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POLYPHENOL EFFECT ON THE INTERACTIONS BETWEEN FUNCTIONAL PROTEINS AND AMYLOID FIBRILS

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Among a wide variety of protein-protein interactions, the complexation of functionally important proteins with pathogenic protein aggregates (amyloid fibrils) attracts particular interest in view of its possible contribution to amyloid cytotoxicity. In the present study we investigated the interactions between the functional proteins (human serum albumin (HSA), hemoglobin (deoxyHb and oxyHb) and insulin Ins)) and amyloid fibrils from Abeta peptide, islet amyloid polypeptide (IAPP), insulin (InsF), apolipoprotein A-I (apoA-I) and apolipoprotein A-II (apoA-II) with an accent on evaluating the possibility of modulating such interactions by polyphenolic compounds including quercetin, curcumin in keto and enol forms, gallic acid, salicylic acid, sesamin and resveratrol. The analysis of the molecular docking data showed that the binding affinities of amyloid fibrils to functional proteins vary in a wide range depending on the structural peculiarities of the examined systems. The most pronounced destabilizing effects of polyphenols on the complexes between the proteins in native and amyloid states were revealed for the systems HSA + QR / CRketo +ApoA-I, HSA +SES +IAPP, deoxyHb + SES / RES +InsF. Further experimental evaluation of these molecular docking predictions will create prerequisites for extending the range of polyphenol applications as anti-amyloid agents.
Keywords: *Amyloid fibrils; Functional proteins; Polyphenols; Molecular docking*
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INTRODUCTION

Protein-protein interactions (PPI) are known to control a diversity of cellular processes, among which are cell growth, signal transduction, immune response, regulation of metabolic pathways, etc. [1, 2]. Over 80% of proteins have been found to function in complexes with other proteins, forming the complex networks of PPI [3]. Along with the functional interactions between protein molecules, there are aberrant PPI that may lead to multiple pathological conditions [4, 5]. In particular, self-association of specific proteins and peptides into elongated ordered aggregates with a core β-sheet architecture (amyloid fibrils) is thought to provoke a number of human disorders such as Alzheimer's, Parkinson's, Huntington's diseases, systemic amyloidosis, type-II diabetes, cancer, etc. [6, 7]. Several lines of evidence indicate that cytotoxic action of amyloid fibrils is associated with predominantly with disintegration of cell membranes and impairment of their functioning, suppression of proteasomal degradation and generation of reactive oxygen species [8-10]. However, the disruption of PPI networks resulting from the complexation between the fibrillized and native proteins may also contribute to amyloid cytotoxicity. This opens a new line of research focusing on investigation of the interactions between proteins in amyloid and natively-folded states. Such kind of research is worthy of attention in at least two aspects. First, amyloid fibrils can impair the structure and function of endogenous proteins, as was demonstrated, particularly, in our recent study for fibrillized N-terminal (1-83) fragment of apolipoprotein A-I with amyloidogenic mutation G26R interacting with hemoglobin, cytochrome c or serum albumin [11]. Second, functional proteins may act as endogenous inhibitors of amyloid formation [12-14] and disaggregating agents for mature fibrils [15]. In particular, human serum albumin (HSA), the predominant protein in blood plasma, has been found to inhibit aggregation of the amyloid-β (Aβ) peptide involved in pathogenesis of Alzheimer's disease [16, 17]. The in vitro experiments demonstrated the ability of HSA to form complexes with various Aβ amyloid intermediates such as monomers, oligomers, and protofibrils [18-20]. The ability to disassemble the preformed amyloid fibrils has been revealed for proteins belonging to the family of molecular chaperones [21]. To exemplify, the shaperones Hsp70 and Hsp90 brought about the disaggregation of tau fibrils [22, 23], while lipocalin-type prostaglandin D synthase and transthyretin disrupted the preformed Aβ fibrils [24, 25]. Obviously, the interactions between the fibrillized and native proteins can be a potential target for therapeutic intervention with various bioactive compounds. One extensively studied group of such compounds is represented by polyphenols (PF), the secondary plant metabolites with a diversity of beneficial biological properties including anticancer, immunomodulating, antioxidative, anti-inflammatory and antimicrobial properties [26, 27]. In view of the above rationales, the aim of the present study was to ascertain whether the polyphenolic compounds of various classes can destabilize the complexes between amyloid fibrils (AF) and functional proteins (FP). To this end, we employed the molecular docking technique to explore the binding characteristics in the systems FP + AF and FP + PF + AF.

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METHODS

The examined molecular systems were designed from four functional proteins (human serum albumin, hemoglobin (in deoxy and oxy forms) and insulin), five types of amyloid fibrils formed by Abeta peptide (Abeta), islet amyloid polypeptide (IAPP), insulin (Ins), apolipoprotein A-I (apoA-I) and apolipoprotein A-II (apoA-II), and seven polyphenols (quercetin (QR), curcumin in keto and enol forms (CRketo, CRenol), gallic acid (GA), salicylic acid (SA), sesamin (SES) and resveratrol (RES)). The crystal structures of the functional proteins were taken from the Protein Data Bank (https://www.rcsb.org/) using the following PDB IDs:1AO6 (human serum albumin), 2DN2 (human deoxyhemoglobin, deoxyHb), 1LFQ (human oxyhemoglobin, oxyHb), 5ENA (human insulin). The structures of the amyloid fibrils from Abeta, ApoA-II and IAPP were derived from the Protein Data Bank using the following PDB IDs: 8OT4 (Aβ amyloid fibrils from Alzheimer's brain tissue), 8OQ4 (ApoA-II) and 6Y1A (IAPP)). The structure of insulin fibril was taken from the archive of M. Sawaya (http://people.mbi.ucla.edu/sawaya/jmol/fibrilmodels/). The model amyloid fibrils of apoliporotein A-I were constructed using the CreateFibril tool with the input structures being generated by PatchDock from the β-stranded ApoA-I monomers. The PDB files of polyphenols were prepared with MarvinSketch as a drawing tool and Avogadro 1.1.0 as a geometry optimization tool. The docking of amyloid fibrils (ligand) to proteins or complexes FP + PF was conducted using the web-based server HDOCK [28]. The most energetically favorable docking complexes were visualized with the UCSF Chimera software (version 1.14).

RESULTS AND DISCUSSION

As seen from Table 1, all examined proteins can form complexes with amyloid fibrils, with the binding affinities decreasing in the rows*:* serum albumin: ApoA-II > IAPP > InsF ≥ Abeta > ApoA-I; deoxyhemoglobin: InsF > Abeta > ApoA-II > IAPP > ApoA-I; oxyhemoglobin: Abeta > IAPP > InsF > ApoA-II > ApoA-I; insulin: Abeta ~ ApoA-II > InsF ~ IAPP > ApoA-I. As judged from the values of the best docking score, the highest binding affinities were observed for oxyHb in its complexes with Abeta (the best docking score -317.95), IAPP (-306.20) and InsF (-289.50), while the weakest complexes were formed by HSA with ApoA-II (-167.26), ApoA-I(-181.51) and insulin with ApoA-I (-187.72).

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

Protein	Amyloid fibrils				
	Abeta	InsF	ApoA-I	ApoA-II	IAPP
HSA	-244.67	-208.32	-181.51	-167.26	-266.13
DeoxyHb	-251.21	-264.10	-213.98	-237.01	-226.21
OxyHb	-317.95	-289.50	-209.58	-272.66	-306.20
Insulin	-250.93	-245.04	-187.72	-250.09	-245.10

Next, it seemed of importance to clarify whether the polyphenols in question are capable of modulating the interactions between functional proteins and amyloid fibrils through altering the binding affinity and the amino acid composition of the binding sites. For this purpose, we performed an extensive docking study of 140 systems FP+PF+AF containing 4 functional proteins, 7 polyphenols and 5 types of amyloid fibrils in different combinations. The analysis of the best score values allowed us to find the complexes in which the presence of polyphenols results in the decreased affinities of amyloid fibrils to proteins.

As can be seen in Fig. 1 and Table 2, there are 11 systems FP+PF+AF in which PF addition results in the pronounced destabilization of the complexes between functional proteins and amyloid fibrils (the decrease in the absolute value of the best docking score exceeds 5%). Of these, five systems, viz. HSA + QR / CRketo +ApoA-I, HSA +SES +IAPP, deoxyHb + SES / RES +InsF appeared to be most promising from the viewpoint of the protective effect of polyphenols against amyloid fibrils.

Table 2. The systems with the strongest destabilizing effect of polyphenols on the affinity of amyloid fibrils for functional proteins

System FP+PF+AF	The changes of the best docking score relative to the system without PF, %
Ins + SA + InsF	-8.7
Ins + GA + InsF	-5.7
HSA + QR + ApoA-I	-10.9
HSA + CRketo + ApoA-I	-11.3
HSA + SES +IAPP	-12.4
DeoxyHb + CRketo + InsF	-7.6
DeoxyHb +SES + InsF	-13.8
DeoxyHb +RES + InsF	-14.4
OxyHb + SA + Abeta	-7.6
OxyHb + QR + InsF	-6.2
OxyHb + RES + InsF	-7.5

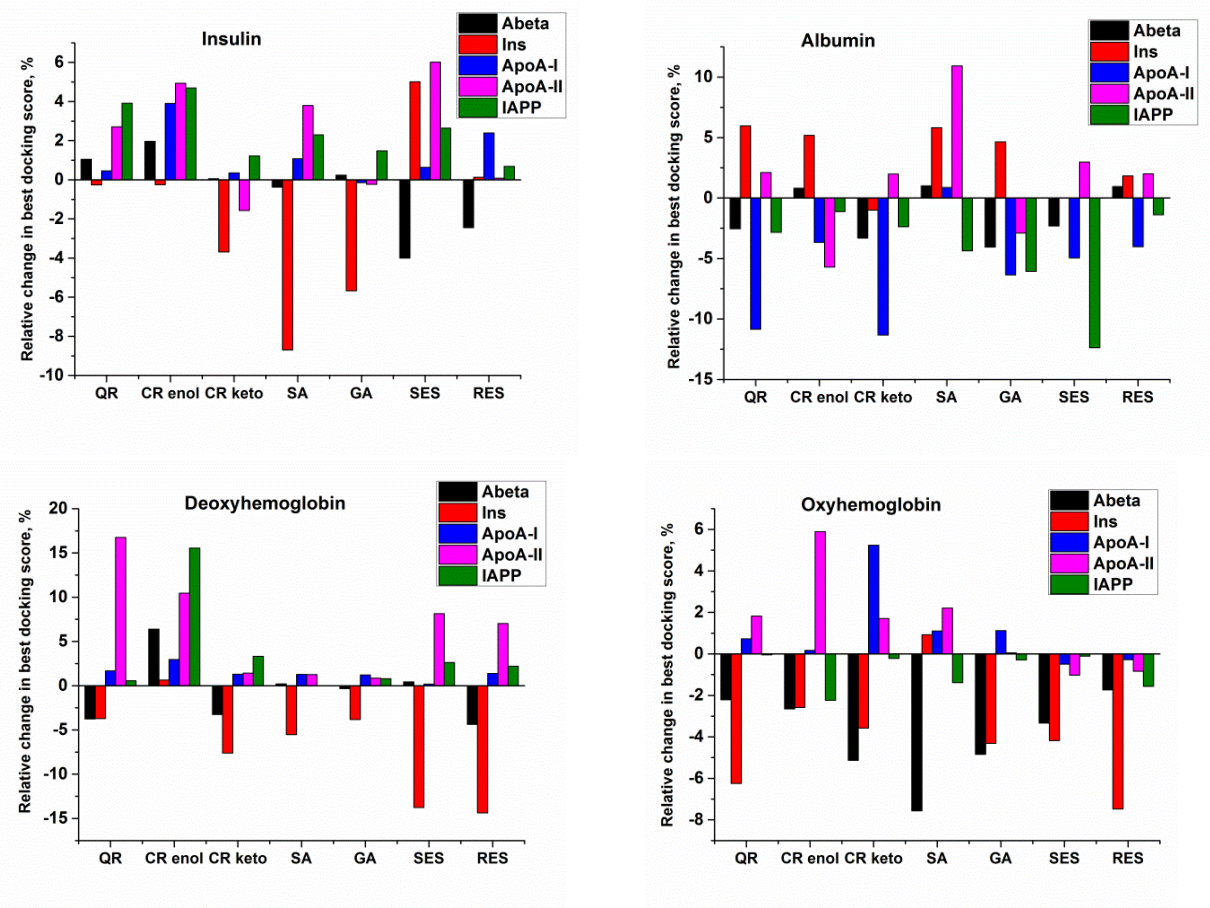

Figure 1. The changes in the best docking score (BDS) values calculated as (BDS (FP+PF+AF) - BDS (FP+AF))·100/BDS (FP+AF)

In the following analysis we compared the amino acid compositions of the binding sites of the functional proteins for polyphenols and amyloid fibrils (in the absence and presence of PF). The insulin binding sites for InsF, SA and GA were found to contain 6 (SA) or 7 (GA) overlapping amino acid residues, all belonging to the protein chain B (marked in gray in Table 3). Therefore, it seems probable that SA and GA can serve as competitive ligands for InsF. Accordingly, the amino acid composition of the insulin binding sites for InsF are essentially different for the systems without and with polyphenols, for SA they contain 5 overlapping residues, while in the interaction of Ins with InsF in the absence and presence of GA occurs through completely different sites.

Table 3. Insulin interface residues in the complexes of insulin with amyloid fibrils in the absence and presence of polyphenols

Ins + InsF	GLN_{5A} CYS_{7A} THR_{8A} SER_{9A} ILE_{10A} CYS_{11A} SER_{12A} LEU_{13A} TYR_{14A} GLN_{15A} PHE_{1B} VAL_{2B} ASN_{3B} GLN_{4B} HIS_{5B} LEU_{6B} CYS_{7B} HIS_{10B} GLU_{13B} ALA_{14B} LEU_{17B}
Ins + SA	PHE_{1B} VAL_{2B} GLN_{4B} LEU_{6B} SER_{9B} HIS_{10B} LEU_{11B} GLU_{13B} ALA_{14B}
Ins + SA + InsF	GLY_{1A} ILE_{2A} GLU_{4A} GLN_{5A} SER_{12A} LEU_{13A} TYR_{14A} GLN_{15A} GLU_{17A} ASN_{18A} TYR_{19A} CYS_{20A} ASN_{21A} GLU_{21B} ARG_{22B} GLY_{23B} PHE_{24B} PHE_{25B} TYR_{26B} THR_{27B} PRO_{28B} LYS_{29B} THR_{30B}
Ins + GA	PHE_{1B} VAL_{2B} GLN_{4B} LEU_{6B} SER_{9B} HIS_{10B} GLU_{13B} ALA_{14B} LEU_{17B}
Ins + GA + InsF	CYS_{20A} ASN_{21A} SER_{9B} VAL_{12B} TYR_{16B} GLY_{20B} GLU_{21B} ARG_{22B} GLY_{23B} PHE_{24B} PHE_{25B} TYR_{26B} THR_{27B} PRO_{28B} LYS_{29B} THR_{30B}

As shown in Table 4, the HSA binding sites for ApoA-I, QR and CRketo possess only two overlapping amino acid residues, LYS_{137A} and GLU_{141A}, so that the competitive interactions between QR / CRketo and ApoA-I seem to be weaker than in the case of insulin and InsF. As a result, the amino acid composition of the HSA binding sites for ApoA-I show significant similarity in the absence and presence of QR / CRketo, differing in five residues in the case of QR and in three residues in the case of CRketo. In contrast to the above albumin-containing systems, the HSA binding sites for IAPP and SES do not have overlapping amino acids, so that HSA-IAPP interactions are mediated by the same amino acid residues, but in the system HSA + IAPP two additional residues, GLU_{376A} and SER_{489A} are involved, compared to the system HSA + SES + IAPP (Table 4).

Table 4. Albumin interface residues in the complexes of insulin with amyloid fibrils in the absence and presence of polyphenols

HSA + ApoA-I	GLN_{33A} CYS_{34A} PRO_{35A} PHE_{36A} GLU_{37A} ASP_{38A} ARG_{81A} GLU_{82A} THR_{83A} TYR_{84A} GLY_{85A} GLU_{86A} ASN_{111A} LEU_{112A} PRO_{113A} VAL_{122A} THR_{125A} ALA_{126A} HSD_{128A} ASP_{129A} LYS_{137A} TYR_{140A} GLU_{141A} ARG_{144A} GLU_{501A} PHE_{502A} ASN_{503A} ALA_{504A} GLU_{505A} THR_{508A} GLU_{565A} ALA_{569A} LYS_{573A} GLN_{580A}
HSA + QR	LEU_{115A} ARG_{117A} PRO_{118A} MET_{123A} PHE_{134A} LYS_{137A} TYR_{138A} GLU_{141A} ILE_{142A} TYR_{161A} LEU_{182A} ASP_{183A} ARG_{186A}
HSA + QR + ApoA-I	GLN_{33A} CYS_{34A} PRO_{35A} PHE_{36A} GLU_{37A} ARG_{81A} GLU_{82A} THR_{83A} TYR_{84A} GLY_{85A} GLU_{86A} ASN_{111A} LEU_{112A} PRO_{113A} PRO_{118A} GLU_{119A} ASP_{121A} VAL_{122A} THR_{125A} ALA_{126A} ASP_{129A} LYS_{137A} TYR_{140A} GLU_{141A} ARG_{144A} ARG_{145A} GLU_{501A} PHE_{502A} ASN_{503A} ALA_{504A} GLU_{505A} THR_{508A} GLU_{565A} ALA_{569A} LYS_{573A} GLN_{580A}
HSA + CRketo	LEU_{115A} VAL_{116A} ARG_{117A} PRO_{118A} PHE_{134A} LYS_{137A} TYR_{138A} GLU_{141A} ILE_{142A} HSD_{146A} PHE_{149A} PHE_{157A} TYR_{161A} LEU_{182A} LEU_{185A} ARG_{186A} GLY_{189A} LYS_{190A}
HSA + CRketo + ApoA-I	GLN_{33A} CYS_{34A} PRO_{35A} PHE_{36A} GLU_{37A} ASP_{38A} ARG_{81A} GLU_{82A} THR_{83A} TYR_{84A} GLY_{85A} GLU_{86A} ASN_{111A} LEU_{112A} PRO_{113A} PRO_{118A} ASP_{121A} VAL_{122A} THR_{125A} ALA_{126A} HSD_{128A} ASP_{129A} LYS_{137A} TYR_{140A} GLU_{141A} ARG_{144A} GLU_{501A} PHE_{502A} ASN_{503A} ALA_{504A} GLU_{505A} THR_{508A} GLU_{565A} ALA_{569A} LYS_{573A} GLN_{580A}
HSA + IAPP	ASP_{375A} GLU_{376A} LYS_{378A} PRO_{379A} GLU_{382A} GLU_{383A} ASN_{386A} LYS_{389A} GLN_{390A} GLU_{393A} LEU_{394A} GLU_{396A} GLN_{397A} LEU_{398A} ASN_{405A} ALA_{406A} LEU_{407A} VAL_{409A} ARG_{410A} LYS_{413A} LYS_{414A} SER_{489A} GLU_{492A} VAL_{493A} GLU_{495A} PRO_{537A} LYS_{538A} THR_{540A} LYS_{541A} GLU_{542A} LYS_{545A}
HSA + SES	LEU_{115A}, ARG_{117A}, PRO_{118A}, MET_{123A}, PHE_{134A}, LYS_{137A}, TYR_{138A}, GLU_{141A}, ILE_{142A}, TYR_{161A}, LEU_{182A}, ASP_{183A}, LEU_{185A}, ARG_{186A}
HSA + SES + IAPP	ASP_{375A} LYS_{378A} PRO_{379A} GLU_{382A} GLU_{383A} ASN_{386A} LYS_{389A} GLN_{390A} GLU_{393A} LEU_{394A} GLU_{396A} GLN_{397A} LEU_{398A} ASN_{405A} ALA_{406A} LEU_{407A} VAL_{409A} ARG_{410A} LYS_{413A} LYS_{414A} GLU_{492A} VAL_{493A} GLU_{495A} PRO_{537A} LYS_{538A} THR_{540A} LYS_{541A} GLU_{542A} LYS_{545A}

In contrast to insulin and albumin, deoxyhemoglobin possesses no overlapping amino acid residues in the binding sites for InsF, CRketo, SES and RES (Table 5), thereby excluding the possibility of competition between InsF and PF for the same HSA sites. As a consequence, the deoxyHb binding sites for InsF without and with PF contain many identical amino acid residues (marked in gray in Table 5), differing in four residues for CRketo, three residues for SES and four residues for RES.

Table 5. Deoxyhemoglobin interface residues in the complexes of insulin with amyloid fibrils in the absence and presence of polyphenols

DeoxyHb + InsF	GLU_{27A} GLU_{30A} PHE_{33A} LEU_{34A} LEU_{48A} SER_{49A} HSD_{50A} GLY_{51A} HSD_{112A} HSD_{2B} THR_{4B} PRO_{5B} GLU_{6B} GLU_{7B} LYS_{8B} SER_{9B} ALA_{10B} THR_{12B} ALA_{13B} TRP_{15B} GLY_{16B} LYS_{17B} LEU_{75B} ALA_{76B} HSD_{77B} ASP_{79B} LYS_{120B} GLU_{121B} PHE_{122B} THR_{123B} PRO_{124B} PRO_{125B} VAL_{126B} GLU_{90D} LEU_{91D} CYS_{93D} ASP_{94D} LYS_{95D} HSD_{97D} HSD_{146D}
DeoxyHb + CRketo	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}
DeoxyHb + CRketo + InsF	GLU_{27A} GLU_{30A} ARG_{31A} PHE_{33A} LEU_{34A} LYS_{40A} LEU_{48A} SER_{49A} HSD_{50A} GLY_{51A} HSD_{112A} HSD_{2B} LEU_{3B} THR_{4B} PRO_{5B} GLU_{6B} LYS_{8B} SER_{9B} ALA_{10B} THR_{12B} ALA_{13B} TRP_{15B} GLY_{16B} LYS_{17B} LEU_{75B} ALA_{76B} HSD_{77B} ASP_{79B} LYS_{120B} GLU_{121B} PHE_{122B} THR_{123B} PRO_{124B} PRO_{125B} VAL_{126B} GLU_{90D} LEU_{91D} CYS_{93D} ASP_{94D} LYS_{95D} LEU_{96D} HSD_{97D} HSD_{146D}
DeoxyHb + SES	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}
DeoxyHb + SES + InsF	GLU_{27A} GLU_{30A} LEU_{34A} LEU_{48A} HSD_{50A} HSD_{112A} HSD_{2B} THR_{4B} PRO_{5B} GLU_{6B} GLU_{7B} LYS_{8B} SER_{9B} ALA_{10B} THR_{12B} ALA_{13B} TRP_{15B} GLY_{16B} LYS_{17B} ASP_{73B} LEU_{75B} ALA_{76B} HSD_{77B} LEU_{78B} ASP_{79B} LYS_{120B} GLU_{121B} THR_{123B} PRO_{124B} PRO_{125B} VAL_{126B} GLU_{90D} LEU_{91D} CYS_{93D} ASP_{94D} LYS_{95D} HSD_{97D} HSD_{146D}
DeoxyHb + RES	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}
DeoxyHb + RES + InsF	GLU_{27A} GLU_{30A} LEU_{34A} LEU_{48A} SER_{49A} HSD_{50A} HSD_{112A} HSD_{2B} THR_{4B} PRO_{5B} GLU_{6B} GLU_{7B} LYS_{8B} SER_{9B} ALA_{10B} THR_{12B} ALA_{13B} TRP_{15B} GLY_{16B} LYS_{17B} VAL_{18B} ASP_{73B} LEU_{75B} ALA_{76B} HSD_{77B} LEU_{78B} ASP_{79B} LYS_{120B} GLU_{121B} PHE_{122B} THR_{123B} PRO_{124B} PRO_{125B} VAL_{126B} GLU_{90D} LEU_{91D} CYS_{93D} ASP_{94D} LYS_{95D} HSD_{97D} HSD_{146D}

Analogously, there is no overlap between the oxyhemoglobin binding sites for Abeta and SA (Table 6). However, only 12 of 31 (oxyHb + Abeta) or 30 (oxyHb + SA + Abeta) amino acids forming the binding sites for Abeta, are identical for the systems without and with SA.

Table 6. Oxyhemoglobin interface residues in the complexes of insulin with amyloid fibrils in the absence and presence of polyphenols

OxyHb + Abeta	VAL_{1A} LEU_{2A} ARG_{92A} ASP_{94A} PRO_{95A} VAL_{96A} ASN_{97A} LYS_{99A} ASP_{126A} LYS_{127A} ALA_{130A} SER_{131A} THR_{134A} LYS_{139A} TYR_{140A} ARG_{141A} VAL_{34B} TYR_{35B} PRO_{36B} TRP_{37B} ARG_{40B} PHE_{41B} GLU_{43B} CYS_{93B} ASP_{94B} HIS_{97B} ASP_{99B} PRO_{100B} GLU_{101B} TYR_{145B} HIS_{146B}
OxyHb + SA	GLU_{27A}, ARG_{31A}, ALA_{111A}, HIS_{112A}, GLY_{119B}, LYS_{120B}, PHE_{122B}, THR_{123B}, PRO_{124B}
OxyHb + SA +Abeta	SER_{35A} PHE_{36A} PRO_{37A} THR_{38A} THR_{39A} THR_{41A} TYR_{42A} ARG_{92A} ASP_{94A} PRO_{95A} VAL_{96A} ASN_{97A} LYS_{99A} LEU_{100A} LYS_{139A} TYR_{140A} VAL_{1B} HIS_{2B} LEU_{3B} PRO_{100B} GLU_{101B} ARG_{104B} GLN_{131B} LYS_{132B} ALA_{135B} ASN_{139B} ALA_{142B} HIS_{143B} TYR_{145B} HIS_{146B}
OxyHb + InsF	PHE_{36A} THR_{38A} ALA_{88A} HIS_{89A} LYS_{90A} LEU_{91A} ARG_{92A} ASP_{94A} PRO_{95A} VAL_{96A} ASN_{97A} PHE_{98A} LYS_{99A} LEU_{100A} SER_{102A} HIS_{103A} LEU_{106A} HIS_{122A} ALA_{123A} ASP_{126A} LYS_{127A} ALA_{130A} LYS_{139A} TYR_{140A} ARG_{141A} VAL_{34B} TYR_{35B} PRO_{36B} TRP_{37B} CYS_{93B} ASP_{94B} HIS_{97B} ASP_{99B} PRO_{100B} GLU_{101B} ASN_{102B} PHE_{103B} ARG_{104B} LEU_{105B} ASN_{108B} VAL_{109B} CYS_{112B} GLN_{131B} VAL_{134B} ALA_{138B} ASN_{139B} ALA_{142B} LYS_{144B} TYR_{145B} HIS_{146B}
OxyHb + QR	LYS_{99A} SER_{102A} HIS_{103A} LEU_{106A} ASP_{126A} LEU_{129A} ALA_{130A} SER_{133A} TYR_{35B} GLU_{101B} ARG_{104B} LEU_{105B} ASN_{108B}
OxyHb + QR + InsF	VAL_{1A} LYS_{7A} HIS_{72A} ASP_{74A} ASP_{75A} MET_{76A} PRO_{77A} ASN_{78A} SER_{81A} SER_{84A} ASP_{85A} HIS_{89A} ASP_{94A} PRO_{95A} LYS_{99A} LYS_{127A} ALA_{130A} THR_{134A} THR_{137A} SER_{138A} LYS_{139A} TYR_{140A} ARG_{141A} VAL_{34B} TYR_{35B} PRO_{36B} TRP_{37B} GLN_{39B} ARG_{40B} GLU_{43B} LEU_{48B} SER_{49B} ASP_{94B} LYS_{95B} LEU_{96B} HIS_{97B} ASP_{99B} LYS_{144B} TYR_{145B} HIS_{146B}
OxyHb + RES	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}
OxyHb + RES + InsF	VAL_{1A} ASP_{6A} LYS_{7A} HIS_{72A} ASP_{74A} ASP_{75A} MET_{76A} PRO_{77A} ASN_{78A} SER_{81A} SER_{84A} ASP_{85A} HIS_{89A} ASP_{94A} PRO_{95A} LYS_{99A} LYS_{127A} ALA_{130A} THR_{134A} THR_{137A} SER_{138A} LYS_{139A} TYR_{140A} ARG_{141A} VAL_{34B} TYR_{35B} PRO_{36B} TRP_{37B} GLN_{39B} ARG_{40B} GLU_{43B} LEU_{48B} SER_{49B} CYS_{93B} ASP_{94B} LYS_{95B} LEU_{96B} HIS_{97B} ASP_{99B} LYS_{144B} TYR_{145B} HIS_{146B}

Unlike Abeta fibrils, the binding sites of oxyHb for InsF and QR or RES have multiple overlapping residues (11 for QR and 13 for RES), so that these polyphenols can be regarded as competitive ligands for InsF (Table 6). Likewise, in the absence of PF the binding site for InsF is more extended (is composed of 50 amino acids), while in the presence of QR or RES it reduces to 40 (QR) or 42 (RES) amino acids, with the number of overlapping residues being 18 for QR and 21 for RES. Overall, our findings suggest that the factors such as the competition between PF and AF for the FP binding sites and ii) the changes in the set of interfacial amino acids play significant role in determining the ability of polyphenols to destabilize the aberrant complexes between functional proteins and amyloid fibrils.

CONCLUSIONS

In summary, we performed the molecular docking study of the binary (functional protein + amyloid fibril) and ternary (functional protein + polyphenol + amyloid fibril) systems to evaluate the protective effects of polyphenolic compounds against toxic action of amyloid fibrils of endogenous proteins. The examined systems were composed of human serum albumin, hemoglobin (in deoxy and oxy forms) and insulin as functional proteins, amyloid fibrils from Abeta peptide, islet amyloid polypeptide, insulin, apolipoprotein A-I and apolipoprotein A-II, and a series of polyphenols including quercetin, curcumin in keto and enol forms, gallic acid, salicylic acid, sesamin and resveratrol. It was found that the strongest complexes are formed between oxyHb and amyloid fibrils from Abeta peptide, IAPP and insulin, while the complexes HSA-ApoA-I, HSA-ApoA-II and Ins-ApoA-I are characterized by the lowest binding affinities. The comparison of the binding affinities for the systems FP+AF and FP+PF+AF revealed 11 ternary combinations in which polyphenols can destabilize the complexes between functional complexes and amyloid fibrils. The systems HSA + QR / CRketo +ApoA-I, HSA +SES +IAPP, deoxyHb + SES / RES +InsF can be recommended for further experimental testing. The results obtained may be of interest for the development of polyphenol-based approaches to reducing the amyloid toxicity.

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ВПЛИВ ПОЛІФЕНОЛІВ НА ВЗАЄМОДІЇ МІЖ ФУНКЦІОНАЛЬНИМИ БІЛКАМИ ТА АМІЛОЇДНИМИ ФІБРИЛАМИ

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Серед великого розмаїття білок-білкових взаємодій, утворення комплексів між функціонально важливими білками та патогенними білковими агрегатами (амілоїдними фібрилами) привертає особливий інтерес з огляду на можливу роль таких комплексів у цитотоксичності амілоїдів. У даній роботі ми дослідили взаємодії між функціональними білками (сироватковим альбуміном людини (HSA), гемоглобіном (deoxyHb та oxyHb) та інсуліном (Ins)) та амілоїдними фібрилами із Абета пептиду (Abeta), амілоїдного поліпептиду (IAPP), інсуліну (InsF), аполіпопротеїну A-I (apoA-I) та аполіпопротеїну A-II (apoA-II). Головний акцент був зроблений на оцінці можливості модуляції таких взаємодій поліфенольними сполуками, включаючи кверцетин, куркумін в кето та єнольній формах, галову та саліцилову кислоти, сесамін та ресвератрол. Аналіз результатів, отриманих методом молекулярного докінгу, показав, що спорідненість амілоїдних фібрил до функціональних білків варіює в широких межах та залежить від структурних особливостей досліджуваних систем. Найбільш виражений дестабілізуючий вплив поліфенолів на комплекси між білками в нативному та амілоїдному станах був виявлений для систем HSA + QR / CRketo +ApoA-I, HSA +SES +IAPP, deoxyHb + SES / RES +InsF. Подальша експериментальна верифікація даних молекулярного докінгу створить передумови для розширення діапазону застосування поліфенолів як антиамілоїних агентів.

Ключові слова: *амілоїдні фібрили; функціональні білки; поліфеноли; молекулярний докінг*