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POLYPHENOL INTERACTIONS WITH FUNCTIONAL PROTEINS: A MOLECULAR DOCKING STUDY

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Polyphenols, bioactive phytochemicals with anticancer, immunomodulating, antioxidative, anti-inflammatory, antimicrobial and many other favorable properties currently attract considerable attention due to their promising therapeutic potential. Biomolecular interactions of polyphenolic compounds, particularly, their association with physiologically important proteins may largely account for their biological effects. In the present study the molecular docking technique was employed to characterize the binding of curcumin (enol and keto forms), resveratrol, sesamin, salycilyc and gallic acids to the functional proteins such as serum albumin, hemoglobin (deoxy and oxy forms), cytochrome c (oxidized and reduced forms). It was found that all examined polyphenols possess the highest affinities for serum albumin and deoxyhemoglobin, while the lowest affinities are observed for cytochrome c. The analysis of the protein-ligand interfacial amino acid residues revealed that there exist specific amino acids with the highest occurrence frequency in the polyphenol binding sites among which are lysine, arginine and tyrosine.
Keywords: *Polyphenols; Serum albumin; Hemoglobin; Cytochrome c; Molecular docking*
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Polyphenols are a chemically diverse class of secondary plant metabolites found in fruits and vegetables, that display a wide spectrum of biological effects beneficial for human health among which are anticancer [1], immunomodulating, antioxidative, anti-inflammatory, antimicrobial and anticoagulant properties [2]. These biological activities are determined to a large extent by polyphenol interactions with various types of functionally important proteins [3, 4]. In particular, it has been demonstrated that polyphenols can form stable complexes with salivary and plasma proteins [5, 6], digestive enzymes [7], amyloidogenic proteins [8], etc. Hydrogen bonding and hydrophobic interactions between polyphenols and proteins are thought to be the main determinants of the specificity of the forming complexes [3]. Despite extensive research efforts, the molecular-level details of polyphenol-protein complexation are far from being fully understood. In view of this, the aim of the present study was to gain deeper insights into the mechanisms of polyphenol association with human serum albumin, hemoglobin and cytochrome c using the molecular docking approach. The choice of the functional proteins was dictated by the following considerations. Being the major protein in human plasma, albumin has multiple functions among which are maintaining the osmotic pressure, transporting various molecules, and modulating the immune response. A diversity of binding sites and multiple hydrophobic pockets account for a high loading and entrapment capacity of human serum albumin (HSA) for a wide variety of substances [9]. Hemoglobin (Hb), representing about 10% of the total proteins of the human organism, accounts for transport of oxygen and carbon dioxide, modulation of erythrocyte metabolism, heat transduction via oxygenation-deoxygenation reactions, etc. [10]. Cytochrome c (cyt c), is a mitochondrial heme protein playing a key role in cellular energetics and metabolism. The redox state of iron atom in the heme group is critical for cyt c functioning as a component of electron transfer chain and its ability to induce the apoptotic cell death [11]. The group of polyphenols under study included curcumin, salicylic acid, gallic acid, sesamin and resveratrol, possessing anti-inflammatory, antioxidant, antimicrobial and neuroprotective activities [12-16].

METHODS

The blind docking of polyphenols to functional proteins was conducted with the HDOCK server using the FFT-based hierarchical algorithm of rigid-body docking [17]. While implementing this algorithm, the receptor and ligand molecules are mapped onto grids and the possible binding modes are ranked according to their binding energy with the shape complementarity scoring method in which one molecule is fixed, while the second one adopts evenly distributed orientations in rotational Euler space and translational space within a grid. The three-dimensional X-ray crystal structures of the investigated proteins were obtained from the Protein Data Bank (https://www.rcsb.org/) using the following PDB IDs 2N9J (human cytochrome c oxidized, cyt c oxy), 2N9I (human cytochrome c reduced, cyt c red), 2DN2 (human deoxyhemoglobin, deoxyHb), 1LFQ (human oxyhemoglobin, oxyHb), 1AO6 (human serum albumin). The structures of polyphenols were prepared in MarvinSketch software, v.18.10, ChemAxon with subsequent geometry optimization in Avogadro 1.1.0 software. The top-scored protein-polyphenol complexes were visualized with the UCSF Chimera software (version 1.14) and analyzed in the protein–ligand interaction profiler (PLIP) [18].

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RESULTS AND DISCUSSION

The analysis of the best score values obtained for the complexes of polyphenols with functional proteins (Table 1) revealed that PF binding affinities decrease in the order: ***Curcumin enol***: Hbdeoxy > HSA > Hboxy > Cyt c red > Cyt c oxy; ***Curcumin keto***: deoxyHb > HSA > oxyHb > > Cyt c oxy > Cyt c red; ***Salicylic acid***: HSA > deoxyHb > Cyt c oxy > oxyHb > Cyt c red; ***Gallic acid***: HSA > deoxyHb > > Cyt c oxy > oxyHb >Cyt c red; ***Sesamin***: HSA > deoxyHb > oxyHb > Cyt c oxy > Cyt c red; ***Resveratrol***: HSA > deoxyHb > oxy Hb> > Cyt c red > Cyt c oxy. Remarkably, all polyphenols possess the highest and comparable affinities for HSA and deoxyHb, while the lowest affinities are observed for cytochrome c.

Table 1. The best score values for the complexes of polyphenols with functional proteins

Polyphenol/Protein	Cyt c oxy	Cyt c red	HSA	deoxyHb	oxyHb
Curcumin enol	-117.68	-125.00	-158.27	-163.65	-148.40
Curcumin keto	-126.71	-120.10	-182.88	-188.42	-145.22
Salicylic (phenolic) acid	-93.14	-74.57	-102.34	-95.84	-83.50
Gallic acid	-104.21	-85.28	-124.03	-112.55	-99.64
Sesamin	-115.33	-126.21	-173.97	-163.87	-145.15
Resveratrol	-89.80	-92.91	-131.52	-125.79	-109.65

While comparing the affinities of different PF to a certain protein it was found that the HSA, deoxyHb and cyt c oxy contain the highest affinity sites for curcumin keto, oxy Hb – for curcumin enol, and cyt c red – for sesamin and curcumin enol. Shown in Figs. 1-3 are the best score docking poses predicted by HDOCK for polyphenol-protein interactions.

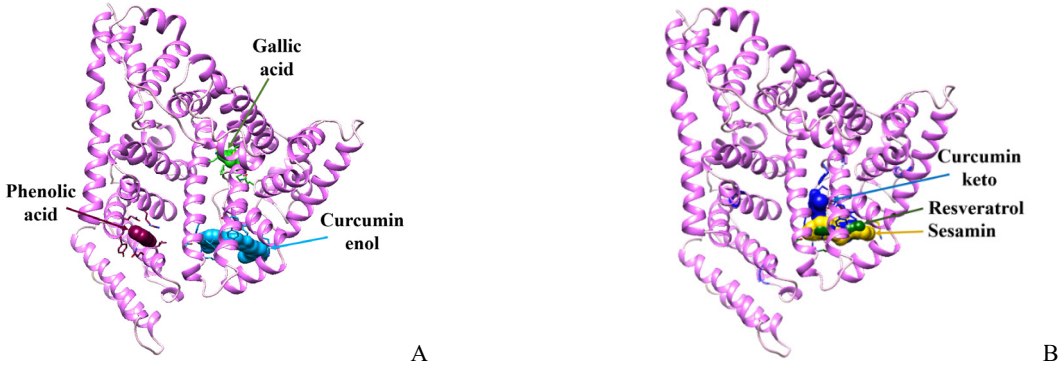

Figure 1. The most energetically favorable complexes between human serum albumin and polyphenols predicted by HDOCK.

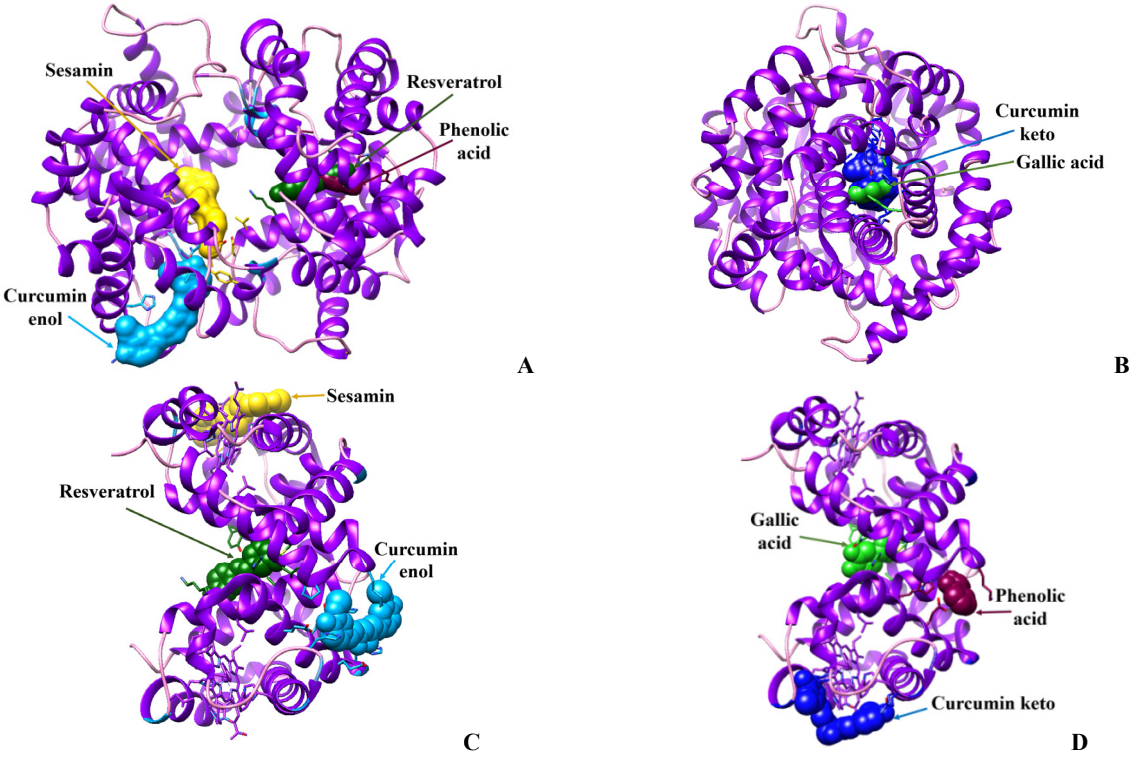

Figure 2. The most energetically favorable complexes between deoxyhemoglobin (A, B) or oxyhemoglobin (C, D) and polyphenols predicted by HDOCK

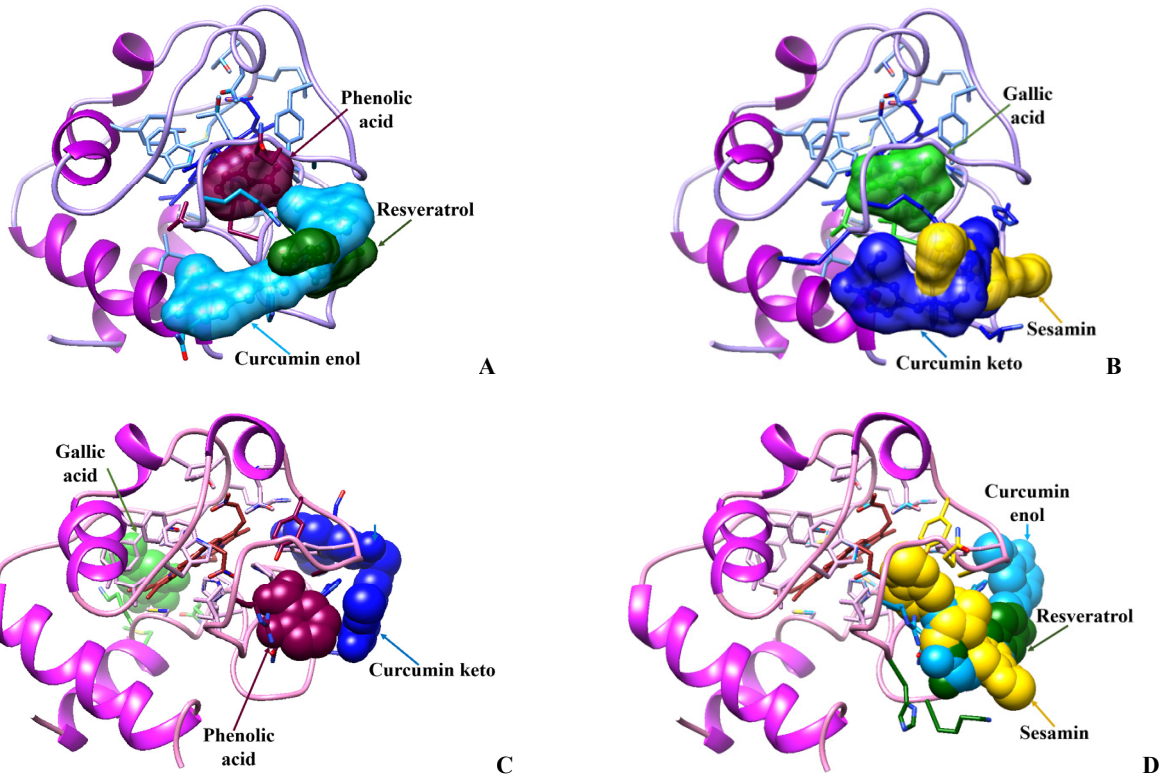

Figure 3. The most energetically favorable complexes between cytochrome c oxy (A, B) or cytochrome c red (C, D) and polyphenols predicted by HDOCK

The amino acid compositions of the binding sites appear to have both similarities and distinctions for different FP-PF systems (Tables 2-6). More specifically, the residues LEU_{115}, ARG_{117}, PRO_{118}, MET_{123}, PHE_{134}, LYS_{137}, TYR_{138}, GLU_{141}, TYR_{161}, LEU_{182}, ASP_{183}, ARG_{186} account for the binding of most polyphenols (except salicylic and gallic acids) to HSA , while the binding sites for SA and GA are quite different (Table 2).

Table 2. The interface residues in the complexes of polyphenols with human serum albumin

HSA +	Amino acid residues forming the HSA binding sites for polyphenols	Type of interactions
Salicylic acid	GLU_{400}, TYR_{401}, GLN_{404}, ARG_{428}, LYS_{519}, GLU_{520}, GLN_{522}, ILE_{523}, GLN_{526}	Hydrophobic interactions, hydrogen bonds, salt bridges
Resveratrol	LEU_{115}, ARG_{117}, PRO_{118}, PHE_{134}, LEU_{135}, LYS_{137}, TYR_{138}, GLU_{141}, TYR_{161}, LEU_{182}, ASP_{183}, ARG_{186}	Hydrophobic interactions, hydrogen bonds
Curcumin (enol form)	PHE_{36}, LEU_{115}, VAL_{116}, ARG_{117}, PRO_{118}, PHE_{134}, LYS_{137}, TYR_{138}, GLU_{141}, TYR_{161}, LEU_{182}, ASP_{183}, ARG_{186}	Hydrophobic interactions, hydrogen bonds
Curcumin (keto form)	LEU_{115}, VAL_{116}, ARG_{117}, PRO_{118}, PHE_{134}, LYS_{137}, TYR_{138}, GLU_{141}, ILE_{142}, HSD_{146}, PHE_{149}, PHE_{157}, TYR_{161}, LEU_{182}, LEU_{185}, ARG_{186}, GLY_{189}, LYS_{190}	Hydrophobic interactions, hydrogen bonds
Sesamin	LEU_{115}, ARG_{117}, PRO_{118}, MET_{123}, PHE_{134}, LYS_{137}, TYR_{138}, GLU_{141}, ILE_{142}, TYR_{161}, LEU_{182}, ASP_{183}, LEU_{185}, ARG_{186}	Hydrophobic interactions, hydrogen bonds
Gallic acid	GLN_{29}, LEU_{103}, LYS_{106}, PRO_{147}, TYR_{148}, PHE_{149}, TYR_{150}, ALA_{151}, GLN_{196}, ARG_{197}, CYS_{200}, CYS_{245}, CYS_{246}, HSD_{247}, GLY_{248}, LEU_{250}	Hydrophobic interactions, hydrogen bonds, salt bridges

The binding sites for curcumin enol and sesamin on deoxyHb have only three similar residues (ASP_{99D}, ASN_{102D}, PHE_{103D}), while the sites for curcumin keto, resveratrol, salicylic and gallic acids contain 14 similar residues from the A and B protein chains (LYS_{99A}, SER_{102A}, HSD_{103A}, LEU_{106A}, PHE_{117A}, HSD_{122A}, ALA_{123A}, ASP_{126A}, VAL_{34B}, TYR_{35B}, LEU_{105B}, ASN_{108B}, VAL_{109B}, CYS_{112B}) (Table 3).

Table 3. The interface residues in the complexes of polyphenols with deoxyhemoglobin

Hb deoxy+	Amino acid residues forming the deoxyHb binding sites for polyphenols	Type of interactions
Salicylic acid	HSD_{103A}, LEU_{106A}, VAL_{107A}, ALA_{110A}, PHE_{117A}, HSD_{122A}, ALA_{123A}, ASP_{126A}, VAL_{34B}, TYR_{35B}, ASN_{108B}, VAL_{109B}, CYS_{112B}	Hydrophobic interactions, hydrogen bonds
Resveratrol	LYS_{99A}, LEU_{100A}, SER_{102A}, HSD_{103A}, LEU_{106A}, PHE_{117A}, HSD_{122A}, ALA_{123A}, ASP_{126A}, VAL_{34B}, TYR_{35B}, LEU_{105B}, ASN_{108B}, VAL_{109B}, CYS_{112B}, VAL_{113B}	Hydrophobic interactions

Hb deoxy+	Amino acid residues forming the deoxyHb binding sites for polyphenols	Type of interactions
Curcumin (enol form)	THR_{41A}, LEU_{28D}, PHE_{41D}, PHE_{42D}, PHE_{45D}, LYS_{59D}, ALA_{62D}, HSD_{63D}, VAL_{67D}, HSD_{97D}, VAL_{98D}, ASP_{99D}, ASN_{102D}, PHE_{103D}	Hydrophobic interactions, hydrogen bonds, π-stacking
Curcumin (keto form)	LYS_{99A}, LEU_{100A}, SER_{102A}, HSD_{103A}, LEU_{106A}, PHE_{117A}, HSD_{122A}, ALA_{123A}, ASP_{126A}, LYS_{127A}, LEU_{129A}, ALA_{130A}, VAL_{34B}, TYR_{35B}, TRP_{37B}, GLU_{101B}, LEU_{105B}, ASN_{108B}, VAL_{109B}, CYS_{112B}, ASP_{94C}, PRO_{95C}, ARG_{141C}	Hydrophobic interactions, hydrogen bonds, π-stacking
Sesamin	TYR_{42A}, ASP_{94A}, PRO_{95A}, VAL_{96A}, ARG_{141A}, LYS_{99C}, SER_{102C}, ASP_{126C}, LEU_{129C}, ALA_{130C}, SER_{133C}, TYR_{35D}, TRP_{37D}, THR_{38D}, ASP_{99D}, GLU_{101D}, ASN_{102D}, LEU_{105D}, ASN_{108D}	Hydrophobic interactions, hydrogen bonds, π-cation interactions
Gallic acid	HSD_{103A}, LEU_{106A}, PHE_{117A}, HSD_{122A}, ALA_{123A}, ASP_{126A}, VAL_{34B}, TYR_{35B}, ASN_{108B}, VAL_{109B}, CYS_{112B}, VAL_{113B}	Hydrophobic interactions, hydrogen bonds

In the case of oxyHb there are 9 similar amino acid residues (LYS_{99A}, SER_{102A}, HIS_{103A}, LEU_{106A}, HIS_{122A}, ASP_{126A}, TYR_{35B}, LEU_{105B}, ASN_{108B}) which are involved in the interactions of resveratrol and gallic caid with the protein, the sites for curcumin enol and salicylic acid contain 4 similar residues (GLU_{27A}, ARG_{31A}, ALA_{111A}, HIS_{112A}), while the sites for curcumin keto and sesamin are completely different from each other (Table 4).

Table 4. The interface residues in the complexes of polyphenols with oxyhemoglobin

Hb oxy +	Amino acid residues forming the oxyHb binding sites for polyphenols	Type of interactions
Salicylic acid	GLU_{27A}, ARG_{31A}, ALA_{111A}, HIS_{112A}, GLY_{119B}, LYS_{120B}, PHE_{122B}, THR_{123B}, PRO_{124B}	Hydrophobic interactions, hydrogen bonds, salt bridges
Resveratrol	PHE_{98A}, LYS_{99A}, SER_{102A}, HIS_{103A}, LEU_{106A}, VAL_{107A}, HIS_{122A}, ASP_{126A}, LEU_{129A}, ALA_{130A}, SER_{133A}, TYR_{35B}, LEU_{105B}, ASN_{108B}, VAL_{109B}, CYS_{112B}	Hydrophobic interactions, hydrogen bonds
Curcumin (enol form)	HIS_{20A}, GLU_{23A}, TYR_{24A}, GLU_{27A}, GLU_{30A}, ARG_{31A}, HIS_{50A}, LYS_{56A}, ALA_{111A}, HIS_{112A}, LEU_{113A}, PRO_{114A}, LYS_{120B}, THR_{123B}, PRO_{124B}	Hydrophobic interactions, hydrogen bonds
Curcumin (keto form)	THR_{41A}, TYR_{42A}, PHE_{43A}, PRO_{44A}, HIS_{45A}, PHE_{46A}, GLN_{54A}, HIS_{58A}, LYS_{61A}, LYS_{90A}, LEU_{91A}	Hydrophobic interactions, hydrogen bonds
Sesamin	ARG_{40B}, PHE_{41B}, PHE_{42B}, GLU_{43B}, SER_{44B}, PHE_{45B}, LYS_{59B}, ALA_{62B}, HIS_{63B}, LYS_{66B}	Hydrophobic interactions, hydrogen bonds
Gallic acid	LYS_{99A}, SER_{102A}, HIS_{103A}, LEU_{106A}, HIS_{122A}, ASP_{126A}, TYR_{35B}, LEU_{105B}, ASN_{108B}, VAL_{109B}, CYS_{112B}	Hydrophobic interactions, salt bridges

An interesting peculiarity of the cyt c oxy – PF complexes is the fact that four amino acid residues, *viz.* ASN_{31}, HIS_{33}, GLY_{34}, and ARG_{38} are present in the binding sites for all polyphenols. Likewise, the high extent of similarity (nine similar residues) was observed for the binding sites of quercetin and resveratrol, curcumin enol and curcumin keto (Table 5).

Table 5. The interface residues in the complexes of polyphenols with oxidized cytochrome c

Cyt c oxy+	Amino acid residues forming the cyt c oxy binding sites for polyphenols	Type of interactions
Salicylic acid	PRO_{30}, ASN_{31}, LEU_{32}, HIS_{33}, GLY_{34}, LEU_{35}, ARG_{38}, LYS_{39}, THR_{40}, GLY_{41}, GLN_{42}, ALA_{43}, TYR_{48}, TRP_{59}	Hydrophobic interactions, hydrogen bonds, π-cation interactions, salt bridges
Resveratrol	VAL_{20}, GLU_{21}, LYS_{22}, GLY_{23}, GLY_{24}, LYS_{25}, HIS_{26}, ASN_{31}, HIS_{33}, GLY_{34}, ARG_{38}	Hydrogen bonds, π-cation interactions
Curcumin (enol form)	HIS_{26}, PRO_{30}, ASN_{31}, LEU_{32}, HIS_{33}, GLY_{34}, LEU_{35}, PHE_{36}, ARG_{38}, GLN_{42}, ALA_{43}, PRO_{44}, GLY_{45}, TYR_{46}, TYR_{48}, THR_{102}, ASN_{103}	Hydrogen bonds
Curcumin (keto form)	VAL_{20}, GLU_{21}, LYS_{22}, GLY_{24}, HIS_{26}, ASN_{31}, HIS_{33}, GLY_{34}, LEU_{35}, PHE_{36}, GLY_{37}, ARG_{38}, THR_{102}, ASN_{103}	Hydrophobic interactions
Sesamin	VAL_{20}, GLU_{21}, LYS_{22}, GLY_{23}, GLY_{24}, LYS_{25}, HIS_{26}, ASN_{31}, HIS_{33}, GLY_{34}, ARG_{38}	Hydrophobic interactions, hydrogen bonds, π-cation interactions
Gallic acid	PRO_{30}, ASN_{31}, LEU_{32}, HIS_{33}, GLY_{34}, LEU_{35}, PHE_{36}, ARG_{38}, LYS_{39}, THR_{40}, GLY_{41}, GLN_{42}, ALA_{43}, TYR_{48}, ILE_{57}, ILE_{58}, TRP_{59}	Hydrophobic interactions, hydrogen bonds, π-cation interactions

The conformational changes of cyt c upon its reduction seem to underlie the observed differences in amino acid composition of PF binding sites compared to cyt c oxy. For the majority of polyphenols the binding sites of cyt c red and cyt c oxy are essentially similar, but for gallic acid they are completely distinct (Table 6). To exemplify, the binding sites for salicylic acid contain the core residues such as PRO_{30}, ASN_{31}, LEU_{32}, HIS_{33}, LEU_{35}, ARG_{38}, ALA_{43} and TYR_{48} that

are conserved across both redox states, suggesting a substantial similarity in the binding mode of salicylic acid to the oxidized and reduced forms of cytochrome c.

Table 6. The interface residues in the complexes of polyphenols with reduced cytochrome c

Cyt c red +	Amino acid residues forming the cyt c red binding sites for polyphenols	Type of interactions
Salicylic acid	HIS_{26}, PRO_{30}, ASN_{31}, LEU_{32}, HIS_{33}, LEU_{35}, ARG_{38}, ALA_{43}, PRO_{44}, TYR_{46}, TYR_{48}	Hydrophobic interactions, Hydrogen bonds, salt bridges
Resveratrol	LYS_{22}, GLY_{23}, GLY_{24}, LYS_{25}, HIS_{26}, ASN_{31}, HIS_{33}, ARG_{38}, ALA_{43}	Hydrophobic interactions, hydrogen bonds
Curcumin (enol form)	LYS_{22}, GLY_{23}, GLY_{24}, LYS_{25}, HIS_{26}, ASN_{31}, HIS_{33}, GLY_{34}, ARG_{38}, ALA_{43}, GLY_{45}, TYR_{46}, SER_{47}, TYR_{48}	Hydrophobic interactions, hydrogen bonds
Curcumin (keto form)	GLY_{23}, GLY_{24}, LYS_{25}, HIS_{26}, LYS_{27}, THR_{28}, GLY_{29}, PRO_{44}, GLY_{45}, TYR_{46}, SER_{47}, TYR_{48}, LYS_{79}	Hydrophobic interactions, hydrogen bonds
Sesamin	LYS_{22}, GLY_{23}, GLY_{24}, HIS_{26}, PRO_{30}, ASN_{31}, LEU_{32}, HIS_{33}, LEU_{35}, ARG_{38}, LYS_{39}, THR_{40}, GLY_{41}, GLN_{42}, ALA_{43}, PRO_{44}, TYR_{48}, TRP_{59}	Hydrophobic interactions, hydrogen bonds, π-stacking, π-cation interactions
Gallic acid	MET_{12}, LYS_{13}, GLN_{16}, CYS_{17}, ILE_{81}, PHE_{82}, VAL_{83}	Hydrophobic interactions, hydrogen bonds, salt bridges

The additional involvement of HIS_{26}, PRO_{44} and TYR_{46} in the reduced form may reflect subtle conformational or electronic differences between the two oxidation states of cyt c. These differences are supposedly affect the dynamics and stability of the PF-cytochrome *c* complexes. To ascertain whether there exist some specific amino acids in the protein binding sites of a given polyphenolic compound we performed the cumulative analysis of the data presented in the Tables 2-6 aimed at determining the occurrence frequency of amino acid residue in the polyphenol binding sites. It appeared that salicylic acid the highest occurrence frequency was observed for tyrosine and arginine (80 %); resveratrol – lysine (100 %); curcumin, enol form – arginine, lysine, tyrosine, leucine (80 %); curcumin, keto form – lysine, histidine (100 %), leucine, tyrosine, proline, phenylalanine (80 %); sesamine – arginine, lysine (100 %), glutamic acid (80 %); gallic acid – leucine, tyrosine, cysteine, phenylalanine, histidine (80 %). Remarkably, most protein binding sites for polyphenols contain positively charged amino acid residues (lysine or arginine) and aromatic residue (tyrosine), while histidine and phenylalanine seem to be essential for the interactions of curcumin keto and gallic acid with proteins. The analysis of the molecular docking data with PLIP showed that most complexes are stabilized by hydrophobic interactions and hydrogen bonds, but salt bridges, π-stacking and π-cation interactions may also contribute to polyphenol association with functional proteins (Tables 2-6).

CONCLUSIONS

In conclusion, the molecular docking study of the complexes between the functional proteins including serum albumin, hemoglobin (deoxy and oxy forms), cytochrome c (oxidized and reduced forms), and representatives of five groups of polyphenolic compounds such as phenolic acids and derivatives (salicylic acid), stilbenes (resveratrol), curcuminoids (curcumin), lignans (sesamin) and tannins (gallic acid) revealed that all polyphenols display the highest affinities for serum albumin and deoxyHb, while the lowest affinities are observed for cytochrome c. The protein-polyphenol binding sites have been characterized in terms of their amino acid composition, the binding energy and the types of protein-ligand interactions. The importance of specific amino acid residues for the association of polyphenols with proteins has been demonstrated, with the highest occurrence frequency in the protein binding sites being found for lysine, arginine and tyrosine.

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ВЗАЄМОДІЯ ПОЛІФЕНОЛІВ З ФУНКЦІОНАЛЬНИМИ БІЛКАМИ: ДОСЛІДЖЕННЯ МЕТОДОМ МОЛЕКУЛЯРНОГО ДОКІНГУ

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Поліфеноли, біоактивні речовини рослинного походження з протипухлинними, імуномоделюючими, антиоксидантними, протизапальними, протимікробними та багатьма іншими властивостями наразі привертають значну увагу завдяки їхньому високому терапевтичному потенціалу. Біомолекулярні взаємодії поліфенольних сполук, зокрема, асоціація з фізіологічно важливими білками, можуть у значній мірі визначати їхні біологічні ефекти. У даній роботі метод молекулярного докінгу був застосований для характеризації зв'язування куркуміну (єнольна та кето форми), ресвератролу, сесаміну, саліцилової та галової кислот з функціональними білками, такими як сироватковий альбумін, гемоглобін (дезокси та окси форми), цитохром с (окислена та відновлена форми). Встановлено, що всі досліджені поліфеноли мають найвищу спорідненість до сироваткового альбуміну та дезоксигемоглобіну, тоді як найнижча спорідненість була виявлена до цитохрому с. Аналіз амінокислотних залишків в контактній області між білком і лігандом показав, що існують специфічні амінокислоти, які найчастіше входять до складу сайтів зв'язування поліфенолів, серед яких лізин, аргінін та тирозин.

Ключові слова: *поліфеноли; сироватковий альбумін; гемоглобін; цитохром с; молекулярний докінг*