

***N*-alkylamides: from plant to brain**

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ABSTRACT

Background: Plant *N*-alkylamides (NAAs) are bio-active compounds with a broad functional spectrum. In order to reach their pharmacodynamic targets, they have to overcome several barriers of the body in the absorption phase. The permeability kinetics of spilanthol (a diene NAA) and pellitorine (a triene NAA) across these barriers (*i.e.* skin, oral/gut mucosa, blood-brain barrier) were investigated.

Methods: The skin and oral mucosa permeability were investigated using human skin and pig mucosa in an *ex vivo in vitro* Franz diffusion cell set-up. The gut absorption characteristics were examined using the *in vitro* Caco-2 cell monolayer test system. The initial blood-brain barrier transport kinetics were investigated in an *in vivo* mice model using multiple time regression and efflux experiments. Quantification of both NAAs was conducted using HPLC-UV and bio-analytical UPLC-MS methods.

Results: We demonstrated that spilanthol and pellitorine are able to penetrate the skin after topical administration. It is likely that spilanthol and pellitorine can pass the endothelial gut as they easily pass the Caco-2 cells in the monolayer model. It has been shown that spilanthol also crosses the oral mucosa as well as the blood-brain barrier.

Conclusion: It was demonstrated that NAAs pass various physiological barriers *i.e.* the skin, oral and gut mucosa, and after having reached the systemic circulation, also the blood-brain barrier. As such, NAAs are cosmenutriceuticals which can be active in the brain.

Key words: Plant *N*-alkylamides, pharmacokinetics, mucosa/skin, blood-brain barrier (BBB), cosmenutriceuticals