg/ml was able to counteract the neuroinflammatory effect produced by CRH through the inhibition of NF-κB nuclear translocation, with a mechanism of action involving the modulation of mitogen-activated protein kinase-activated protein kinase 2 (MKK2), extracellular signal-regulated kinase 1/2 (ERK 1/2) and c-Jun n-terminal kinase (JNK), resulting in a reduction of Hsp70 expression.

Conclusion In conclusion, the *in vitro* model of stress-induced neuroinflammation gave information on the molecular mechanism involved in *R. rosea* anti-stress activity and may be useful for the study of other adaptogen drugs.

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