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Docking Studies of Plant Polyphenols with Aβ Fragments Suggests Determinants That Enable Design of Inhibitors towards Preventing Aggregation Events during Alzheimer's

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ABSTRACT

The aggregation of Amyloid beta peptides is considered as one of the causative events in the pathogenesis of Alzheimer's disease (AD). Polyphenols present in different plant sources, which have acclaimed therapeutic values, are known to inhibit the formation of Amyloid fibrils. Hence, docking studies with different polyphenols were carried out to appreciate their binding modes and plausible molecular interactions. The results reveal a consensus pattern of association, exhibiting that all the ligands preferentially dock to the metal coordinating residues in the peptide fragments. In fact, the metal interacting geometries in the Aβ segments are known to be implicated in aggregation events. Further, due to non-specific binding, these polyphenols are expected to have a competitive inhibitory efficacy over a range of amyloid peptide fragments. Thus, these findings suggest that the polyphenolic compounds could become promising lead molecules that aid in the development of inhibitors and neuroprotectors towards prevention of amyloid fibril formations and AD.

Keywords: Alzheimer's disease, Amyloid fibrils, Amyloid peptide, Neuroprotectors, Polyphenols.

INTRODUCTION

Alzheimer's disease (AD) is a brain disorder that is categorized by deterioration of neurons, and formation of amyloid plaques, neurofibrillary tangles, synaptic and memory loss and cognitive dysfunctions. [1] Amyloid Beta (Aβ) peptide deposition is the major pathological feature of AD. Approximately 35 Million individuals worldwide are likely to be affected by AD growing propensity which is projected to double each 20 years and would touch 66 million by 2030. [2] Till date, the exact cause and cure are blurred and the increasing number of AD cases would thus prioritize the search for a proper diagnosis and precise cure. Despite deciphering the neuropathological events taking place during AD, the progression and initial trigger for the disease is unclear. Hence, effective prognosis and defined treatments are need of the hour.

The neurotoxic effects of Aβ were first shown by Yankner *et al* [3] in rat hippocampal neurons in culture. Aβ when in solution exists in equilibrium between random coil and β-sheet structures and enhances neurotoxicity. Studies indicate.

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that Aβ peptides exhibit a transition from random coil to β-sheet during fibrillation. [4-5] The β-sheet structure self assembles into fibrils [6] which can form soluble and insoluble aggregates. Experiments with Circular Dichroism (CD) spectroscopy, Electron Microscopy and Nuclear Magnetic Resonance [7] have been carried out so far for characterizing the structural conformations of Aβ. A hypothesis also suggests that aromatic stacking may play a role in acceleration of the assembly process in many cases of amyloid fibril formation. [8-9] Current drugs for AD aim across cholinergic and glutamatergic neurotransmission, showing developing indications but, their neuroprotective action is less understood. [10-11] Hence, there is a dire need to explore and screen compounds that could act as desirable neuroprotective agents.

Table 1: Details of Aβ Fragments with their sequence

Aβ Fragments (number of residues)	Molecular Weight *in kilo Daltons*	PDB ID	Sequence Details
1-42 (42)	4.5	1IYT	DAEFRHDSGYEVHHQKL VFFAEDVGSNKGAIIGLM YGGVVIA
1-28 (28)	3.2	1AMC	DAEFRHDSGYEVHHQKL VFFAEDVGSNK
1-16 (16)	1.9	Unpublished	DAEFRHDSGYEVHHQK
1-12 (12)	1.4	Unpublished	DAEFRHDSGYEV

Phytochemicals are class of molecules found at high concentrations in tea, wine, berries, cocoa, and a wide variety of other plants, with diverse pharmacological properties. [12-13] More than 8000 polyphenolic compounds have already been identified, and well characterized for their natural properties i.e. to protect plants from diseases and ultraviolet radiations, and protect the seeds till they germinate. [14]

MATERIALS AND METHODS

The protocol followed in the project is as illustrated in Fig. 1. It is found that, some of the polyphenols present in plant sources have a promising role in the treatment of Neurodegenerative disorders and crosses the Blood brain barrier. [15-37]

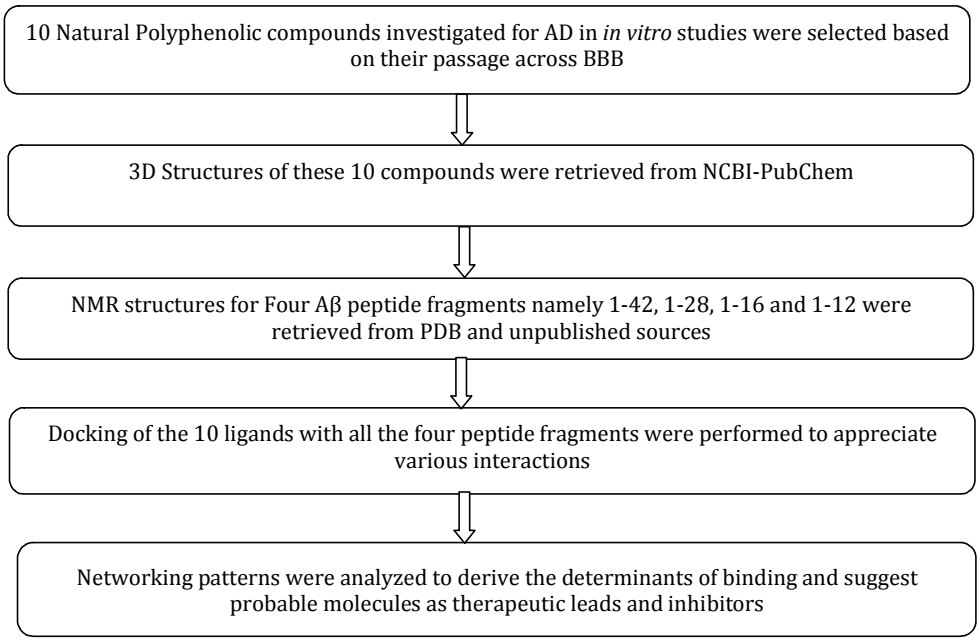


Fig. 1: Protocol of the Project

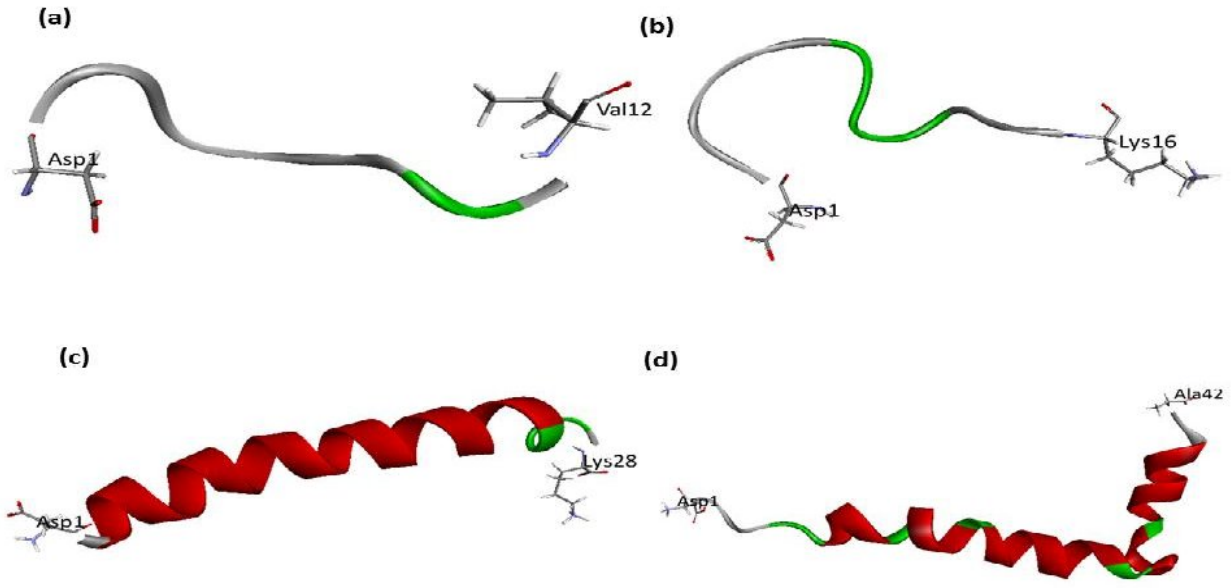


Fig. 2: Conformations of different Aβ Fragments: (a) Amyloid beta 1-12 fragment (b) Amyloid beta 1-16 fragment (c) Amyloid beta 1-28 fragment-1AMC (d) Amyloid beta 1-42 fragment -1IYT

Based on these illustrations in literature, 10 pharmacologically relevant compounds were retrieved from NCBI (PubChem database) and selected for docking studies with the Aβ structural segments 1-42, 1-28, 1-16 and 1-12. The 3D coordinates for 1-42 and 1-28 peptide fragments were retrieved from NMR structures deposited in the Protein Data Bank (PDB), whose IDs are 1IYT and 1AMC respectively. Similarly, the 3D coordinates of 1-16 and 1-12 segments were taken from the NMR structures solved by Narayan *et* al. [38] The amino acid compositions of the four peptides are provided in Table.1 and the conformations of the four Aβ peptide fragments are illustrated in (Fig. 2)

Naturally, the bigger fragment (1-42) exhibits regular secondary structural geometries. However, as the peptide length decreases, its structure diffuses into random coil folds. The properties and structures of the 10 polyphenols are tabulated in Table 2. Similarities in their geometries were analyzed using SPDBV tool via the RMSD calculations, and are tabulated in Table 3. The RMSD values between the various ligands indicated that the structures are three-dimensionally similar, as their range lie in between 0.25 to 1.04Å. All the polyphenols were converted into appropriate formats, suitable for docking exercises with FlexX. [39] To determine all possible determinants of the peptide fragments, which would probably network with the ligands, non-covalent interactions like hydrogen bonds were analyzed around 5Å distances from the ligand/peptide atoms. The overall picture indicating the strengths of interactions are consolidated in Table 4. The set of residues in the peptide fragments 1-42, 1-28, 1-16 and 1-12 interacting with the polyphenols, are detailed in Table 5. These set of pharmacophoric interactions for different Aβ fragments would not only help in understanding as to why these selective polyphenols have similar binding patterns but also, aid in providing probable clues for designing a drug like molecule to inhibit AD.

Table 2: Structures and Properties of different ligands used in the study

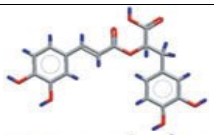
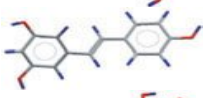
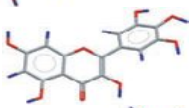
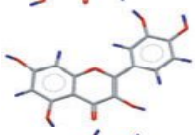
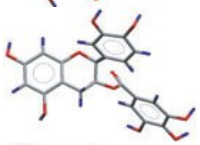
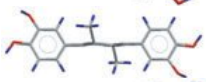
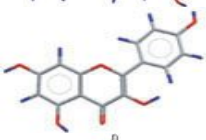
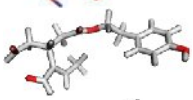
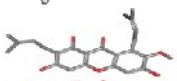
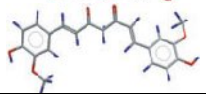
Ligand Name	3D structure	Source (common Name)	PubChem ID	Molecular Formula	Molecular weight (g/mol)	IC50 values (Aβ1-42 Fragment)	References
Rosmarinic acid		*Salvia officinalis* (Sage)	5281792	$C_{14}H_{12}O_3$	360.31	1.1	[15,16,17]
Resveratrol		*Vitis vinifera* (Red Grapes)	445154	$C_{14}H_{12}O_3$	228.24	5.6	[17,18,19,20]
Myricetin		*Vitis vinifera* (Red Grapes)	5281672	$C_{15}H_{10}O_8$	318.24	0.40	[17,21]
Quercetin		*Vitis vinifera* (Red Grapes)	5280343	$C_{15}H_{10}O_7$	302.24	0.72	[17,22]
Epigallocatechin gallate (EGCG)		*Camellia sinensis* (Green Tea)	65064	$C_{22}H_{18}O_{11}$	458.37	0.18	[17, 23,24]
Nordihydroguaiaretic acid (NDGA)		*Larrea tridentata* (Creosote bush)	4534	$C_{18}H_{22}O_4$	302.36	0.86	[17,25]
Kaempferol		*Camellia sinensis* (GreenTea)	5280863	$C_{15}H_{10}O_6$	286.24	3.2	[17,26]
Oleocanthal		*Olea europea* (Olive Oil)	11652416	$C_{17}H_{20}O_5$	304.34	N.A	[27,28]
α-Mangostin		*Garcinia mangostana* (mangosteen)	5281650	$C_{24}H_{26}O_6$	410.46	N.A	[29,30]
Curcumin		*Curcuma longa* (turmeric)	969516	$C_{21}H_{20}O_6$	368.38	0.63	[17,31,32]

Table 3: RMSD values between the Ligands

Polyphenolic Compounds (Ligands)	Rosmarinic acid (42 atoms)	Curcumin (32 toms)	Oleocanthal (42 atoms)	Mangostin (53 atoms)	NDGA (44 atoms)	Resveratrol (29 atoms)	EGCG (51 atoms)	Myricetin (33 atoms)	Kaempferol (31 atoms)
Curcumin	0.69	-	-	-	-	-	-	-	-
Oleocanthal	0.71	0.65	-	-	-	-	-	-	-
Mangostin	0.75	0.59	0.85	-	-	-	-	-	-
NDGA	0.86	0.83	0.94	0.54	-	-	-	-	-
Resveratrol	0.54	0.52	0.55	0.68	0.46	-	-	-	-
EGCG	0.77	0.72	0.89	0.75	1.04	0.63	-	-	-
Myricetin	0.67	0.67	0.65	0.59	0.65	0.53	0.79	-	-
Kaempferol	0.41	0.43	0.49	0.53	0.25	0.54	0.71	0.54	-
Quercetin	0.63	0.52	0.73	0.67	0.44	0.54	0.60	0.58	0.25

Table 4: Strength of interactions of Aβ fragments with different ligands

# of H-bonds within 5 Å	Rosmarinic acid	Quercetin	Kaempferol	Oleocanthal	Mangostin	Myricetin	NDGA	EGCG	Curcumin	Resveratrol
For 1-42	6	5	4	4	6	6	5	6	6	3
Strength of interaction	Very Strong	Very Strong	Strong	Strong	Very Strong	Very Strong	Very Strong	Very Strong	Very Strong	Less Strong
For 1-28	5	9	7	7	5	5	5	10	9	9
Strength of interaction	Less Strong	Very Strong	Strong	Strong	Less Strong	Less Strong	Less Strong	Very Strong	Very Strong	Very Strong
For 1-16	7	7	5	6	4	8	5	7	6	8
Strength of interaction	Very Strong	Very Strong	Strong	Strong	Less Strong	Very Strong	Strong	Very Strong	Strong	Very Strong
For 1-12	7	6	5	7	5	5	5	6	8	6
Strength of interaction	Very Strong	Very Strong	Strong	Very Strong	Strong	Strong	Strong	Very Strong	Very Strong	Very Strong

Table 5: Residues belonging to 1-42, 1-28, 1-16 and 1-12 fragments interacting with the ligands within 5Å

Residues Involved in ligand interactions (within 5Å)		Rosmarinic- acid	Quercetin	Kaempferol	Oleocanthal	Mangostin	Myricetin	NDGA	EGCG	Curcumin	Resveratrol
For 1-42	S8	2.77	-	-	-	2.79	4.07	-	-	5.00	-
	G9	4.72	3.05	2.82	-	4.50	-	2.49	-	-	2.70
	Y10	-	2.57	3.77	-	-	-	2.76	-	-	3.94
	E11	4.13	4.35	-	-	4.96	2.65	4.99	2.91	4.25	-
	V12	3.00	-	-	4.31	3.69	2.90	-	2.40	3.00	-
	H13	-	2.51	2.51	3.65	-	5.00	3.19	4.30	5.00	2.70
	H14	-	2.80	2.80	-	-	-	3.83	4.24	-	-
	Q15	2.68	-	-	2.66	2.29	2.75	-	2.73	2.77	-
	K16	3.18	-	-	2.71	4.24	3.12	-	3.78	3.08	-
For 1 - 28	D1	-	2.62	-	4.23	-	-	-	2.79	3.27	2.76
	A2	-	2.94	4.32	4.25	-	-	-	3.84	3.96	3.04
	E3	-	4.25	-	4.73	-	-	-	4.53	4.02	4.83
	F4	-	4.71	-	-	-	-	-	4.61	4.19	4.73
	R5	3.14	-	2.48	-	2.72	2.98	2.51	3.31	3.17	3.72
	H6	2.84	3.54	2.75	3.36	4.57	2.44	2.46	2.66	3.24	4.19
	G9	2.74	2.68	2.74	2.74	2.85	2.70	3.09	2.64	2.73	2.76
	Y10	3.44	3.60	4.27	4.07	4.59	3.53	4.29	3.80	3.71	4.43
	E11	-	5.00	3.96	-	-	-	-	4.77	-	-
	H13	3.21	3.16	3.14	3.08	2.78	2.71	4.79	3.26	3.33	2.71
For 1-16	D1	-	-	4.14	-	2.96	2.81	-	3.77	4.95	4.00
	D7	2.96	4.53	-	-	-	2.79	3.01	2.52	-	2.81
	G9	5.00	4.85	-	2.94	-	3.65	-	-	-	3.50
	Y10	3.81	3.32	3.57	2.70	-	2.87	3.96	2.78	2.61	2.75
	E11	5.00	5.00	3.06	2.98	-	4.78	-	4.97	4.73	5.00
	H13	3.79	2.76	2.81	3.58	4.90	4.74	2.80	2.78	3.13	5.00
	H14	2.73	2.66	3.77	2.76	3.13	2.90	3.30	2.58	2.68	2.85
	Q15	3.59	2.74	-	3.04	2.95	3.59	2.62	2.46	4.07	3.31
For 1-12	F4	3.13	-	-	3.53	-	-	2.95	-	4.83	4.75
	R5	2.55	-	-	2.79	-	-	2.74	4.49	3.12	2.63
	H6	4.55	3.00	2.20	4.84	2.85	2.63	4.68	2.71	4.71	4.54
	D7	4.71	4.17	4.04	-	5.00	4.60	-	2.88	4.66	5.00
	S8	4.99	3.05	3.04	4.04	4.31	2.68	-	3.35	4.78	4.51
	G9	2.79	3.08	2.59	2.61	3.16	2.88	3.22	2.69	2.66	-
	Y10	3.02	2.75	2.79	2.89	3.85	3.04	2.64	3.15	2.94	3.00
	E11	-	5.00	-	4.79	-	-	-	-	5.00	-

RESULTS AND DISCUSSIONS

The docking studies of various polyphenols to the fragments of Aβ reveal that the stretch of residues from Asp1 to Lys16 in the various peptide segments, broadly interact with all the ligands and interestingly coincide with the key metal coordinating residues that are proposed to be responsible for initiation of aggregation events. As illustrated in the Tables 4 & 5, the set of residues (S8, G9, Y10, E11, V12, H13, H14, Q15, K16) in Aβ1-42, the amino acids (D1, A2, E3, F4, R5, H6, G9, Y10, E11, H13) in Aβ1-28, the atoms in the peptide units belonging to (D1, A2, E3, F4, R5, H6, G9, Y10, E11, H13, H14, Q15) in Aβ1-16, and the molecular moieties (F4, R5, H6, D7, S8, G9, Y10, E11) of Aβ1-12, exhibit preferential binding to various polyphenols. All the 9 ligands, except Resveratrol, exhibits favored binding to 1-42 segment. Similarly, polyphenolic compounds Quercetin, Kaempferol, Oleocanthal, EGCG, Curcumin, Resveratrol display strong interactions with 1-28 peptide. Likewise, for the fragment 1-16 all the 9 ligands except Mangostin demonstrate good binding. Interestingly, the smallest fragments of the lot namely 1-12, indicate concerted binding for all the 10 ligands. The results emphasize that, key residues namely G9, Y10, E11 are essential to bind to the polyphenolic ligands in all these peptide fragments. The study further signify that, the binding set of determinants common to all diverse ligands, could be exploited towards exploring these polyphenols as competitive inhibitors to facilitate prevention of aggregation events and AD.

In conclusion, it is known that amyloid peptide fragments (Aβ1-12, Aβ1-16, Aβ1-28, Aβ1-42) are important for initiation of aggregation events in AD. Docking studies with the plant polyphenols demonstrate clear interactions with

metal binding moieties in the peptides, thereby offering promising leads towards development of therapeutics for Alzheimer's disease.

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