Dietary Natural Products as Potential Tumor Chemo-Sensitizers

Reza Mamizadeh a*, Nima Razzaghi-Asl a

Abstract
P-glycoprotein (P-gp) is a membrane ATP-binding transporter that detoxifies cells from different xenobiotics. Multiple drug resistant (MDR) cells can be sensitized toward anticancer agents when treated with P-gp inhibitors/modulators (chemo-sensitizers). Regarding the requirement of high serum concentrations of P-gp inhibitors leading to potential toxicity, dietary phytochemicals are very important and they may interact with co-administered pharmaceuticals as P-gp substrates, leading to altered pharmacokinetics. In silico models for predicting probable binding mode of dietary phytochemicals to P-gp are useful in the early phase of drug discovery projects since they describe structural features in binding to P-gp and hence designing novel anti-MDR scaffolds.

Introduction: As a part of our ongoing studies on virtual analysis of bioactive phytochemicals and to explore new substances that do not exhibit significant toxicity at doses required for P-gp inhibition, we aimed to get more insight into the interactions of P-gp and a few dietary natural constituents as tumor chemosensitizing agents.

Methods and Results: Radiographic 3D holo structure of P-gp was retrieved from protein data bank (4XWK; www.rcsb.org). Lamarckian genetic algorithm of AutoDock 4.2 was used to simulate the binding of dietary compounds. All ab initio studies were done with functional B3LYP associated with split valence basis set using polarization functions (Def2-SVP) by ORCA quantum chemistry package. Our study proposed the dominant role of R-site in binding to Curcuminoids (Curcumin II; -8.17 kcal/mol). In the case of black pepper, hydrophobic contacts seemed to be important in Piperine/P-gp complex. It was also proposed that Piperine carbonyl might be a good mimic of Curcumin II enone group due to the formation of H-bonds (Gln986). Among the catechins of green tea, Epicatechin gallate might not be identified as modulator/substrate since relatively similar ΔGₙₕₕ were recorded within M, H and R sites. Quercetin was not preferentially docked within H-site (-4.77 kcal/mol) in accordance to the previous reports. Within the H-site, Epigallocatechin (green tea) was the weakest binder (-4.31 kcal/mol) and amino acid decomposition analysis dedicated -2.66 and -8.76 kcal/mol attractive forces for interaction with Glu180 and Lys185, respectively.

Conclusions: Combined molecular docking/quantum mechanical studies revealed that among assessed phytochemicals, Bergapten (grape fruit) might be identified as P-gp modulator. Other constituents exhibited more affinity toward R-site with Curcumionoids being the top-ranked ones. Results indicated Lys185, Glu871 and Glu986 as important interacted residues with Curcumionoids due to strong hydrogen bondings.

Key words: Cancer; P-gp; MDR; Natural products; Substrate

Grants: Supports of this project by Ardabil University of Medical Sciences are acknowledged.