Dietary Natural Products as Potential Tumor Chemo-Sensitizers

Reza Mamizadeh [a]*, Nima Razzaghi-Asl [a]

Authors' Affiliations:
Department of Medicinal Chemistry, School of Pharmacy, Ardabil University of Medical Sciences, PO Box: 5618953141, Ardabil, Iran

Abstract Presener:
Reza Mamizadeh; Department of Medicinal Chemistry, School of Pharmacy, Ardabil University of Medical Sciences, PO Box: 5618953141, Ardabil, Iran
E-mail: re74za@gmail.com

***Correspondance:**
Reza Mamizadeh; Department of Medicinal Chemistry, School of Pharmacy, Ardabil University of Medical Sciences, PO Box: 5618953141, Ardabil, Iran
E-mail: re74za@gmail.com

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 ΔG_bs 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 Curcuminoids due to strong hydrogen bondings.

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