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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]
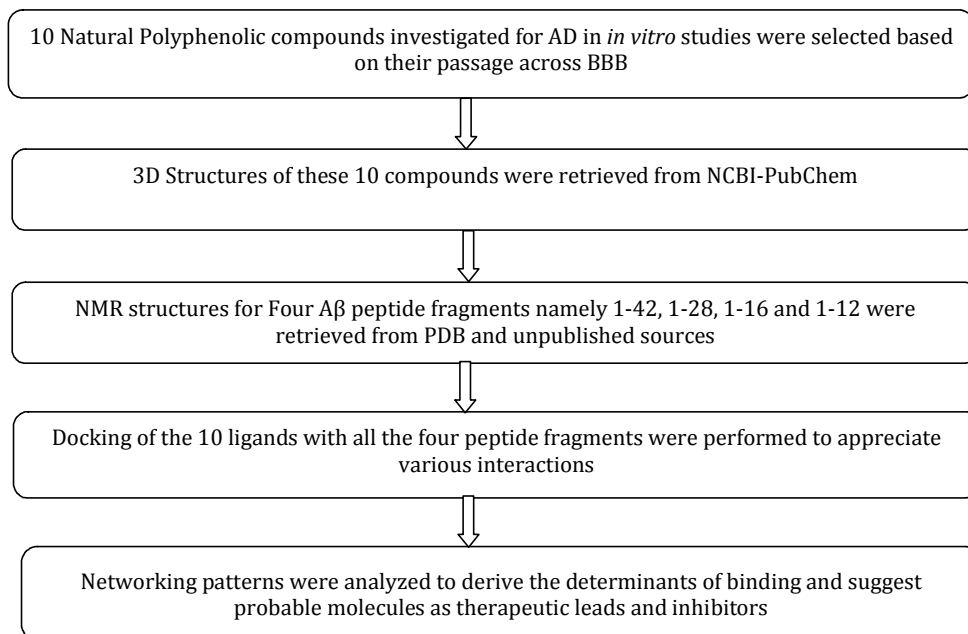
10 Natural Polyphenolic compounds investigated for AD in *in vitro* studies were selected based on their passage across BBB

3D Structures of these 10 compounds were retrieved from NCBI-PubChem

NMR structures for Four Aβ peptide fragments namely 1-42, 1-28, 1-16 and 1-12 were retrieved from PDB and unpublished sources

Docking of the 10 ligands with all the four peptide fragments were performed to appreciate various interactions

Networking patterns were analyzed to derive the determinants of binding and suggest probable molecules as therapeutic leads and inhibitors

Fig. 1: Protocol of the Project

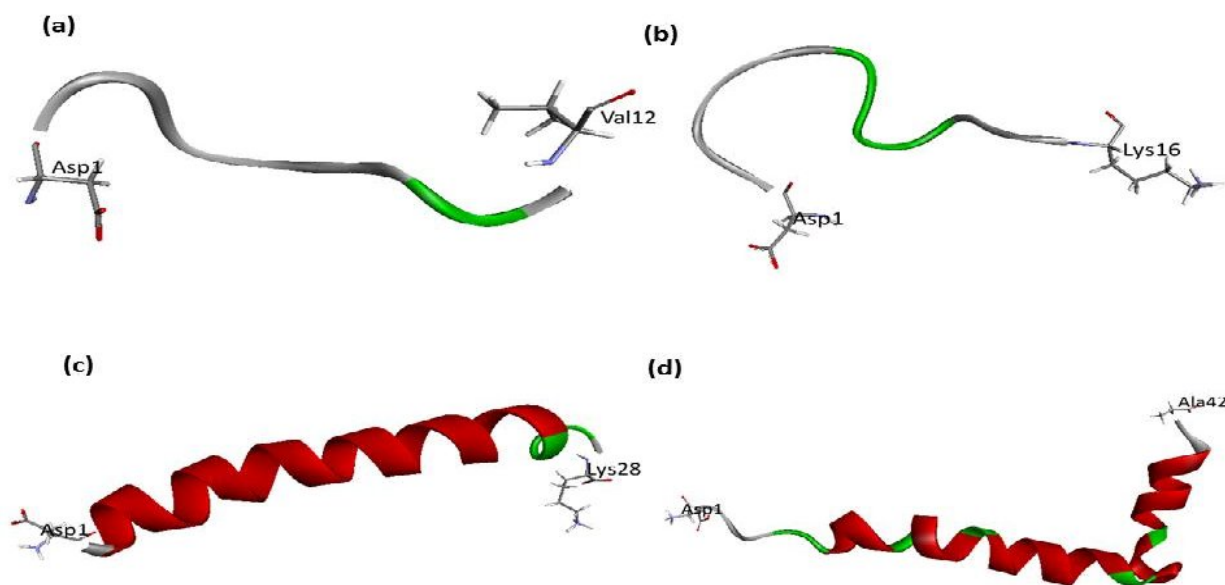**Fig. 2: Conformations of different Aβ Fragments:** (a) Amyloid beta 1-12 fragment (b) Amyloid beta 1-16 fragment (c) Amyloid beta 1-28 fragment- 1AMC (d) Amyloid beta 1-42 fragment -1IYT
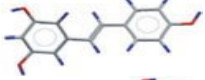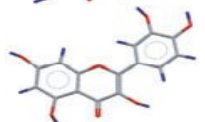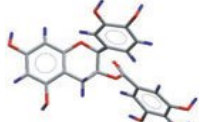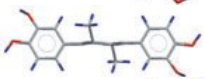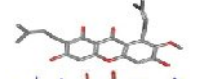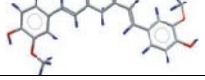
Based on these illustrations in literature, 10 pharmacologically relevant compounds were retrieved from NCBI (PubChem database) and selected for docking studies with the Aβ structural segments 1-42, 1-28, 1-16 and 1-12. The 3D coordinates for 1-42 and 1-28 peptide fragments were retrieved from NMR structures 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	0.94	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.

REFERENCES

1. Ana Budimir. Metal ions, Alzheimer's disease and chelation therapy. Acta.Pharm 2011; 61:1-14.
2. Finder V H. Alzheimer's disease: a general introduction and pathomechanism. Journal of Alzheimer's disease 2010; 22:3: 5-19.
3. Yankner BA., Duffy L. and Kirschner D. Neurotrophic and neurotoxic effects of amyloid-β protein: reversal by tachykinin neuropeptides. Science 1990; 250:279-282.
4. Terzi E., Holzemann G. and Seelig J. Reversible random coil beta-sheet transition of the Alzheimer beta-amyloid fragment (25–35). Biochemistry 1994; 33:1345-1350.
5. Anthony W. Fitzpatrick, Tuomas P. J. Knowles, Christopher A.Waudby, Michele Vendruscolo, Christopher M. Dobson. Inversion of the Balance between Hydrophobic and Hydrogen Bonding Interactions in Protein Folding and Aggregation. PLoS. Comput. Biol. 2011; 7:e1002169.
6. Shen C. and Murphy R. M. Solvent effects on self-assembly of beta-amyloid peptide.Biophys. J. 1995; 69:640-651.
7. Snyder S. W., Ladror U. S., Wade W. S., Wang G. T., Barrett L. W., Matayoshi E. D., Huffaker H. J., Krafft G. A. and Holzman T. F. Amyloid- β aggregation: selective inhibition of aggregation in mixtures of amyloid with different chain lengths. Biophys. J. 1994; 67:1216-1228.
8. Tartaglia G.G., Cavalli A., Pellarin R., Caflisch A. The role of aromaticity, exposed surface, and dipole moment in determining protein aggregation rates. Protein. Sci. 2004; 3:1939-1941.
9. Gazit E. A possible role for p-stacking in self-assembly of amyloid fibrils. FASEB. J . 2002; 16:77-83.
10. Francesca Mangialasche, Alina Solomon, Bengt Winblad, Patrizia Mecocci, Miia Kivipelto. Alzheimer's disease: clinical trials and drug development. Lancet.Neurol. 2010; 9:7: 702–716.
11. Gao X, Zheng CY, Yang L, Tang XC, Zhang HY. Huperzine A protects isolated rat brain mitochondria against beta-amyloid peptide. Free. Radic .Biol .Med. 2009; 46:11: 1454–1462.
12. Claudine Manach, Andrzej Mazur, Augustin Scalbert. Polyphenols and prevention of cardiovascular diseases. Lippincott Williams & Wilkins 2005; 16:1:77-84.
13. Amalesh Samanta, Gouranga Das, Sanjoy Kumar Das. Roles of Flavonoids In Plants. Int.J. Pharm. Sci. Tech. 2011; 6: 12-135.
14. Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: A review of their intracellular targets. European Journal of Pharmacology. 2006; 545:1: 51–64.
15. Luan H, Kan Z, Xu Y, Lv C, Jiang W. Rosmarinic acid protects against experimental diabetes with cerebral ischemia: relation toinflammation response. J.Neuroinflammation 2013; 10:28: 10-28.
16. Teresa Iuvone, Daniele De Filippis, Giuseppe Esposito, Alessandra D'Amico, and Angelo A. Izzo. The Spice Sage and Its Active Ingredient Rosmarinic Acid Protect PC12 Cells from Amyloid Peptide-Induced Neurotoxicity. J.P.E.T. 2006; 317:3: 1143–1149.
17. Yair Porat, Adel Abramowitz and Ehud Gazit. Inhibition of Amyloid Fibril Formation by Polyphenols: Structural Similarity and Aromatic Interactions as a Common Inhibition Mechanism. Chem.Biol. Drug. Des. 2006; 67:1: 27–37.
18. Antoni Camins , Felix Junyent , Ester Verdaguer , Carlos Beas-Zarate , Argelia E. Rojas-Mayorquín , Daniel Ortuño-Sahagún and Mercè Pallàs. Resveratrol: An Anti-aging Drug with Potential Therapeutic Applications in Treating Diseases. Pharmaceuticals. 2009; 2:3: 194-205.
19. Valérie Vingtdeux, Ute Dreses-Werringloer, Haitian Zhao, Peter Davies and Philippe Marambaud. Therapeutic potential of resveratrol in Alzheimer's disease. BMC. Neuroscience 2008; 9:2: S6.
20. Gonzales AM, OrlandoRA. Sensitive Aβ Oligomerization Assay for Identification of Small Molecule Inhibitors. The Open Biotechnology Journal 2009; 3:1: 108-116.
21. Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H. Multifunction of myricetin on A beta: neuroprotection via a conformational change of A beta and reduction of A beta via the interference of secretases. J Neurosci Res. 2008; 86:2: 368-377.
22. Mubeen Ahmed Ansari, Hafiz Mohammed Abdul, Gururaj Joshi, Wycliffe O.Opii, D.Allan Butterfield. Protective Effect of Quercetin in Primary Neurons against Aβ (1-42): Relevance to Alzheimer's Disease. J. Nutr. Biochem. 2009; 20:4: 269–275.
23. Sabu M Chacko, Priya T Thambi, Ramadasan Kuttan, Ikuo Nishigaki Chacko et al. Beneficial effects of green tea: A literature review . Chinese Medicine 2010; 5:13.
24. Silvia Mandel, Orly Weinreb, Tamar Amit and Moussa B. H. Youdim. Cell signaling pathways in the neuroprotective actions of the green tea polyphenol (-)-epigallocatechin-3-gallate: implications for neurodegenerative diseases. Journal of Neurochemistry 2004; 88:6: 1555-1569.
25. Melissa A. Moss, Nicholas H. Varvel,1 Michael R. Nichols, Dana Kim Reed, Terrone L. Rosenberry. Nordihydroguaiaretic Acid Does Not Disaggregate-Amyloid(1–40) Protofibrils but Does Inhibit Growth Arising from Direct Protofibril Association. Mol Pharmacol. 2004; 66:3: 592–600.
26. Jae Kyeom Kim, Soo Jung Choi, Hong Yon Cho, Han-Joon Hwang, Young Jun Kim, Seung Taik Lim, Chang-Ju Kim, Hye Kyung Kim, Sabrina Peterson, Dong Hoon Shin. Protective effects of kaempferol against amyloid beta peptide induced neurotoxicity in ICR mice. Biosci. Biotechnol.Biochem. 2010; 74:2: 397-401.
27. Jason Pitt a,, William Roth a, Pascale Lacor a, Amos B. Smith III b,c, Matthew Blankenship d, Pauline Velasco a, Fernanda De Felice e, Paul Breslin b,f,, William L. Klein a. Alzheimer's-associated Aβ oligomers show altered structure, immunoreactivity and synaptotoxicity with low doses of oleocanthal. Toxicology and Applied Pharmacology 2009; 240:2: 189-197.
28. Alaa H. Abuznait, Hisham Qosa, Belnaser A. Busnena, Khalid A. El Sayed, and Amal Kaddoumi. Olive-Oil-Derived Oleocanthal Enhances β Amyloid Clearance as a Potential Neuroprotective Mechanism against Alzheimer's disease: In Vistro and in Vivo Studies. ACS.Chem.Neurosci 2013; 4:6: 973-982.
29. Wang Y, XIa Z, Xu JR, Wang YX, Hou LN, Qiu Y,Chen HZ . α-mangostin, a polyphenolic xanthone derivative from mangosteen, attenuates β-amyloid oligomers-induced neurotoxicity by inhibiting amyloid aggregation. Neuropharmacology 2012; 62:2: 871-81.
30. Reyes-Fermín LM, González-Reyes S, Tarco-Álvarez NG, Hernández-Nava M, Orozco-Ibarra M, Pedraza-Chaverri J. Neuroprotective effect of α-mangostin and curcumin against iodoacetate-induced cell death. Nutr Neurosci. 2012; 15:5: 34-41.
31. Shrikant Mishra and Kalpana Palanivelu.The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Ann Indian Acad Neurol. 2008; 11:1: 13-19.
32. Fusheng Yang, Giselle P. Lim, Aynun N. Begum, Oliver J. Ubeda, Mychica R. Simmons, Surendra S. Ambegaokar, Pingping Chen, Rakez Kayed, Charles G. Glabe, Salley A. Frautschy, and Gregory M. Cole. Curcumin Inhibits Formation of Amyloid Oligomers and Fibrils, Binds Plaques, and Reduces Amyloid in Vivo. J.Biol. Chem 2005; 280:7: 5892-5901.
33. Wang Q, Xu J,Rottinghaus GE, Simonyi A, Lubahn D, Sun GY, Sun AY. Resveratrol protects against global cerebral ischemic injury in gerbils. Brain.Res 2002; 958:2: 439-447.
34. Mario Caruana , Tobias Högen , Johannes Levin , Andreas Hillmer , Armin Giese , Neville Vassallo. Inhibition and disaggregation of a-synuclein oligomers by natural polyphenolic compounds. FEBS Letters 2011; 585:8: 1113-1120.
35. Youdim KA, Qaiser MZ, Begley DJ, Rice-Evans CA, Abbott NJ. Flavonoid permeability across an in situ model of the blood-brain barrier. Free Radic Biol Med. 2004; 36:5: 592-604.
36. Guedj F, Se´brie´ C, Rivals I, Ledru A, Paly E, et al. Green Tea Polyphenols Rescue of Brain Defects Induced by Overexpression of DYRK1A. PLoS. ONE. 2009; 4:2: e4606
37. Young Jin Jang, Jiyoung Kim, Jaesung Shim, Jaekyoon Kim, Sanguine Byun, Min-Ho Oak, Ki Won Lee, and Hyong Joo Lee. Kaempferol Attenuates 4-Hydroxynonenal-Induced Apoptosis in PC12 Cells by Directly Inhibiting NADPH Oxidase. JPET. 2011; 337:3: 747-754.
38. Narayan P, Krishnarjuna B, Vishwanathan V, Jagadeesh Kumar D, Babu S, Ramanathan KV, K Easwaran KR, Nagendra H G, Raghothama S.Does Aluminium bind to Histidine? An NMR investigation of Amyloid β12 and Amyloid β16 fragments. Chem. Biol. Drug. Des. 2013; 82:1: 48-59.
39. Kramer B, Rarey M, Lengauer T. Evaluation of the FLEXX Incremental Construction Algorithm for Protein–Ligand Docking. Proteins: Structure, Function, and Genetics 1999; 37:2: 228-241.