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MEETING ABSTRACT

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In silico analysis of molecular descriptors for quercetin analogues: a way to improve blood–brain barrier permeation

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Background: Numerous studies suggest the neuroprotective effects of quercetin. A recent structure/activity analysis confirmed that quercetin can significantly affect the activity of inositol phosphate multikinase (IPMK), which produces phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which is very important in patients with Huntington's disease. Despite its beneficial effects, the therapeutic use of quercetin is limited due to its poor aqueous solubility, low oral bioavailability and low permeation through the brain–blood barrier (BBB). The aim of this study was to identify quercetin analogues with improved BBB permeation and possessing high binding affinities towards IPMK.

Methods: The 3D crystal structure of human IPMK in a complex with quercetin was retrieved from the Protein Data Bank, and the ZINC database was used for screening of ligand structures using the structural similarity search method, which resulted in the identification of 34 quercetin analogues. Docking studies were performed using the Molegro Virtual Docker (MVD) software. Molecular descriptors relevant to membrane permeability for quercetin analogues were predicted using the VolSurf+ software. Permeation through BBB was also predicted using the SwissADME web tool, while the interactions of quercetin and its analogues with P-glycoprotein (P-gp) were predicted using the PgpRules Server. The values of size/shape and physicochemical molecular descriptors for each compound were calculated using the VolSurf+ software and principal component analysis (PCA) was performed.

Results: Binding energies of all tested compounds at the IPMK active site, *i.e.* the potential energies of the formed ligand–receptor complexes, were in the range from −91.827 kcal/mol for geraldol to −72.415 kcal/mol for 3,5-dihydroxy-2-(4-phenyl)chromen-4-one. Quercetin had a binding energy of −82.233 kcal/mol at the IPMK active site, and 19 compounds exerted higher affinity towards the IPMK active site. The calculated values of the logarithm of the blood–brain barrier distribution (LgBB) were lower than −0.5 for all quercetin analogues (range: −3.311 to −1.263), indicating poor brain permeation. Similarly to logP values, 27 analogues had higher values of LgBB than quercetin, with compound 33 (quercetin 3,4′-dimethyl ether) having the highest LgBB value. The 'BOILED-Egg' method also showed that none of the analyzed compounds can pass through the BBB, but the majority of them can be passively absorbed in the intestines. Besides, only 2 compounds, quercetin 3,4′-dimethyl ether and 3-*O*-methylquercetin, were shown to be substrates for P-gp. The results of PCA suggested that intrinsic solubility and logP have the dominant influence on the ability of quercetin analogues to permeate through the BBB. The exceptions from the rule were compounds 27 and 33, which are special, since they are the only two quercetin analogues that are substrates for P-gp.

Discussion: Using several *in silico* methods, we showed that none of 34 analyzed quercetin analogues have sufficient BBB permeability. However, the application of the PCA statistical method in this study proved to be significantly beneficial in the analysis of data regarding the relationship between molecular descriptors and their properties, enabling the synthesis of new compounds with desired properties reflected in favourable values of molecular descriptors.

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Keywords: quercetin analogues – blood–brain barrier – molecular docking – *in silico* analysis

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