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Istraživanje medicinskog značaja fenolnih spojeva primjenom molekularnog modeliranja i molekularnog pristajanja

Implementation of molecular modeling and molecular docking for study of phenolic compounds medicinal significance

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INTRODUCTION

Oxidative stress is a condition caused by excess free radicals that leads to the development of various chronic and aging-associated diseases. Phenolic compounds as potent antioxidants have an important role in removing excess free radicals and terminating oxidative stress. These compounds can also inhibit various enzymes and by doing so have an important role in anti-inflammatory and anticancer therapy. In our work, molecular modelling was used to study free radical scavenging mechanisms of selected phenolic compounds (hydrogen atom transfer (HAT), single-electron transfer followed by proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET)), while molecular docking was used to study inhibition of cyclooxygenase-2 and multidrug resistance protein 1.

METHODOLOGY

Radical scavenging mechanisms of selected phenolic compounds (anthraquinones, 3-hydroxyphenylacetic acid (3-HPAA), 4-hydroxyphenylpropionic acid (4-HPPA)) were studied in (non)polar environment by DFT method using Gaussian 09.
Geometry optimizations and frequency calculations were carried out using the M06-2X/6-311++G(d,p) level of theory, in conjunction with the SMD continuum solvation model.

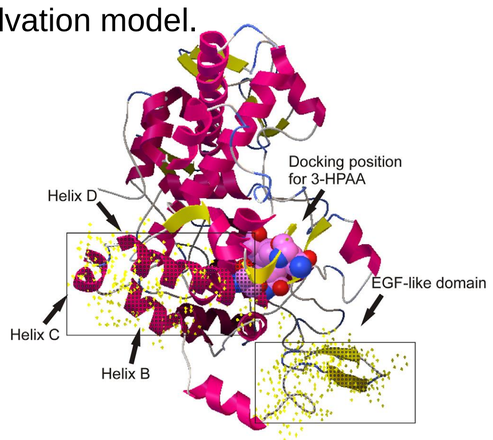

Figure 1. Structure of one monomer of *Mus musculus* COX-2 with selected and labelled EGF-like domain, constituents of MBD domain and docking position for 3-HPAA ligand.

Structure of COX-2 (**Fig. 1**) and Pgp were found in Protein Data Bank and prepared for docking using VMD program. Docking with particular selected ligand was performed using AutoDock 4.2 . Obtained results were visualized and analysed using BIOVIA Discovery Studio. Inhibitory potency of anthraquinones, 3-HPAA, 4-HPPA and their mono- and di-anionic forms were investigated. Free energy of binding and inhibition constant at the most favourable binding positions were estimated. Docking of Pgp with anthracycline (doxorubicin (DX), daunorubicin (DA)), anthracene drugs (mitoxantrone (MX), bisantrene (BA)) was also studied (**Fig 6.**).

RESULTS

Table 1. Reaction enthalpies (in kcal/mol) of radical scavenging mechanisms for 3- HPA, 4-HPP, 3-HPAA and 4-HPPA.

		HAT	SET-PT		SPLET	
specie	solvent	BDE	IP	PDE	PA	ETE
3-HPA$^-$	water	84.33	82.98	1.31	31.12	53.18
4-HPP$^-$	water	82.25	80.47	1.75	31.71	50.51
3-HPAA	pentyl ethanoate	88.67	143.16	9.15	70.03	82.28
4-HPPA	pentyl ethanoate	87.34	140.36	10.62	70.84	80.14

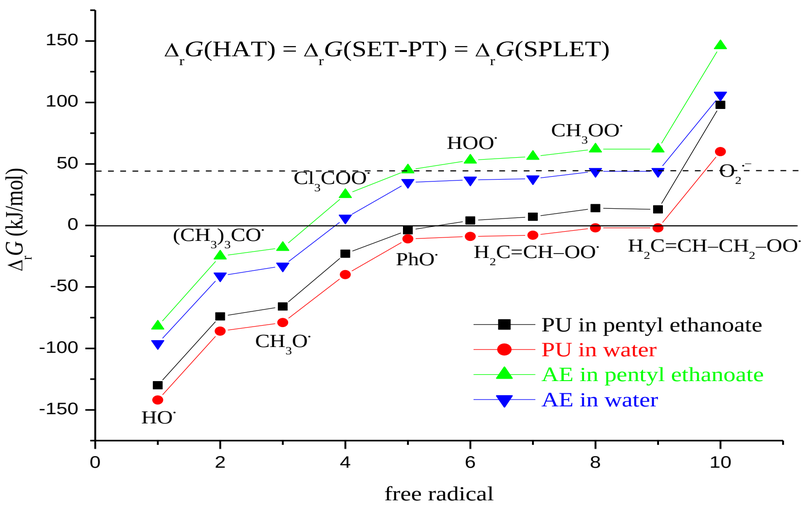

Figure 2. The overall energy requirements for scavenging of selected free radicals by purpurin (PU) and aloeemodin (AE).

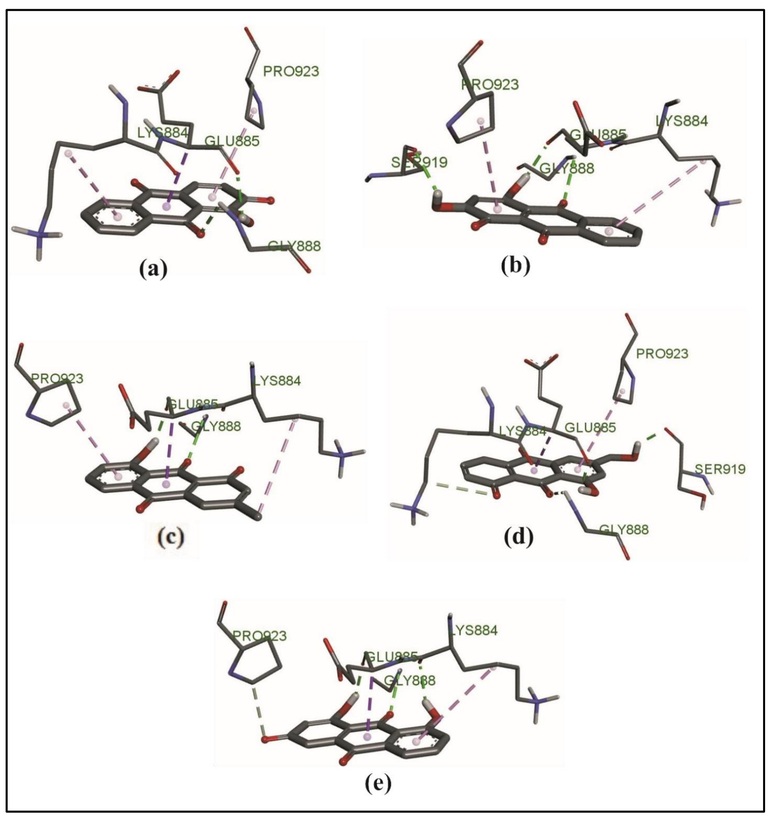

Figure 5. Docking positions of anions of alizarin (a), purpurin (b), chrysophanol (c), aloeemodin (d) and 1,3,8-trihydroxyanthraquinone (e) with Pgp.

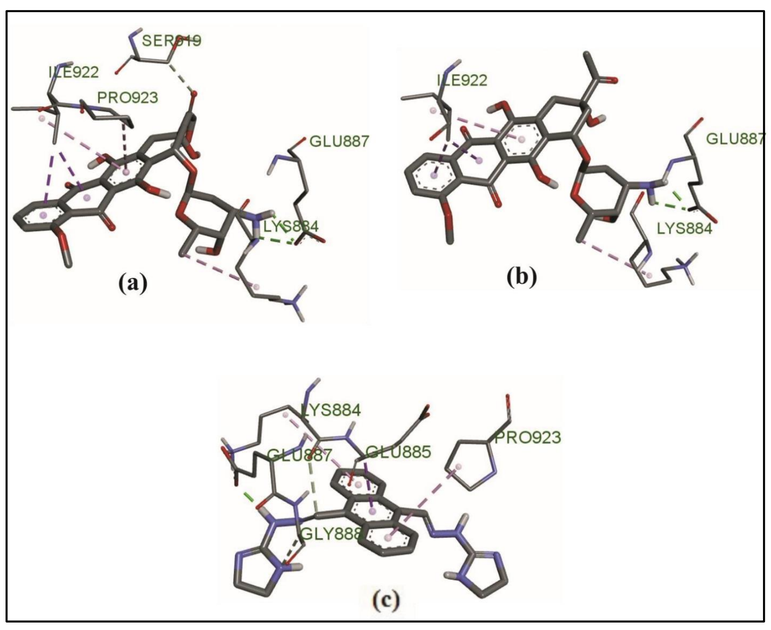

Figure 6. Docking positions of doxorubicin (a), daunorubicin (b) and bisantrene (c) with Pgp.

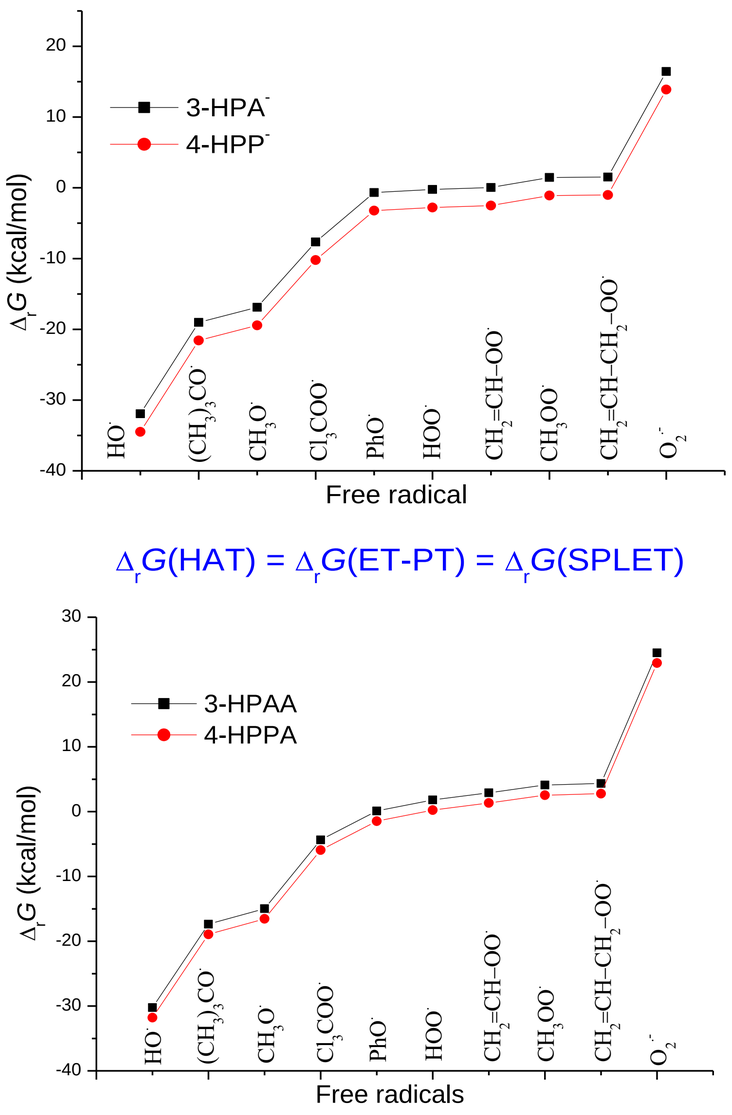

Figure 3. Reaction free energies for free radical scavenging by 3-HPAA and 4-HPPA in water (down) and in pentyl ethanoate (up).

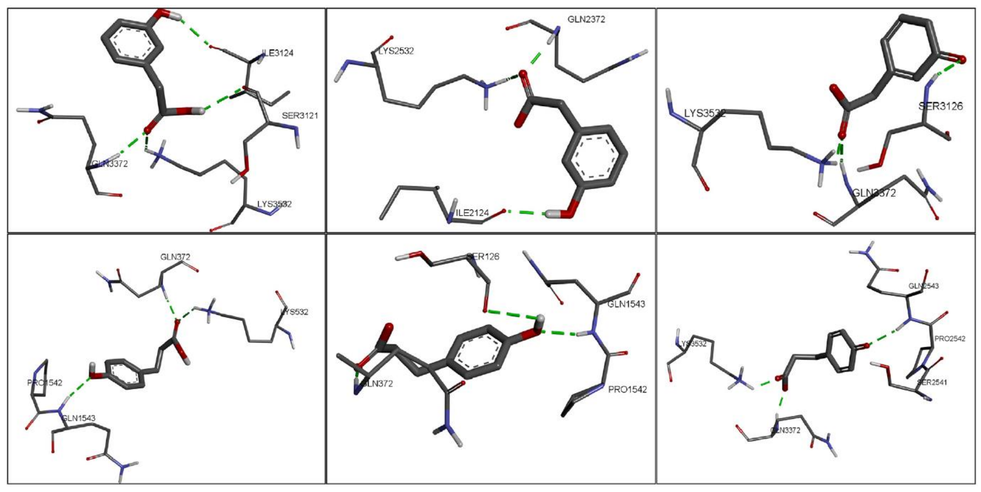

Figure 4. Position of ligand-COX-2 docking for all investigated ligands (up from the left to the right: 3-HPAA, 3-HPA, 3-HPA2; down from the left to the right: 4-HPPA, 4-HPP, 4-HPP2).

CONCLUSIONS

HAT and SPLET mechanisms are thermodynamically probable and competitive processes in both media while SET-PT is not favorable mechanism. The Gibbs free energy change for reaction of inactivation of radicals indicate selected phenolic compounds as potent scavengers (**Table 1.**, **Fig. 2 and 3**). Additional calculations showed that AL and PU have the highest reactivity, CH and AE have the lowest, while EM and THA have moderate antioxidant capacity.
Docking analysis (**Fig. 4**) indicates dianionic ligands as potent inhibitors of COX-2. 4-HPP^{2-} has the highest inhibitory effect. 3-HPAA has higher inhibitory potency in lipid environment, as is cell membrane. Anthraquinone monoanions of selected anthraquinones bind Pgp over the same amino-acids as doxorubicin, daunorubicin, mitoxantrone and bisantrene (**Fig. 5 and 6**). Monoanions form stronger bonds with Pgp (except BA) → potential Pgp inhibitors and protectors against Pgp-dependent multidrug resistance.
Polyphenolic metabolites may contribute to health benefits associated with regular intake of polyphenol-rich diet.