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A MOLECULAR DOCKING STUDY OF AMYLOID-POLYSACCHARIDE COMPOSITES: I. INTERACTIONS WITH POLYPHENOLS

Valeriya Trusova*, Uliana Malovytsia, Olga Zhytniakivska, Galyna Gorbenko
Department of Medical Physics and Biomedical Nanotechnologies, V.N. Karazin Kharkiv National University
4 Svobody Sq., Kharkiv, 61022, Ukraine
**Corresponding Author email: valerija.trusova@karazin.ua*

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Filamentous protein aggregates, amyloid fibrils, currently attract considerable interest as a prospective nanomaterial for a variety of biomedical and industrial applications. Among their advantages are biocompatibility, high stability and mechanical strength, self-assembly capability, etc. The integration of other biopolymers such as polysaccharides into amyloid matrix enables creating novel nanomaterials with improved mechanical characteristics and higher loading capacity for biologically active compounds. In the present study we employed the molecular docking technique to ascertain the molecular details of the interactions between the lysozyme amyloid fibrils and a series of polyphenolic compounds including curcumin, gallic acid, salicylic acid, quercetin, resveratrol and sesamin, and to explore the effect of polysaccharide chitosan on such kind of interactions. It was shown that curcumin in enol form has the highest binding affinity for fibrillar lysozyme, while the lowest affinity was observed for salicylic acid. The binding sites for curcumin, gallic acid, quercetin, resveratrol and sesamin appear to occupy the groove on the wet fibril surface, while salicylic acid binds to the dry surface of the fibril. The interfacial amino acid residues in the fibril complexes with polyphenols and chitosan are identified. Chitosan was found to display the ability to interact with polyphenolic compounds within amyloid matrix, resulting in the enhancement of polyphenol binding. The data obtained provide a basis for further designing and experimental testing of the amyloid-chitosan nanocomposites loaded with polyphenols.

Keywords: *Lysozyme amyloid fibrils; Chitosan; Polyphenols; Binding sites; Binding affinity; Molecular docking*
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The last decade has seen a paradigm shift in nanoscience with the growing accent on the use of proteins as building blocks for a variety of functional nanomaterials [1]. Particular attention in this context is paid to filamentous protein aggregates with a core cross-β sheet structure, amyloid fibrils that are featured by structural stability, unique mechanical properties, sequence-controlled surface functionalities, biocompatibility, self-healing ability, etc. [2]. Amyloid-based nanomaterials have been designed for a variety of biomedical and industrial applications [3]. To exemplify, amyloid fibrils with specific binding sites have been engineered for biosensing of disease biomarkers [5, 6] and environmental pollutants [7]. The drug delivery applications of fibrillized proteins showed high efficiency of encapsulation and controlled drug release [8]. Amyloid assemblies have been explored as biocompatible coatings for implants and medical devices [9] and scaffolds for tissue engineering and regeneration [10]. Functionalized amyloid fibrils appeared to be suitable for advanced energy storage due to their high conductivity and mechanical strength [11]. Likewise, optical properties of fibrillar aggregates doped with organic dyes or quantum dots enable their use for energy transfer and light harvesting [4]. A promising approach to the development of amyloid nanomaterials involves integration of protein fibrils with other biopolymers, particularly, polysaccharides [12]. Of these, the polymer of β-1,4-D-glucosamine, chitosan, attracts a lot of interest due to a wide spectrum of favorable properties among which are antimicrobial, immunomodulatory and antitumor activities, the abilities to enhance blood coagulation and promote wound healing [13]. In the recent work of Tian and coauthors the double network hydrogels have been prepared from the lysozyme amyloid fibrils and chitosan [14]. These composite hydrogels were found to have enhanced mechanical strength depending on chitosan concentration and high loading capacity for a polyphenolic compound, gallic acid. Another polyphenol, ferulic acid, was loaded into combined hydrogels from wheat gluten amyloid fibrils and chitosan [15]. It was demonstrated that such double networks can be used for more efficient delivery of ferulic acid with improvement of its bioavailability and bioaccessibility.

As the first step towards engineering the double hydrogels loaded by biologically active agents, the aim of the present study was to gain molecular docking insights into the interactions between the lysozyme amyloid fibrils, chitosan and a series of polyphenolic compounds including curcumin (enol and keto forms), gallic acid, salicylic acid, quercetin, resveratrol and sesamin. Lysozyme is an enzyme hydrolyzing the cell wall of Gram-positive bacteria and possessing anti-inflammatory, immunomodulatory and antiviral activities [16]. In the native state lysozyme is capable of hydrolyzing the cell wall of only Gram-positive bacteria, while in the fibrillar state it acts on both Gram-positive and Gram-negative bacteria, so that hydrogel matrix from lysozyme fibrils possesses additional functionality associated with its antibacterial activity [17]. Since lysozyme is an endogenous antibiotic, this functionality is especially important in the context of the problem of multidrug resistance. The biological activities of polyphenols are known to involve antimicrobial, anticancer, antioxidative, anti-inflammatory and anticoagulant effects [18, 19].

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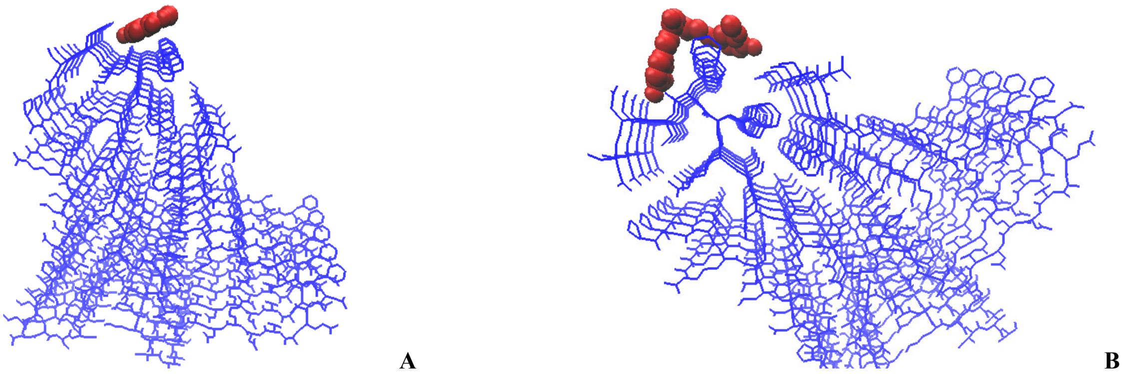
METHODS

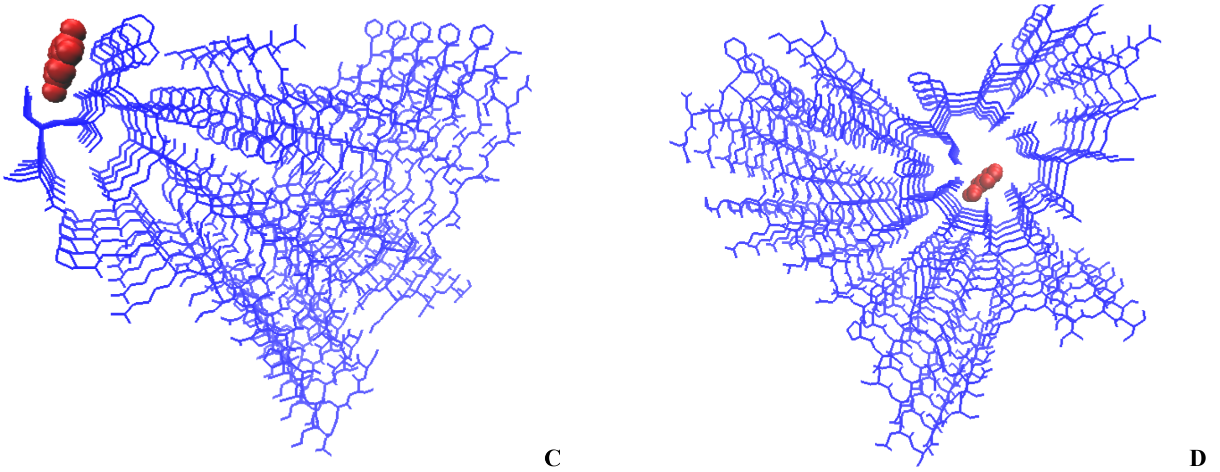
The structures of the examined polyphenolic compounds were drawn in MarvinSketch software, v.18.10, ChemAxon with subsequent geometry optimization in Avogadro 1.1.0 software using the Universal Force Field21. The structure of amyloid fibrils from hen egg white lysozyme deciphered by combining atomic force microscopy, cryo-electron microscopy and solid-state NMR was taken from the Protein Data Bank (PDB ID 8QV8) [20]. The structure of chitosan (CS) 12-mer was obtained from a database of polysaccharide 3D structures (http://polysac3db.cermav.cnrs.fr), protonated and optimized in Avogadro 1.1.0 software. The docking of polyphenols to amyloid fibrils was performed with the web-based server HDOCK that uses hybrid algorithm of template-based modeling and free docking [21]. The selected docking poses were visualized with the VMD software.

RESULTS AND DISCUSSION

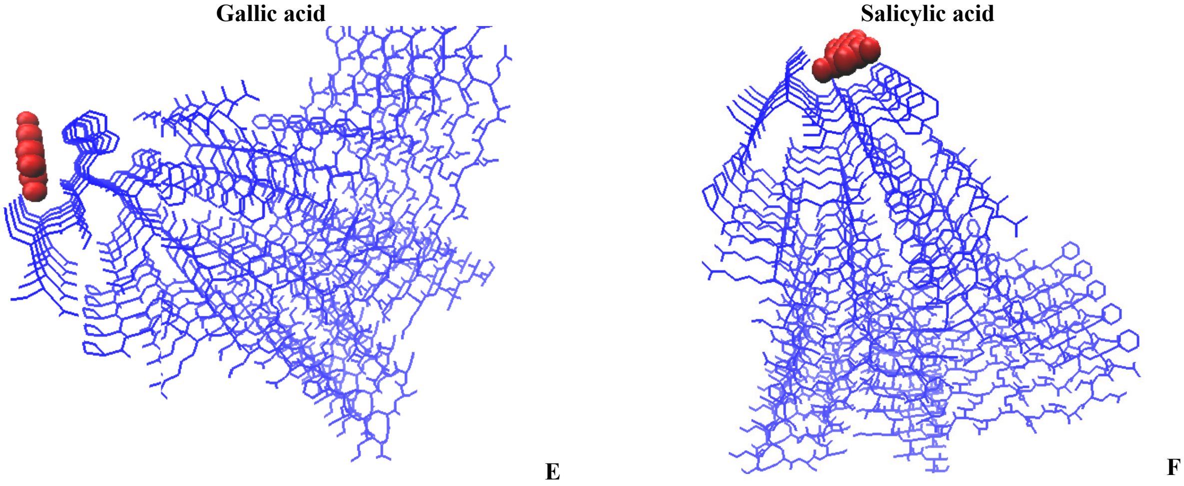
Shown in Fig. 1 are the most energetically favorable complexes between the lysozyme amyloid fibrils and the examined polyphenolic compounds. As can be seen, most polyphenols bind to the wet surface of the fibril, and only salicylic acid associates with the dry surface.



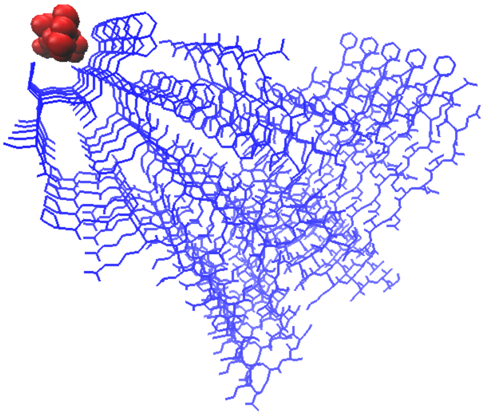
Curcumin enol **Curcumin keto**



Gallic acid **Salicylic acid**



Quercetin **Resveratrol**



G

Sesamin

Figure 1. The best-score complexes of lysozyme fibrils with polyphenols.

The comparison of the best score values (Table 1) showed that curcumin (enol) forms the strongest complexes with the fibrils, with the binding affinities decreasing in the row: curcumin (enol) > quercetin ≥ sesamin > curcumin (keto) > resveratrol > gallic acid > salicylic acid.

Table 1. The best score values for the complexes of polyphenols with lysozyme amyloid fibrils and its composite with chitosan

Polyphenol	Lysozyme fibrils	Lysozyme fibrils + chitosan
		-316.62 (0.966)
Curcumin enol	-178.12 (0. 637)*	-178.27 (0.638)
Curcumin keto	-145.05 (0. 475)	-159.73 (0.549)
Gallic acid	-94.88 (0.249)	-115.91 (0.336)
Salicylic acid	-81.35 (0.202)	-95.93 (0.253)
Quercetin	-159.61 (0.548)	-169.16 (0.595)
Resveratrol	-120.92 (0.359)	-133.95 (0.420)
Sesamin	-157.11 (0.536)	-185.75 (0.671)

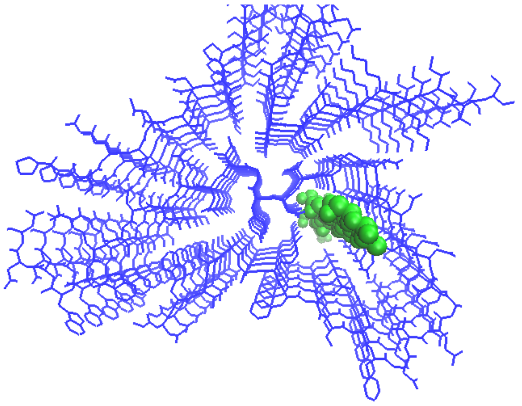
*Given in parentheses are the values of a confidence score for binding probability, with the values > 0.7 being considered as high confidence, 0.5-0.7 as moderate, and < 0.5 as low probability.

Notably, all polyphenols bound to the wet fibril surface reside in the groove with the interface residues such as tryptophan, cysteine and asparagine, while in the complexes of salicylic acid with the dry fibril surface the interface residues are represented by lysine, threonine, serine and aspartic acid (Table 2).

Table 2. The interface residues in the complexes of polyphenols with lysozyme amyloid fibrils and its composite with chitosan

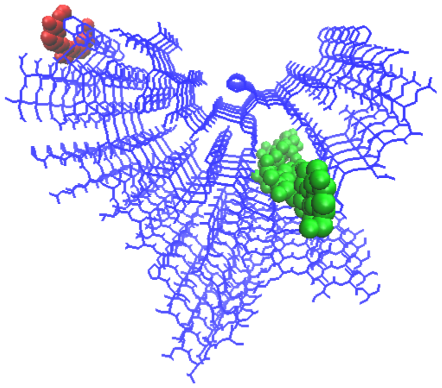
Polyphenol	Lysozyme fibrils	Lysozyme fibrils + chitosan
		LYS$_{33A}$ ARG$_{45A}$ ASN$_{46A}$ THR$_{47A}$ SER$_{50A}$ THR$_{51A}$ ASP$_{52A}$ LYS$_{33C}$ GLU$_{35C}$ ARG$_{45C}$ ASN$_{46C}$ THR$_{47C}$ SER$_{50C}$ THR$_{51C}$ ASP$_{52C}$ LYS$_{33E}$ ARG$_{45E}$ ASN$_{46E}$ THR$_{47E}$ SER$_{50E}$ THR$_{51E}$ ASP$_{52E}$ LYS$_{33G}$ ARG$_{45G}$ THR$_{47G}$ SER$_{50G}$ THR$_{51G}$ ASP$_{52G}$ LYS$_{33I}$ ARG$_{45I}$ ASN$_{46I}$ THR$_{47I}$ SER$_{50I}$ THR$_{51I}$ ASP$_{52I}$
Curcumin enol	TRP$_{63A}$ ASN$_{65A}$ TRP$_{63C}$ CYS$_{64C}$ ASN$_{65C}$ TRP$_{63E}$ CYS$_{64E}$ ASN$_{65E}$ TRP$_{63G}$ CYS$_{64G}$ ASN$_{65G}$ TRP$_{63I}$	TRP$_{63A}$ ASN$_{65A}$ TRP$_{63C}$ CYS$_{64C}$ ASN$_{65C}$ TRP$_{63E}$ CYS$_{64E}$ ASN$_{65E}$ TRP$_{63G}$ CYS$_{64G}$ ASN$_{65G}$ TRP$_{63I}$
Curcumin keto	TRP$_{63C}$ CYS$_{64C}$ ASN$_{65C}$ TRP$_{63E}$ CYS$_{64E}$ ASN$_{65E}$ GLY$_{26G}$ TRP$_{63G}$ ASN$_{65G}$	LYS$_{33I}$ GLU$_{35I}$ ARG$_{45I}$ SER$_{50I}$ THR$_{51I}$ ASP$_{52I}$ TYR$_{53I}$ ASN$_{93I}$ CS$_{9}$ CS$_{10}$ CS$_{11}$
Gallic acid	TRP$_{63A}$ TRP$_{63C}$ CYS$_{64C}$ ASN$_{65C}$ TRP$_{63E}$ CYS$_{64E}$ ASN$_{65E}$ TRP$_{63G}$ ASN$_{65G}$	LYS$_{33E}$ GLU$_{35E}$ ARG$_{45E}$ ASP$_{52E}$ LYS$_{33G}$ GLU$_{35G}$ ARG$_{45G}$ ASP$_{52G}$ LYS$_{33I}$ GLU$_{35I}$ ARG$_{45I}$ ASP$_{52I}$ CS$_{7}$ CS$_{8}$ CS$_{9}$
Salicylic acid	LYS$_{33E}$ THR$_{47E}$ SER$_{50E}$ THR$_{51E}$ ASP$_{52E}$ LYS$_{33G}$ THR$_{47G}$ SER$_{50G}$ THR$_{51G}$ ASP$_{52G}$ THR$_{51I}$ ASP$_{52I}$	GLU$_{35E}$ LYS$_{33G}$ GLU$_{35G}$ ARG$_{45G}$ ASP$_{52G}$ LYS$_{33I}$ GLU$_{35I}$ ARG$_{45I}$ ASP$_{52I}$ CS$_{8}$ CS$_{9}$ CS$_{10}$
Quercetin	TRP$_{63C}$ CYS$_{64C}$ ASN$_{65C}$ TRP$_{63E}$ CYS$_{64E}$ ASN$_{65E}$ TRP$_{63G}$ CYS$_{64G}$ ASN$_{65G}$ TRP$_{63I}$ ASN$_{65I}$	LYS$_{33E}$ PHE$_{34E}$ GLU$_{5E}$ ARG$_{45E}$ LYS$_{33G}$ PHE$_{34G}$ GLU$_{35G}$ ARG$_{45G}$ LYS$_{33I}$ PHE$_{34I}$ GLU$_{35I}$ ARG$_{45I}$ CS$_{7}$ CS$_{8}$ CS$_{9}$ CS$_{10}$ CS$_{11}$
Resveratrol	TRP$_{63C}$ CYS$_{64C}$ ASN$_{65C}$ TRP$_{63E}$ CYS$_{64E}$ ASN$_{65E}$ TRP$_{63G}$ CYS$_{64G}$ ASN$_{65G}$ TRP$_{63I}$ ASN$_{65I}$	LYS$_{33G}$ GLU$_{35G}$ ARG$_{45G}$ LYS$_{33I}$ GLU$_{35I}$ ARG$_{45I}$ ASP$_{52I}$ CS$_{8}$ CS$_{9}$ CS$_{10}$ CS$_{11}$
Sesamin	ASN$_{65A}$ TRP$_{63C}$ CYS$_{64C}$ ASN$_{65C}$ TRP$_{63E}$ CYS$_{64E}$ ASN$_{65E}$ TRP$_{63G}$ CYS$_{64G}$ ASN$_{65G}$ TRP$_{63I}$ CYS$_{64I}$ ASN$_{65I}$	LYS$_{33E}$ PHE$_{34E}$ GLU$_{35E}$ ARG$_{45E}$ LYS$_{33G}$ PHE$_{34G}$ GLU$_{35G}$ ARG$_{45G}$ LYS$_{33I}$ GLU$_{35I}$ ARG$_{45I}$ ASP$_{52I}$ CS$_{7}$ CS$_{8}$ CS$_{9}$ CS$_{10}$ CS$_{11}$

The best score and confidence score values observed for the chitosan complexes with fibrillar lysozyme suggest that this polysaccharide displays very high binding affinity for the lysozyme fibril (Table 1), accommodating within the grooves on the dry fibril surface (Fig. 2, A). The interface residues forming contacts with chitosan include amino acids with polar uncharged side chains (threonine, serine, asparagine, glutamine), positively charged (lysine, arginine), and negatively charged (aspartic acid) amino acid residues (Table 2).



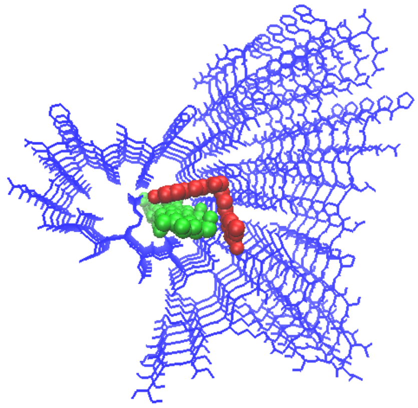
A

Lysozyme fibrils + Chitosan



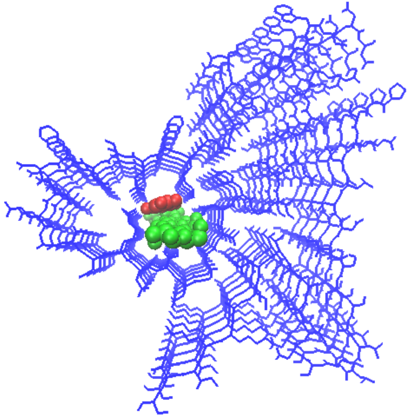
B

Lysozyme fibrils + Chitosan + Curcumin (enol)



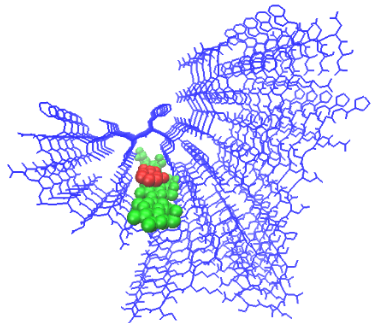
C

Lysozyme fibrils + Chitosan + Curcumin (keto)



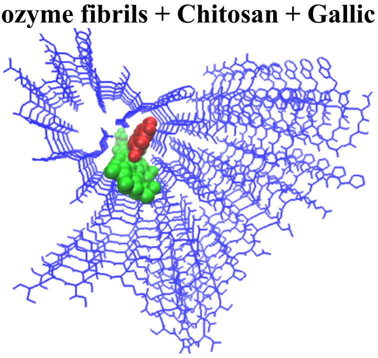
D

Lysozyme fibrils + Chitosan + Gallic acid



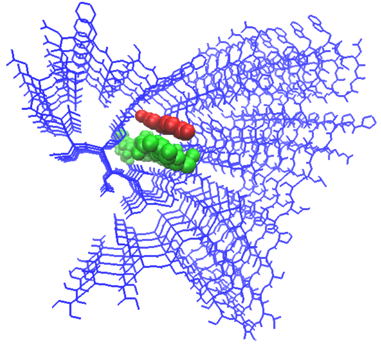
E

Lysozyme fibrils + Chitosan + Salicylic acid



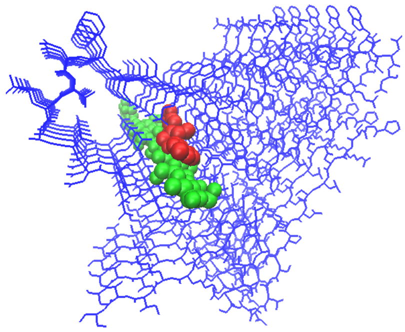
F

Lysozyme fibrils + Chitosan + Quercetin



G

Lysozyme fibrils + Chitosan + Resveratrol



H

Lysozyme fibrils + Chitosan + Sesamin

Figure 2. The best-score complexes of lysozyme fibrils with chitosan and polyphenols.

In the absence and presence of chitosan the binding site for curcumin enol remains the same, embracing TRP, CYS and ASN (Table 2). However, the other polyphenols exhibit unexpected behavior – they are localized within the same groove as chitosan and form contacts with both, fibril and polysaccharide (Fig. 2, C-H). Their binding motif involves LYS, GLU and ARG, complemented by PHE for quercetin and sesamin (Table 2). Accordingly, while for curcumin enol the binding affinity was not affected by chitosan, all other explored compounds showed marked increase in the binding affinity compared to the corresponding systems without the polysaccharide (Table 1). The strength of complexation between polyphenols and two-component binding matrix appeared to decrease in the order: sesamin > curcumin enol >quercetin > curcumin keto > resveratrol > gallic acid > salicylic acid. It should also be noted that the greatest enhancement of the binding affinity in the presence of chitosan was observed for gallic acid, salicylic acid and sesamin. These findings suggest that integration of lysozyme amyloid fibrils with chitosan may result in the increase of the extent of polyphenol loading and stimulate experimental efforts in this direction.

CONCLUSIONS

To summarize, the molecular docking of polyphenols representing different classes of these compounds to the fibrillar lysozyme and its complexes with chitosan revealed that: (i) the binding affinity of polyphenols to the lysozyme amyloid fibril decreases in the row: curcumin (enol) > quercetin ≥ sesamin > curcumin (keto) > resveratrol > gallic acid > salicylic acid; (ii) curcumin, gallic acid, quercetin, resveratrol and sesamin reside within the groove on the wet fibril surface with the repeating binding motif tryptophan, cysteine, asparagine; (iii) salicylic acid is localized on the dry fibril surface interacting with lysine, threonine, serine and aspartic acid; (iv) chitosan forms strong complexes with fibrillar lysozyme, and resides parallel to the fibril axis interacting with lysine, arginine, threonine, serine, asparagine, glutamine and aspartic acid; v) in the presence of chitosan the binding affinity of polyphenols markedly increases, with the magnitude of this effect being greatest for gallic acid, salicylic acid and sesamin; vi) in the double system fibrillar lysozyme + chitosan the examined polyphenolic compounds are capable of forming contacts with both amino acid residues and chitosan subunits. These findings can be regarded as a starting point for further development of the composite bionanomaterials for biomedical applications based on fibrillar lysozyme and chitosan.

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ORCID

Valeriya Trusova, https://orcid.org/0000-0002-7087-071X; **Uliana Malovytsia,** https://orcid.org/0000-0002-7677-0779
Olga Zhytniakivska, https://orcid.org/0000-0002-2068-5823; **Galyna Gorbenko,** https://orcid.org/0000-0002-0954-5053

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ДОСЛІДЖЕННЯ АМІЛОЇД – ПОЛІСАХАРИДНИХ КОМПОЗИТІВ МЕТОДОМ МОЛЕКУЛЯРНОГО ДОКІНГУ: I. ВЗАЄМОДІЯ З ПОЛІФЕНОЛАМИ

Валерія Трусова, Уляна Маловиця, Ольга Житняківська, Галина Горбенко
Кафедра медичної фізики та біомедичних нанотехнологій, Харківський національний університет імені В.Н. Каразіна
м. Свободи 4, Харків, 61022, Україна

Філаментні білкові агрегати, амілоїдні фібрили, наразі викликають значний інтерес як перспективні наноматеріали для різноманітних біомедичних та промислових застосувань. Серед їхніх переваг такі властивості як біосумісність, висока стабільність та механічна стійкість, здатність до самоорганізації тощо. Інтеграція інших біополімерів, зокрема, полісахаридів в амілоїдний матрикс дозволяє створити нові наноматеріали з покращеними механічними характеристиками та вищою здатністю до навантаження біологічно активними речовинами. В даній роботі ми застосували метод молекулярного докінгу для з'ясування молекулярних деталей взаємодії між амілоїдними фібрилами лізоциму та серією поліфенольних сполук включаючи куркумін, галову кислоту, саліцилову кислоту, кверцетин, ресвератрол і сесамін, та дослідити вплив полісахариду хітозану на взаємодії такого типу. Було показано, що куркумін в єнольній формі має найвищу спорідненість до фібрилярного лізоциму, тоді як найнижча спорідненість була виявлена для саліцилової кислоти. Сайти зв'язування для куркуміну, галової кислоти, кверцетину, ресвератролу та сесаміну розташовуються в борозенці на зовнішній поверхні фібрили лізоциму, а саліцилова кислота зв'язується з внутрішньою поверхнею фібрили. Ідентифіковані амінокислотні залишки, що локалізуються на контактній ділянці в комплексах фібрил з поліфенолами та хітозаном. Встановлено, що хітозан здатний до взаємодії з поліфенольними сполуками всередині амілоїдного матриксу, що призводить до посилення зв'язування поліфенолів. Отримані дані створюють підґрунтя для подальшого дизайну та експериментального тестування амілоїд-хітозанових нанокомпозитів навантажених поліфенолами.

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