QUANTITATIVE STRUCTURE – ADME PROPERTIES RELATIONSHIP OF BOERAVINONES A-J

Nataša Milošević[1*], Maja Milanović[1], Nebojša Pavlović[1], Larisa Đurić[1], Nunzio Antonio Cacciola[2], Francesca Borrelli[3], Nataša Milić[1]

[1]*University of Novi Sad, Faculty of Medicine, Department of Pharmacy, Novi Sad, Serbia*

[2]*University of Naples Federico II, Department of Veterinary Medicine and Animal Productions, Naples, Italy*

[3]*University of Naples Federico II, School of Medicine and Surgery, Department of Pharmacy, Naples, Italy*

**email: natasa.milosevic@mf.uns.ac.rs*

INTRODUCTION:

Boeravinones A-J, rotenoids extracted from Indian ayurvedic herb, *Boerhaavia diffusa* are identified as potent antioxidants, spasmolytics as well as inhibitors of the BCRP multidrug transporter and their structure has been confirmed by 1H NMR and 13C NMR spectroscopy. However, most of the drug candidates do not meet the expected strict criteria for new drugs and only 4.3% of them proceed from the preclinical stage to the Phase III trial with a positive outcome. The main causes for high attrition rates are toxicity, inadequate pharmacokinetics and low bioavailability. Therefore, it is crucial to optimize the ADME (absorption, distribution, metabolism and excretion) profile of the new drug candidates and to understand how structural changes can affect their pharmacokinetic/pharmacodynamic relationship.

OBJECTIVES:

To conduct *in silico* analysis of physico-chemical properties and ADME behaviour for ten boeravinones.

METHOD / DESIGN:

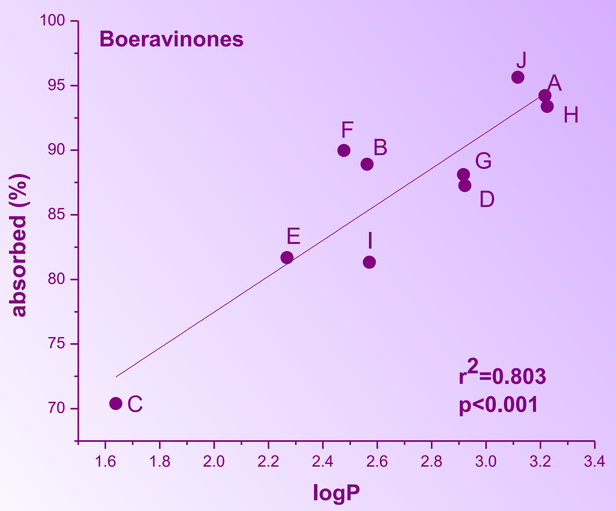
In silico analysis of molecular properties and pharmacokinetic characteristics of ten boeravinones (A-J) was conducted based on their structure. Molecular properties of the analysed boeravinones as fraction of sp3 hybridized carbon atoms (Fsp3) and polar surface area (PSA) were determined by SwissADME software. Software pkCSM was applied for the calculation of lipophilicity (logP), the percent of intestinal absorption (%IA), volume of distribution in stationary state (Vdss), fraction of unbound compound (FU) for plasma proteins, permeation through blood brain barrier (log BBB) and skin permeability (logKp).

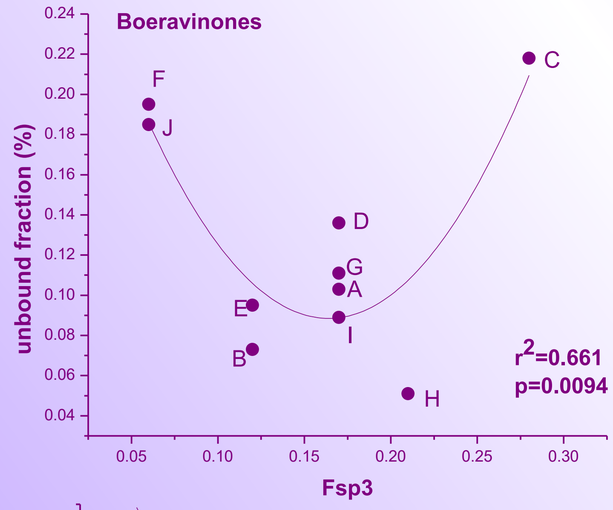
RESULTS:

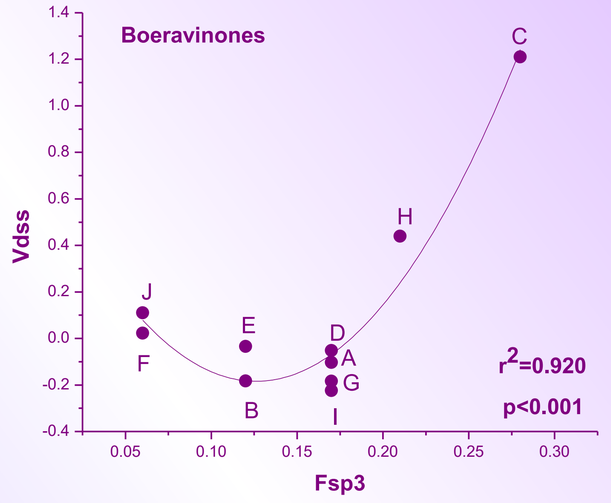
The percent of intestinal absorption (%IA) of boeravinones A-J can be presented as a linear function (r^2=0.803, p<0.001) of lipophilicity expressed as logP. Distribution parameters such as volume of distribution in stationary state (Vdss) and fraction of drug unbound to plasma proteins (FU) were statistically significant associated to molecular flatness expressed as fraction of sp3 hybridized carbon atoms (Fsp3).

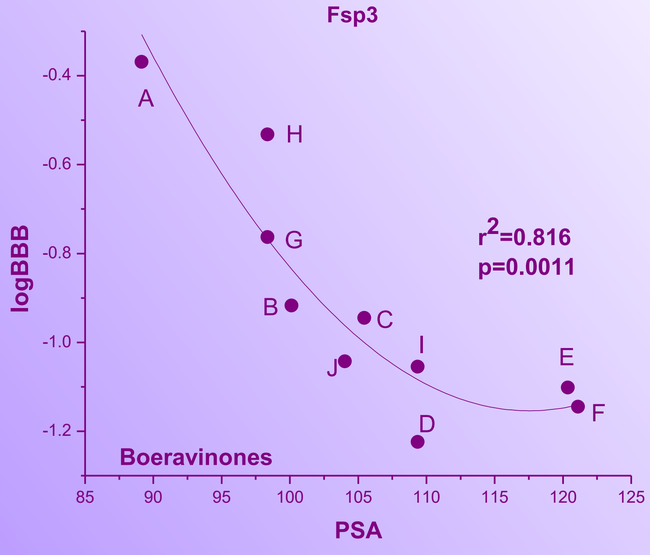
Both Vdss and FU can be described as parabolic function of Fsp3 (r^2=0.920, p<0.001 and r^2=0.661, p=0.009) for boeravinones A-J.

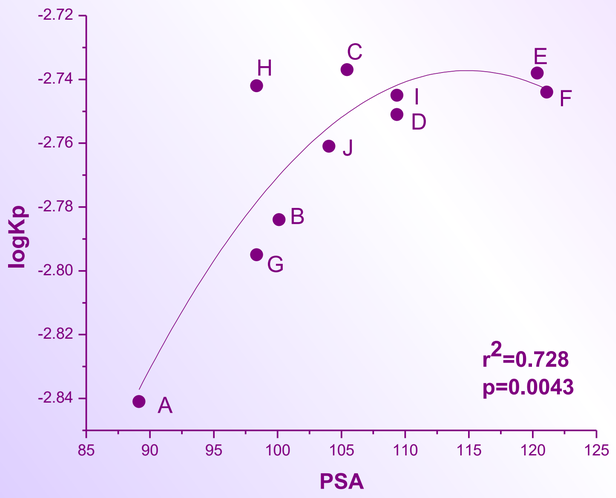
The permeability through different membranes was governed by the polarity of boeravinones A-J quantified as PSA. Additionally, the permeability through the brain-blood barrier (logBB) and the skin (logKp) were correlated with PSA with high statistical quality (r^2=0.816, p=0.001 and r^2=0.729, p=0.004) and the parabolic functions were also obtained.

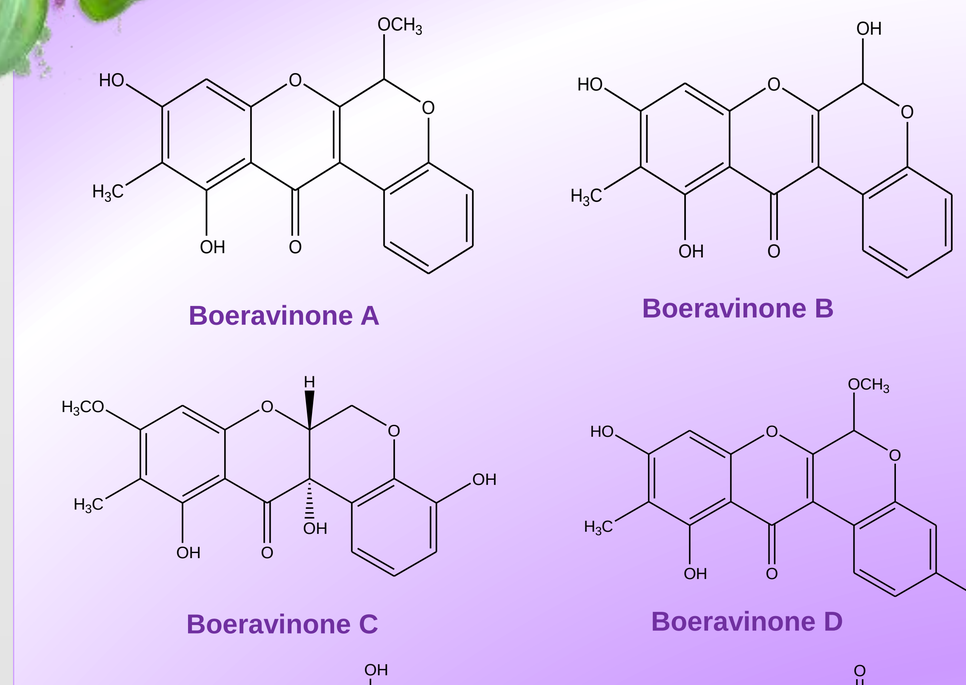












CONCLUSIONS:

Pharmacokinetic behaviour of boeravinones A-J based on *in silico* analysis is strongly affected by their physico-chemical characteristics. Lipophilicity governs the intestinal absorption of the analysed boeravinones, while the distribution process is depended mainly on their flatness. Polarity of the observed boeravinones controls their permeability through different membranes, and limits their permeation through both the blood-brain barrier and the skin. The obtained results are applicable only for investigated structurally homogenous series of boeravinones A-J and should not be taken for general predictions.

References:

Milošević N, Milanović M, Pavlović N, Đurić L, Antonio Cacciola N, Borrelli F, Milić N. Indian ayurvedic herb, Boerhaavia diffusa as BCPR inhibitor: The story behind the curtains. J Mol Struct 2022;1249:131564