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POLYPHENOL INTERACTIONS WITH AMYLOID FIBRILS: A MOLECULAR DOCKING STUDY

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Polyphenols, a versatile group of naturally occurring compounds with many favorable biological properties currently attract increasing research interest in the context of their ability to inhibit the formation and to destabilize special protein aggregates, amyloid fibrils, associated with a number of human diseases. In the present study the molecular docking technique was used to gain insights into molecular details of the interactions between polyphenolic compounds such as quercetin, curcumin, resveratrol, sesamin, salicylic and gallic acids with the mature amyloid fibrils from Abeta peptide, islet amyloid polypeptide, insulin, apolipoprotein A-I and apolipoprotein A-II. All examined polyphenols displayed the highest binding affinities for amyloid fibrils from apolipoprotein A-II and insulin, while the lowest affinities were observed for the fibrillar apolipoprotein A-I. The hydrophobicity/hydrophilicity analysis of amino acid composition of the binding sites showed that hydrophobic and neutral residues play a predominant role in the polyphenol complexation with amyloid fibrils from apolipoprotein A-I, apolipoprotein A-II and insulin, the basic residues essentially contribute to polyphenol association with fibrillar Abeta and islet amyloid polypeptides, while the involvement of acidic residues was revealed only for the complexes sesamin + apolipoprotein A-I / Abeta fibrils and curcumin keto + insulin fibrils. The results obtained may prove useful in the development of novel polyphenol-based anti-amyloid strategies.
Keywords: *Amyloid fibrils; Polyphenols; Binding sites, Binding affinity, Molecular docking*
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Amyloid fibrils, specific protein aggregates with a core β-sheet structure, in the past decades continue to attract enormous attention in two main aspects associated with amyloid involvement in pathogenesis of more than forty human diseases [1] and great nanotechnological potential of amyloid assemblies [2]. Considerable research efforts are currently focused on the development of anti-amyloid strategies and searching for small molecule inhibitors of amyloid formation [3]. One class of such inhibitors is represented by polyphenols, naturally occurring compounds with a wide range of biological activities [4, 5]. Growing evidence indicates that polyphenols can interfere with the process of amyloid formation through: i) preventing the structural transitions of protein molecules into the aggregation-prone states; ii) hindering the conversion of oligomeric intermediates into mature amyloid fibrils; and iii) disrupting and remodeling the preformed fibrillar assemblies [6-9]. To exemplify, epigallocatechin gallate displayed the abilities not only to inhibit the growth of fibrils from Abeta and α-synuclein, but also to induce their remodeling into nontoxic amorphous aggregates [10, 11]. Resveratrol has been reported to prevent large-scale Abeta fibrillization without affecting the oligomer formation [12, 13]. Polyphenols baicalein, epigallocatechin gallate, rutin and gallic acid have been found to produce disassembly of glycation-mediated mature amyloid fibrils from bovine serum albumin (BSA) [14]. The inhibition of amyloid formation from insulin, lysozyme and Aβ1–40 peptide, and disassembly of the preformed fibrils were revealed for rottlerin. It was hypothesized that this polyphenol is capable of interrupting the fibril-stabilizing bonds of β-sheets [15]. Gallic acid, caffeic acid, rutin and quercetin suppressed the fibrillization of the islet amyloid polypeptide (IAPP), while rutin and quercetin disaggregated the preformed amyloid fibrils of IAPP [16]. It has been proposed that improvement of the water solubility and bioavailability of polyphenols through nanonization enhances their anti-amyloid activities, as was demonstrated for the nanosheet form of polyphenolic fraction from propolis which displayed more efficient inhibition of amyloid growth and clearance of the preformed fibrils of bovine insulin [17]. It has been also shown that polyphenol association with fibrillized proteins is governed by hydrogen bonding, π–π stacking and hydrophobic interactions, and may lead to self-assembly of amyloid fibrils into complex hierarchical structures [9]. All the above findings point to the necessity of a more thorough investigation of the mechanisms underlying the interactions between polyphenols and proteins, especially the amyloid protein aggregates. For this reason, the aim of the present study was to scrutinize the interactions between a series of chemically diverse polyphenols (PF) with mature amyloid fibrils from structurally different proteins using the molecular docking technique. The group of the examined polyphenolic compounds included quercetin (QR), curcumin (CR), gallic acid (GA), salicylic acid (SA), sesamin (SES) and resveratrol (RES), while the amyloid-forming proteins were represented by Abeta peptide (Abeta), islet amyloid polypeptide, insulin (Ins), apolipoprotein A-I (apoA-I) and apolipoprotein A-II (apoA-II).

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METHODS

The structures of polyphenols were prepared in MarvinSketch software, v.18.10, ChemAxon with subsequent geometry optimization in Avogadro 1.1.0 software using the Universal Force Field21. The insulin fibril model was taken from the archive provided by M. Sawaya (http://people.mbi.ucla.edu/sawaya/jmol/fibrilmodels/). The model amyloid fibrils of apoliporotein A-I were constructed using the CreateFibril tool based on the translational and rotational affine transformations providing several copies of a certain fragment of fibril core, whose subsequent stacking produces the elongated fibrillar aggregate. The input structures for CreateFibril were generated from the monomers in the β-strand conformation with PatchDock. The structures of the amyloid fibrils from Abeta, IAPP and ApoAII were taken from the Protein Data Bank using the following PDB IDs: 8OT4 (Aβ amyloid fibrils from Alzheimer's brain tissue), 6Y1A (IAPP) and 8OQ4 (ApoAII). The docking of polyphenols to amyloid fibrils was performed using the web-based server HDOCK [18]. The selected docking poses were visualized with the UCSF Chimera software (version 1.14).

RESULTS AND DISCUSSION

The molecular docking study of the interactions between the selected polyphenolic compounds and amyloid fibrils provided evidence for the presence of different types of polyphenol binding sites on the amyloid aggregates (Figs.1-3). The association of polyphenols with fibrillar Abeta (Fig. 1, A, B,) and ApoAII (Fig. 3) occurs mainly through the dry surface of the fibrils, while the PF binding sites on the fibrils of IAPP (Fig. 1, C, D) and ApoAI (Fig. 2, A) are located on the wet surface of amyloid assemblies. The insulin fibrils appear to contain the binding sites for PF on both the dry and wet surfaces (Fig. 2, B).

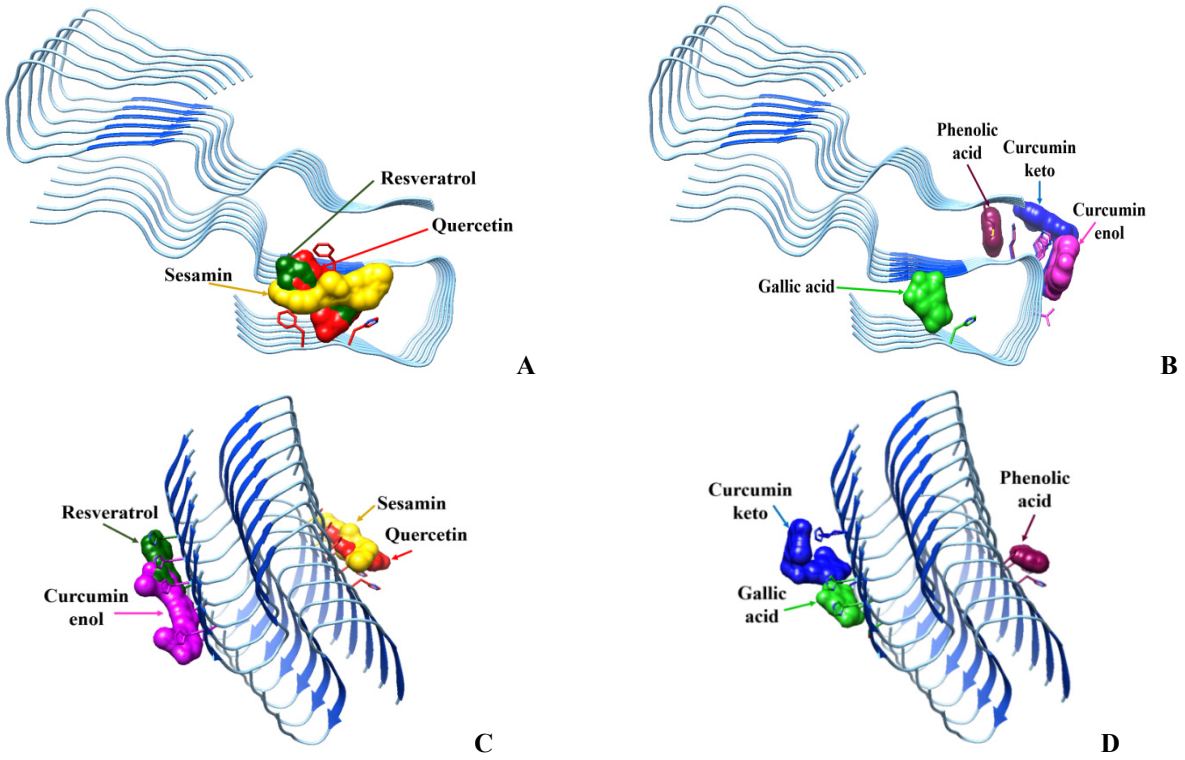

Figure 1. The best-score complexes of Abeta (A, B) and IAPP (C, D) fibrils with polyphenols.

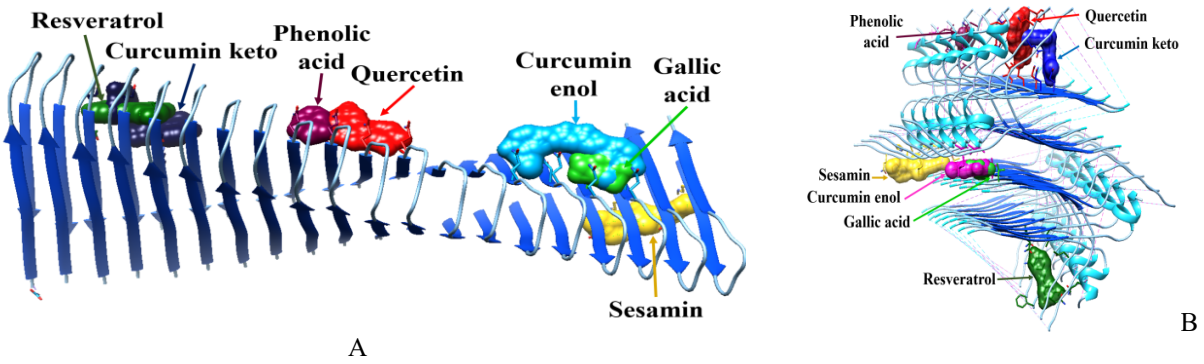

Figure 2. The best-score complexes of the fibrillar ApoAI (A) and insulin (B) with polyphenols.

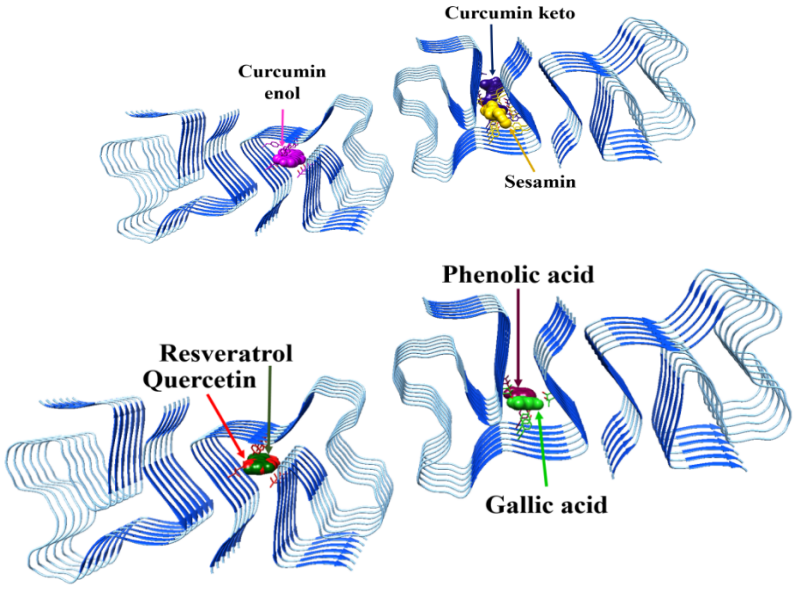

Figure 3. The best-score complexes of the fibrillar ApoAII with polyphenols.

As judged from the comparison of the best score values (Table 1), all polyphenols form the strongest complexes with the fibrils from ApoAII and insulin, with the binding affinities decreasing in the rows: ***Quercetin:*** ApoAII >Ins > IAPP > ApoAI ≥ Abeta; ***Curcumin enol;*** ApoAII >Ins ≥ IAPP > Abeta ≥ ApoAI; ***Curcumin keto***: ApoAII >Ins > Abeta ≥ IAPP > ApoAI; ***Phenolic acid:*** ApoAII >Ins > IAPP ≥Abeta ≥ ApoAI; ***Gallic acid:*** ApoAII >Ins > IAPP≥ Abeta ≥ ApoAI; ***Sesamin:*** ApoAII >Ins > IAPP > Abeta ≥ ApoAI; ***Resveratrol:*** ApoAII >Ins > IAPP > Abeta ≥ ApoAI.

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

Polyphenol	Abeta	InsF	ApoAI	ApoAII	IAPP
Quercetin	-121.18	-163.80	-122.73	-211.93	-139.19
Curcumin enol	-135.49	-169.26	-118.84	-239.82	-163.48
Curcumin keto	-118.42	-140.44	-104.32	-161.14	-118.00
Salicylic (phenolic) acid	-71.07	-91.79	-70.36	-103.85	-73.63
Gallic acid	-80.34	-110.86	-78.72	-123.75	-83.94
Sesamin	-117.59	-153.37	-109.44	-220.44	-147.60
Resveratrol	-91.71	-115.26	-80.58	-164.03	-109.11

Presented in Tables 2-8 are the amino acid compositions of polyphenol binding sites on the examined amyloid fibrils. The hydrophobicity/hydrophilicity analysis performed using the Peptide 2.0 software (https://www.peptide2.com/N_peptide_hydrophobicity_hydrophilicity.php) allowed to identify the types of amino acid residues that predominantly determine the complexation of polyphenols with the fibrillized proteins. As seen in Table 2, the fibril binding sites for quercetin are composed mainly of hydrophobic and neutral residues, with their content being the highest for Abeta and ApoA-I fibrils, respectively. An exception is the fibrillar IAPP in which there are no hydrophobic residues at the quercetin binding sites. The association of quercetin with amyloid fibrils from Abeta, IAPP and Ins is mediated also by the basic residues, especially, histidine. Notably, the strongest complexes formed by quercetin with ApoA-II and Ins, are stabilized mainly by the interactions of this polyphenol with hydrophobic and neutral amino acid residues.

Table 2. The interface residues in the complexes between amyloid fibrils and quercetin

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for quercetin
1	ApoA-I	GLN_{271J}, LEU_{272J}, ASN_{273J}, GLN_{298K}, LEU_{299K}, ASN_{300K}, GLN_{325L}, LEU_{326L}, ASN_{327L}, ASN_{354M} *Hydrophobic: 30%, Acidic: 0%, Basic: 0%, Neutral: 70%*
2	ApoA-II	LEU_{10H}, THR_{12H}, TYR_{14H}, TYR_{21H}, ALA_{56H}, GLY_{57H}, THR_{58H}, LEU_{10N}, THR_{12N}, TYR_{14N}, TYR_{21N}, ALA_{56N}, GLY_{57N}, THR_{58N}, LEU_{10R}, THR_{12R}, TYR_{14R}, TYR_{21R}, ALA_{56R}, GLY_{57R}, THR_{58R}, LEU_{10V}, TYR_{21V}, ALA_{56V}, THR_{58V} *Hydrophobic: 32%, Acidic: 0%, Basic: 0%, Neutral: 68%*

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for quercetin
3	Abeta	PHE_{4K}, ARG_{5K}, HIS_{6K}, VAL_{18K}, PHE_{19K}, PHE_{20K}, ALA_{21K}, VAL_{24K} *Hydrophobic: 75%, Acidic: 0%, Basic: 25%, Neutral: 0%*
4	IAPP	HIS_{18D}, SER_{19D}, SER_{20D}, HIS_{18F}, SER_{19F}, SER_{20F}, HIS_{18H}, SER_{19H}, SER_{20H}, HIS_{18J}, SER_{19J} *Hydrophobic: 0%, Acidic: 0%, Basic: 36.36%, Neutral: 63.64%*
5	Ins	GLN_{115G}, PHE_{201G}, VAL_{202G}, ASN_{203G}, GLN_{204G}, HSD_{205G}, ILE_{2I}, LEU_{13I}, GLN_{15I}, LEU_{113I}, VAL_{202I}, ASN_{203I}, GLN_{204I}, HSD_{205I}, LEU_{206I}, GLN_{5K} *Hydrophobic: 43.75%, Acidic: 0%, Basic: 12.5%, Neutral: 43.75%*

As judged from Table 3, all amyloid fibrils except Abeta possess the binding sites for salicylic acid containing the neutral amino acid residues in rather large amounts (from 44 % to 70 %). The hydrophobic amino acids do not participate in the SA association with IAPP, while the basic amino acids contribute to the complexation of SA with Abeta, IAPP and Ins fibrils.

Table 3. The interface residues in the complexes between amyloid fibrils and salicylic acid

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for salicylic acid
1	ApoA-I	GLN_{217H}, GLN_{244I}, LEU_{245I}, ASN_{246I}, GLN_{271J}, LEU_{272J}, ASN_{273J} *Hydrophobic: 28.57%, Acidic: 0%, Basic: 0%, Neutral: 71.43%*
2	ApoA-II	LEU_{10F}, THR_{12F}, TYR_{14F}, TYR_{21F}, ALA_{56F}, GLY_{57F}, THR_{58F}, TYR_{21L}, ALA_{56L}, GLY_{57L}, THR_{58L}, THR_{58P} *Hydrophobic: 25%, Acidic: 0%, Basic: 0%, Neutral: 75%*
3	Abeta	GLN_{15A}, LYS_{16A}, LEU_{17A}, MET_{35B}, GLN_{15C}, LYS_{16C}, LEU_{17C} *Hydrophobic: 42.86%, Acidic: 0%, Basic: 28.57%, Neutral: 28.57%*
4	IAPP	SER_{19F}, HIS_{18H}, SER_{19H}, SER_{20H}, HIS_{18J}, SER_{19J}, SER_{20J}, HIS_{18L} *Hydrophobic: 0%, Acidic: 0%, Basic: 37.5%, Neutral: 62.5%*
5	Ins	VAL_{202A}, ASN_{203A}, GLN_{204A}, HSD_{205A}, ILE_{2C}, ASN_{203C}, GLN_{204C}, HSD_{205C}, LEU_{206C}, GLN_{5E} *Hydrophobic: 30%, Acidic: 0%, Basic: 20%, Neutral: 50%*

The types of amino acids in the amyloid binding sites for gallic acid are largely similar to those for salicylic acid, however, in contrast to SA, the basic residues do not participate in the GA interaction with fibrillar insulin (Table 4).

Table 4. The interface residues in the complexes between amyloid fibrils and gallic acid

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for gallic acid
1	ApoA-I	GLN_{433P}, LEU_{434P}, ASN_{435P}, GLN_{460Q}, LEU_{461Q}, ASN_{462Q}, GLN_{487R}, LEU_{488R}, ASN_{489R} *Hydrophobic: 33.33%, Acidic: 0%, Basic: 0%, Neutral: 66.67%*
2	ApoA-II	LEU_{10L}, THR_{12L}, TYR_{14L}, TYR_{21L}, ALA_{56L}, LEU_{10P}, THR_{12P}, TYR_{14P}, TYR_{21P}, ALA_{56P}, GLY_{57P}, THR_{58P}, ALA_{56T}, GLY_{57T}, THR_{58T} *Hydrophobic: 33.33%, Acidic: 0%, Basic: 0%, Neutral: 66.67%*
3	Abeta	PHE_{4K}, ARG_{5K}, HIS_{6K}, VAL_{18K}, PHE_{19K}, PHE_{20K} *Hydrophobic: 66.67%, Acidic: 0%, Basic: 33.33%, Neutral: 0%*
4	IAPP	HIS_{18G}, SER_{19G}, SER_{20G}, HIS_{18I}, SER_{19I}, SER_{20I}, HIS_{18K}, SER_{19K}, SER_{20K} *Hydrophobic: 0%, Acidic: 0%, Basic: 33.33%, Neutral: 66.67%*
5	Ins	ILE_{102I}, CYS_{307I}, LEU_{217J}, VAL_{218J}, CYS_{219J}, LEU_{317J}, VAL_{318J}, CYS_{319J}, LEU_{306K}, CYS_{307K}, GLY_{308K}, LEU_{217L}, VAL_{218L}, CYS_{219L} *Hydrophobic: 57.14%, Acidic: 0%, Basic: 0%, Neutral: 42.86%*

Both hydrophobic and neutral amino acids account for the binding of resveratrol to amyloid fibrils from ApoA-I, ApoA-II and Ins, while the basic amino acids play a marked role in the complexation of this polyphenol with fibrillar Abeta, IAPP and Ins (Table 5).

Table 5. The interface residues in the complexes between amyloid fibrils and resveratrol

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for resveratrol
1	ApoA-I	GLN_{55B}, ASN_{57B}, GLN_{82C}, LEU_{83C}, ASN_{84C}, GLN_{109D}, LEU_{110D}, ASN_{111D}, GLN_{136E}, LEU_{137E}, ASN_{138E}, ASN_{165F} *Hydrophobic: 25%, Acidic: 0%, Basic: 0%, Neutral: 75%*

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for resveratrol
2	ApoA-II	LEU_{10H}, THR_{12H}, TYR_{14H}, TYR_{21H}, LEU_{10N}, THR_{12N}, TYR_{14N}, TYR_{21N}, ALA_{56N}, THR_{58N}, LEU_{10R}, THR_{12R}, TYR_{14R}, TYR_{21R}, ALA_{56R}, GLY_{57R}, THR_{58R}, LEU_{10V}, TYR_{21V}, ALA_{56V}, GLY_{57V}, THR_{58V} *Hydrophobic: 31.82%, Acidic: 0%, Basic: 0%, Neutral: 68.18%*
3	Abeta	PHE_{4K}, ARG_{5K}, HIS_{6K}, VAL_{18K}, PHE_{19K}, PHE_{20K}, ALA_{21K}, GLU_{22K}, ASP_{23K}, VAL_{24K} *Hydrophobic: 60%, Acidic: 20%, Basic: 20%, Neutral: 0%*
4	IAPP	HIS_{18C}, SER_{19C}, SER_{20C}, HIS_{18E}, SER_{19E}, SER_{20E}, HIS_{18G}, SER_{19G}, SER_{20G}, HIS_{18I}, SER_{19I}, SER_{20I} *Hydrophobic: 0%, Acidic: 0%, Basic: 33.33%, Neutral: 66.67%*
5	Ins	GLN_{115H}, PHE_{201H}, VAL_{202H}, ASN_{203H}, GLN_{204H}, HSD_{205H}, ILE_{2J}, LEU_{13J}, GLN_{15J}, VAL_{202J}, ASN_{203J}, GLN_{204J}, HSD_{205J}, LEU_{206J}, GLN_{5L} *Hydrophobic: 40%, Acidic: 0%, Basic: 13.33%, Neutral: 46.67%*

Interestingly, the molecular docking analysis revealed noticeable differences between the two tautomeric forms of curcumin in their fibril-associating abilities: i) the binding affinities of enol form of CR appeared to be markedly higher than those of the keto form, especially for ApoA-II fibrils (Table 1); ii) the basic amino acids are present in the binding sites of ApoA-I and Ins for CR enol, but not for keto CR; iii) the contribution of the basic residues in the stabilization of Abeta-CR complexes decreases in the case of keto CR in favor of the neutral residues; iv) the hydrophobic residues participate in the association of only CR keto with IAPP fibrils; v) in contrast to enol CR, the acidic residues are involved in the binding of keto CR to InsF (Table 6, 7).

Table 6. The interface residues in the complexes between amyloid fibrils and curcumin enol

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for curcumin enol
1	ApoA-I	GLN_{379N}, GLN_{406O}, LEU_{407O}, ASN_{408O}, GLN_{433P}, LEU_{434P}, ASN_{435P}, GLN_{460Q}, LEU_{461Q}, ASN_{462Q}, GLN_{487R}, LEU_{488R}, ASN_{489R}, ASN_{516S} *Hydrophobic: 28.57%, Acidic: 0%, Basic: 0%, Neutral: 71.43%*
2	ApoA-II	THR_{12D}, LEU_{10H}, THR_{12H}, TYR_{14H}, TYR_{21H}, LEU_{10N}, THR_{12N}, TYR_{14N}, TYR_{21N}, ALA_{56N}, GLY_{57N}, THR_{58N}, LEU_{10R}, THR_{12R}, TYR_{14R}, TYR_{21R}, ALA_{56R}, GLY_{57R}, THR_{58R}, LEU_{10V}, THR_{12V}, TYR_{14V}, TYR_{21V}, ALA_{56V}, GLY_{57V}, THR_{58V}, TYR_{21K}, ALA_{56K}, THR_{58K} *Hydrophobic: 27.59%, Acidic: 0%, Basic: 0%, Neutral: 72.41%*
3	Abeta	HIS_{13C}, HIS_{14C}, VAL_{12E}, HIS_{13E}, HIS_{14E}, VAL_{12G}, HIS_{13G}, HIS_{14G}, VAL_{12I}, HIS_{13I}, HIS_{14I}, VAL_{12K}, HIS_{13K}, HIS_{14K} *Hydrophobic: 28.57%, Acidic: 0%. Basic: 71.43%, Neutral: 0%*
4	IAPP	HIS_{18E}, SER_{19E}, HIS_{18G}, SER_{19G}, SER_{20G}, HIS_{18I}, SER_{19I}, SER_{20I}, HIS_{18K}, SER_{19K}, SER_{20K}, HIS_{18M}, SER_{19M}, SER_{20M}, HIS_{18O} *Hydrophobic: 0%, Acidic: 0%, Basic: 40%, Neutral: 60%*
5	Ins	ILE_{102G}, LEU_{306G}, CYS_{307G}, GLY_{308G}, LEU_{217H}, VAL_{218H}, CYS_{219H}, LEU_{317H}, VAL_{318H}, CYS_{319H}, ILE_{102I}, LEU_{306I}, CYS_{307I}, GLY_{308I}, LEU_{217J}, VAL_{218J}, CYS_{219J}, LEU_{317J}, VAL_{318J}, CYS_{319J}, LEU_{306K}, CYS_{307K}, GLY_{308K}, LEU_{217L}, VAL_{218L}, CYS_{219L} *Hydrophobic: 57.69%, Acidic: 0%, Basic: 0%, Neutral: 42.31%*

Table 7. The interface residues in the complexes between amyloid fibrils and curcumin keto

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for curcumin keto
1	ApoA-I	GLN_{82C}, LEU_{83C}, ASN_{84C}, GLN_{109D}, LEU_{110D}, ASN_{111D}, LYS_{113D}, ASN_{138E}, LYS_{140E}, ASN_{165F}, LYS_{167F} *Hydrophobic: 18.18%, Acidic: 0%, Basic: 27.27%, Neutral: 54.55%*
2	ApoA-II	LEU_{10B}, THR_{12B}, TYR_{14B}, TYR_{21B}, ALA_{56B}, GLY_{57B}, THR_{58B}, SER_{59B}, LEU_{60B}, LEU_{10F}, THR_{12F}, TYR_{14F}, TYR_{21F}, ALA_{56F}, GLY_{57F}, THR_{58F}, LEU_{10L}, TYR_{21L}, THR_{58L} *Hydrophobic: 31.58%, Acidic: 0%, Basic: 0%, Neutral: 68.42%*
3	Abeta	HIS_{13A}, HIS_{14A}, GLN_{15A}, GLY_{37B}, VAL_{12C}, HIS_{13C}, HIS_{14C}, GLN_{15C}, VAL_{12E}, HIS_{13E}, HIS_{14E} *Hydrophobic: 18.18%, Acidic: 0%, Basic: 54.55%, Neutral: 27.27%*
4	IAPP	LEU_{16E}, HIS_{18E}, SER_{19E}, SER_{20E}, LEU_{16G}, HIS_{18G}, SER_{19G}, SER_{20G}, LEU_{16I}, HIS_{18I} *Hydrophobic: 30%, Acidic: 0%, Basic: 30%, Neutral: 40%*
5	Ins	PHE_{201G}, VAL_{202G}, ASN_{203G}, GLN_{204G}, HSD_{205G}, ILE_{2I}, GLN_{15I}, LEU_{16I}, GLU_{17I}, GLN_{115I}, LEU_{116I}, GLU_{117I}, VAL_{202I}, ASN_{203I}, GLN_{204I}, HSD_{205I}, GLN_{15K} *Hydrophobic: 35.29%, Acidic: 11.76%, Basic: 11.76%, Neutral: 41.18%*

The contact residues of sesamin complexes with ApoA-I fibrils are represented by the acidic and basic residues, with the amino acid composition of the binding sites being completely different from that of the other polyphenols (Table 8). Likewise, the acidic residues take part in the association of sesamin with Abeta fibrils.

Table 8. The interface residues in the complexes between amyloid fibrils and sesamin

	Amyloid fibrils	Amino acid residues forming the fibril binding sites for sesamin
1	ApoA-I	ARG_{445Q}, ARG_{446Q}, ASP_{447Q}, ARG_{472R}, ARG_{473R}, ASP_{474R}, ARG_{499S}, ARG_{500S}, ASP_{501S}, ARG_{526T}, ARG_{527T}, ASP_{528T} *Hydrophobic: 0%, Acidic: 33.33%, Basic: 66.67%, Neutral: 0%*
2	ApoA-II	LEU_{10F}, THR_{12F}, TYR_{21F}, ALA_{56F}, GLY_{57F}, THR_{58F}, LEU_{10L}, THR_{12L}, TYR_{14L}, TYR_{21L}, ALA_{56L}, GLY_{57L}, THR_{58L}, LEU_{10P}, THR_{12P}, TYR_{14P}, TYR_{21P}, ALA_{56P}, THR_{58P}, LEU_{10T}, THR_{12T}, TYR_{14T}, TYR_{21T} *Hydrophobic: 30.43%, Acidic: 0%, Basic: 0%, Neutral: 69.57%*
3	Abeta	PHE_{4K}, HIS_{6K}, LYS_{16K}, LEU_{17K}, VAL_{18K}, PHE_{19K}, PHE_{20K}, ALA_{21K}, GLU_{22K} *Hydrophobic: 62.5%, Acidic: 12.5%, Basic: 25%, Neutral: 0%*
4	IAPP	SER_{19B}, HIS_{18D}, SER_{19D}, SER_{20D}, HIS_{18F}, SER_{19F}, SER_{20F}, HIS_{18H}, SER_{19H}, SER_{20H}, HIS_{18J}, SER_{19J}, SER_{20J} *Hydrophobic: 0%, Acidic: 0%, Basic: 30.77%, Neutral: 69.23%*
5	Ins	ILE_{102A}, VAL_{103A}, GLN_{304A}, HSD_{305A}, LEU_{306A}, CYS_{307A}, VAL_{218B}, CYS_{219B}, LEU_{317B}, VAL_{318B}, CYS_{319B}, GLN_{304C}, HSD_{305C}, LEU_{306C}, CYS_{307C}, LEU_{217D}, VAL_{218D}, CYS_{219D} *Hydrophobic: 50%, Acidic: 0%, Basic: 11.11%, Neutral: 38.89%*

Overall, PF association with Abeta fibrils is governed mainly by the hydrophobic and basic residues, while acidic residues make some contribution to stabilization of the Abeta complexes with sesamin and resveratrol. The binding of polyphenols to fibrillar ApoA-I and ApoA-II is mediated predominantly by hydrophobic and neutral amino acids, although in some cases the basic residues are also involved (*viz.* in the complexes ApoA-I + curcumin keto / sesamin, Ins + curcumin keto). The hydrophobic, basic and neutral residues account for the interactions of polyphenols with the insulin fibrils, while the basic and neutral amino acids play a key role in polyphenol complexation with IAPP fibrils.

CONCLUSIONS

In summary, the molecular docking study of the complexes between the representatives of the six groups of polyphenolic compounds such as flavonoids (quercetin), phenolic acids and derivatives (salicylic acid acid), stilbenes (resveratrol), curcuminoids (curcumin), lignans (sesamin), tannins (gallic acid) and the five types of amyloid fibrils showed that all examined polyphenols have the highest binding affinities for the fibrillar forms of apolipoprotein A-II and insulin, while the lowest affinities were observed for the fibrillar apolipoprotein A-I. The hydrophobicity/hydrophilicity analysis of the amino acid composition of the binding sites revealed that hydrophobic and neutral residues dominate in the association of polyphenols with amyloid fibrils from apoA-I, apoA-II and insulin, the basic residues to a large extent control polyphenol binding to Abeta and IAPP fibrils, whereas the involvement of the acidic residues was revealed only for the complexes sesamin + ApoA-I / Abeta and curcumin keto + Ins. These findings may be of value for deeper understanding of polyphenol ability to destroy or remodel the mature amyloid fibrils and the development of novel anti-amyloid strategies.

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ВЗАЄМОДІЯ ПОЛІФЕНОЛІВ З АМІЛОЇДНИМИ ФІБРИЛАМИ: ДОСЛІДЖЕННЯ МЕТОДОМ МОЛЕКУЛЯРНОГО ДОКІНГУ

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Поліфеноли, група різноманітних сполук природного походження, які мають цілу низку корисних біологічних властивостей, наразі привертають все більший інтерес в контексті їх здатності інгібувати утворення і викликати дестабілізацію особливих білкових агрегатів, амілоїдних фібрил, пов'язаних із багатьма захворюваннями людини. У даній роботі метод молекулярного докінгу був застосований для з'ясування молекулярних деталей взаємодії між поліфенольними сполуками, включаючи кверцетин, куркумін, ресвератрол, сесамін, саліцилову та галову кислоти зі зрілими амілоїдними фібрилами із Абета пептиду, амілоїдного поліпептиду, інсуліну, аполіпопротеїнів А-І та А-ІІ. Усі досліджені поліфеноли мали найвищу спорідненість до амілоїдних фібрил із аполіпопротеїну А-ІІ та інсуліну, тоді як найнижча спорідненість спостерігалась до фібрилярного аполіпопротеїну А-І. Аналіз амінокислотного складу сайтів зв'язування з використанням шкали гідрофобності/гідрофільності показав, що гідрофобні та нейтральні залишки відіграють ключову роль у комплексоутворенні поліфенолів з амілоїдними фібрилами із аполіпопротеїну А-І, аполіпопротеїну А-ІІ та інсуліну, позитивно заряджені залишки у значній мірі визначають зв'язування поліфенолів з фібрилярними формами Абета та амілоїдного поліпептидів, тоді як внесок негативно заряджених залишків був виявлений тільки для комплексів сесамін + фібрили аполіпопротеїну А-І /Абета та куркумін кето + фібрили інсуліну. Отримані результати можуть бути корисними при розробці нових анти-амілоїдних стратегій на основі поліфенолів.

Ключові слова: *амілоїдні фібрили; поліфеноли; сайти зв'язування, спорідненість зв'язування, молекулярний докінг*