Medical Hypotheses 125 (2019) 94–99

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Tea polyphenols as multi-target therapeutics for Alzheimer's disease: An *in silico* study

Muhammed Khairujjaman Mazumder*, Shuvasish Choudhury

Central Instrumentation Laboratory, Assam University, Silchar 788011, Assam, India

ARTICLE INFO

Keywords:
Acetylcholine
Amyloid-β
Molecular docking
Neurodegeneration
Neuroprotection
Neurofibrillary tangles
Polyphenols

ABSTRACT

Alzheimer's disease (AD) is the most common progressive neurodegenerative disease characterized by cognitive decline, dementia, and in later stages complete loss of feelings, sensation and death. The global prevalence of the disease is on the rise, and it affects 35–40% of the population above 80 years. The pathological hallmarks of the disease include extra-neuronal deposition of amyloid-β (Aβ) as plaques and intra-neuronal hyperphosphorylated tau protein as neurofibrillary tangles, which cause neurodegeneration and cerebral atrophy. Aβ deposition is catalyzed by β-secretase and γ-secretase, while tau hyperphosphorylation is catalyzed by glycogen synthase kinase – 3β (GSK-3β). With neurodegeneration, the level of the neurotransmitter acetylcholine (ACh), as well as acetylcholinesterase (AChE), decreases in the synaptic cleft, called cholinergic deficiency. This leads to the cardinal behavioural abnormalities of AD, which is referred to as cholinergic hypothesis of AD. The other enzyme which degrades ACh is the butyrylcholinesterase (BuChE). Thus, current treatment options of AD include symptomatic treatment to elevate the levels of ACh by inhibiting AChE. However, the currently used drugs cause several side effects, and the quest for novel drugs remains an interesting and essential venture. Since the disease has multiple pathophysiologies, there is an unrelenting need to develop novel drugs and lead molecules capable of inhibiting multiple pathways. The present study hypothesizes use of tea polyphenols against the key drug targets of AD, viz. β–Secretase, γ-Secretase, GSK-3β, AChE and BuChE. The hypothesis has been validated using molecular docking tools. The result indicates that the polyphenols may potentially inhibit these enzymes, similar to their known inhibitors. Thus, the findings are of immense significance in the therapeutic interventions of AD, using tea polyphenols as exciting multi-target drugs.

Introduction

AD is the most common progressive neurodegenerative disorder, affecting 12.8% of the global population above 65 years age, and 35–40% above 80 years [41]. An estimated 46.8 million people are affected by AD globally, which is expected to quadruple by 2050 [14,27]. AD is the most common cause of dementia, accounting to more than 80% of such cases [41]. Starting from mild cognitive impairment, AD affects sleep, mood, communication, judgment, learning, senses, feelings, emotions, motor abilities, and the subjects fail to perform daily activities and depend on others for basic needs in advanced stages [32]. AD is characterized by the deposition of extra-neuronal Aβ plaques [11,31,36], and intra-neuronal neurofibrillary tangles of hyperphosphorylated tau protein in the hippocampus and cerebral cortex of the brain [30,31]. These further spread to other brain regions. Deposition of Aβ plaques and the tangles leads to chronic inflammation, oxidative stress, mitochondrial dysfunctions, and ultimately neuronal dysfunctions and death [8,15,35]. With these neurodegenerative processes in operation, the neurons lose connections among one another, which lead to neuronal death and the resultant atrophy of the brain [5,39].

Aβ is derived from amyloid precursor protein (APP) through proteolytic cleavage by secretases: β-secretase and γ-secretase. β-Secretase is the first protease which processes APP leading to the production of Aβ [9,37]. Accumulation of Aβ (peptide of length 38–43 amino acids), accompanied by its reduced clearance and subsequent change in conformation, results in the formation of the plaques [11]. While amyloid plaques trigger oxidative stress, and chronic inflammation [15,8], they also modulate N-methyl-D-aspartate receptors thereby leading to excitotoxicity [24]. GSK-3β is responsible for hyperphosphorylation of tau protein, and thereby the formation of neurofibrillary tangles within the neurons [28,29,40]. Thus, targeting the secretases and GSK-3β are the most important strategies for amelioration of the AD pathophysiology [34] (Fig. 1).

* Corresponding author.
E-mail address: khairujjaman1987@gmail.com (M.K. Mazumder).

https://doi.org/10.1016/j.mehy.2019.02.035
Received 26 December 2018; Accepted 13 February 2019

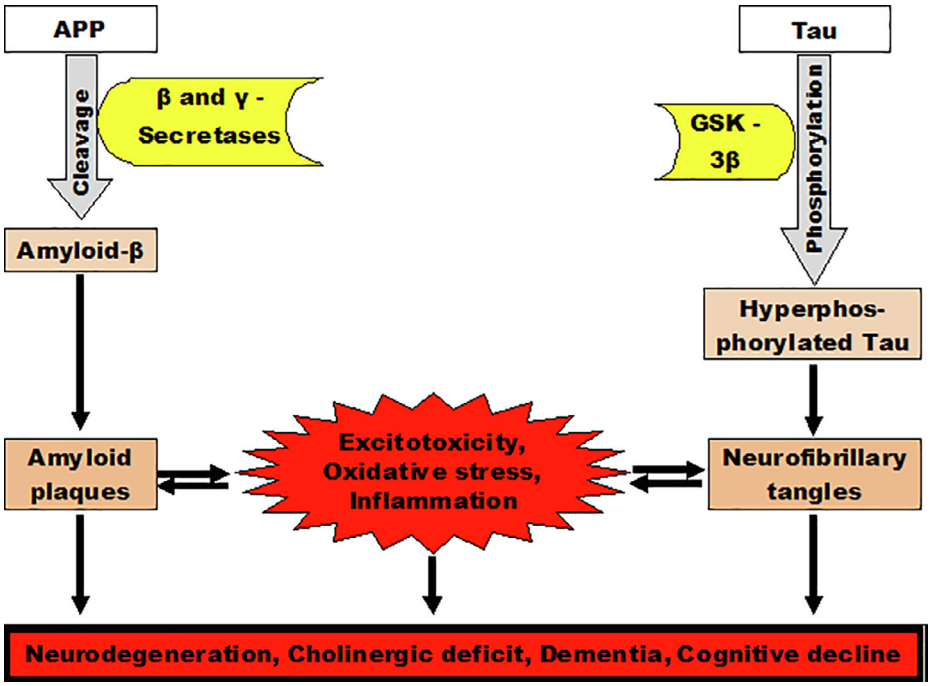

Fig. 1. Simplified pathophysiology of AD. Cleavage of APP by β- and γ-Secretases (Sec) leads to the production of Aβ which aggregates to produce Amyloid plaques. Hyperphosphorylation of tau protein by GSK-3β leads to the formation of neurofibrillary tangles. Plaques and tangles lead to chronic inflammation, oxidative stress and excitotoxicity, and thereby degeneration of the cholinergic neurons. This results in cholinergic deficit, and the resultant dementia and cognitive decline in AD.

The cholinergic hypothesis of AD postulates that degeneration of cholinergic neurons and the resultant decrease in the activity of AChE and depletion in the level of ACh are the immediate and consistent causes of the cognitive decline and dementia in AD ([25,42]). AChE is responsible for breakdown of the neurotransmitter ACh at the synaptic cleft, and thus leads to dementia and cognitive decline in AD. The presently available treatment in restoring the level of ACh is the use of inhibitors of AChE [4]. Although AChE is the predominant cholinesterase in healthy brain, the activity of BuChE increases in the brain of AD patients [10,26] (Fig. 1). Thus, inhibition of AChE and BuChE should be targeted to effectively enhance the level of ACh in the synaptic cleft. Therefore, inhibition of the secretases and GSK-3β is essential to prevent the progression of AD, while inhibition of the cholinesterases (AChE and BuChE) to elevate the level of ACh is the gold standard symptomatic treatment of the disease. Unfortunately, the currently used drugs for the treatment of AD target the symptoms and are also associated with serious side effects, thereby necessitating novel drugs. Further, since AD is associated with several pathophysiological processes, multiple drugs are needed to ameliorate the symptoms and disease progression, which cause drug burden. Thus, there is an unrelenting need to develop novel drugs and lead molecules capable of inhibiting multiple neurodegenerative pathways.

Tea polyphenols have been extensively reported to confer protection against neurodegenerative diseases including AD and Parkinson's disease [6,12,38]. Most of these studies focused on anti-oxidant and anti-inflammatory properties of these polyphenols. Further, (−)-epigallocatechin-3-gallate, the major component of green tea, has been reported to inhibit Aβ fibril formation [43]. However, the mechanism underlying the inhibition of Aβ fibril formation by the polyphenol is least elucidated. Moreover, since the polyphenols have several interacting groups which can form hydrogen bonds as well as weaker interactions, it is hereby hypothesized that they may inhibit the enzymes responsible for the pathophysiological processes underlying AD. The present study investigates the possible inhibitory role of four tea polyphenols on five key drug targets of AD, viz. β-secretase, γ-secretase, GSK-3β, AChE and BuChE.

Methodology

Receptors

Five drug targets (enzymes) were selected for the present study, viz. β-Secretase, γ-Secretase, GSK-3β, AChE and BuChE. The 3-dimensional structures of these enzymes were downloaded from Protein Databank (PDB) (www.rcsb.org/pdb) in *.pdb* format. The structures were selected based on their completeness, source organism, expression system, resolution, bound ligands, etc. All the selected structures were human receptors, the details of which have been provided in Table 1.

Table 1
Details of the receptors used in the study. Except BuChE with one chain, all other receptors have two chains. Stereochemical quality was studied using PROCHECK module available at PDB Sum server (www.ebi.ac.uk/), and the % of residues of the receptors falling in the most favoured and additionally allowed regions of the Ramachandran plot are shown.

Sl. No.	Name of the Receptor (PDB ID)	No. of residues	Co-crystallized/bound ligand	Resolution; R-factor; R-free	Reference	% of residues in different regions		No. of residues in disallowed region
						Most favoured	Additionally allowed	
1	β-Secretase (1FKN)	794	Memapsin	1.90 Å; 0.180; 0.224	Hong et al. [13]	87.2%	11.7%	2
2	γ-Secretase (5FN2)	1309	DAPT	4.2 Å	[2]	82.0%	14.4%	21
3	GSK-3β (1Q5K)	689	AR-A014418	1.94 Å; 0.222; 0.242	Bhat et al. [3]	87.6%	10.5%	5
4	AChE (4EY6)	1065	Galantamine	2.40 Å; 0.169;0.206	Cheung et al. [7]	89.4%	10.3%	1
5	BuChE (4BDS)	524	Tacrine	2.10 Å; 0.177; 0.209	Nachon et al. [23]	87.7%	11.9%	0

Table 2
Details of the ligands used in the present study. HBD: Hydrogen bond donor group; HBA: Hydrogen bond acceptor group.

Sl. No.	Name of ligand	PubChem compound ID	Mol. Wt. (g/mol)	Mol. Formula	No. of HBD	No. of HBA	Type of ligand
1	Elenbecestat	CID_57827330	437.414	$C_{19}H_{18}F_3N_5O_2S$	2	9	β-Secretase inhibitor
2	Segamacestat	CID_9843750	361.442	$C_{19}H_{27}N_3O_4$	3	4	γ-Secretase inhibitor
3	AR-A014418	CID_448014	308.312	$C_{12}H_{12}N_4O_4S$	2	6	GSK-3β inhibitor
4	Galantamine	CID_9651	287.359	$C_{17}H_{21}NO_3$	1	4	AChE inhibitor
5	Tacrine	CID_1935	198.269	$C_{13}H_{14}N_2$	1	2	BuChE inhibitor
6	Catechin	CID_9064	290.271	$C_{15}H_{14}O_6$	5	6	Tea polyphenol
7	Epicatechin	CID_72276	290.271	$C_{15}H_{14}O_6$	5	6	Tea polyphenol
8	Epigallocatechin	CID_72277	306.27	$C_{15}H_{14}O_7$	6	7	Tea polyphenol
9	Epigallocatechin gallate	CID_65064	458.375	$C_{22}H_{18}O_{11}$	8	11	Tea polyphenol

Stereological quality of the receptors

To determine stereological quality of the receptors, Ramachandran plots of the receptors were determined using the online tool PROCHECK available at PDB Sum server (www.ebi.ac.uk/).

Ligands

Four tea polyphenols, viz. (+)-Catechin (CAT), (−)-Epicatechin (EPC), (−)-Epigallocatechin (EGC) and (−)-Epigallocatechin gallate (EGCG) were selected for the present study. The 3-D structures of these polyphenols were downloaded from the NCBI PubChem Compounds database (www.pubchem.ncbi.nlm.nih.gov/) in *.sdf* format. The structures of the known inhibitors of the receptors were likewise downloaded from the database. Details of the ligands, the polyphenols and the known inhibitors, are given in Table 2.

Molecular docking

Molecular docking was performed between the ligands and the receptors using Molegro Virtual Docker (MVD) software to determine the docking scores, and optimal geometry of binding of the ligands at the active sites of the receptors [33]. The PDB structures were selected based on availability of co-crystallized/bound ligand, and these ligands were used as the reference of binding sites for each receptor while performing docking. Amino acids within a radius of 15 Å were included in the docking simulation, and 1500 iterations per ligand per receptor were evaluated. For γ-Secretase, the largest binding pocket of 38 amino acids, as reported to be the active site [2], was selected as the docking site. The best ligand geometry in terms of docking scores was considered for further analysis, following Mazumder et al. [16,17,20–22].

Results

Stereological quality of the receptors

The Ramachandran plot generated for the receptors reveal that 98.9%, 96.4%, 98.1%, 99.7% and 99.6% of the residues of the receptors β-Secretase, γ-Secretase, GSK-3β, AChE and BuChE respectively fall in the most favoured and additionally allowed regions (Table 1). This shows adequate stereochemical qualities of the receptors for molecular docking studies.

Docking poses of the ligands

The docking poses of the ligands (reference ligands and tea polyphenols) revealed that the ligands bind to the same pocket of the respective receptors (Fig. 2). It further demonstrates that all the ligands have the same binding pocket, similar to the known and co-crystallized inhibitors. However, for the receptor γ-Secretase, we determined the largest cavity of the receptor using MVD, and the same was used for reference of binding site. All the ligands, including the known inhibitor, were found to dock to this pocket of the receptor.

Inhibition of the receptors

When a ligand binds to the active site of a receptor, it interferes and competes with the natural ligand thereby bringing about inhibition of the activity of the receptor. EGCG showed higher docking scores (i.e., more negative values) against all the receptors, except β-Secretase, compared to all other ligands including known inhibitors. Against β-Secretase, while the known inhibitor Elenbecestat has the highest score, EGCG has highest score among the tea polyphenols (Table 3).

Discussion

Tea polyphenols are among natural products which are frequently being tested for beneficial effects in different disease pathophysiologies, including neurodegenerative disorders [6,12,38]. The compounds have also been tested for their beneficial roles in AD. The current treatment for AD includes use of inhibitors of AChE to enhance the levels of ACh in the synaptic cleft, and thereby ameliorate dementia and cognitive decline [29]. However, since the neurodegenerative processes of the disease include production of Aβ by the actions of β- and γ-secretases, and hyperphosphorylation of tau proteins by GSK – 3β [8,11,15,31,35,36], targeting only AChE does not provide inclusive neuroprotection, thus the disease progression is not halted. Other prominent factors which contribute to the neurodegeneration in AD include oxidative stress, inflammation and excitotoxicity [15,35]. Thus, development of drugs which target multiple pathophysiologies is being postulated. The present study investigates the inhibitory role of four tea polyphenols, CAT, EPC, EGC and EGCG on five different drug targets of AD, viz. β-secretase, γ-secretase, GSK-3β, AChE and BuChE. Inhibition of the secretases (β and γ), GSK-3β and the cholinesterases (AChE and BuChE) prevent formation of amyloid plaques, hyperphosphorylation of tau protein and enhance the level of ACh respectively [1,4]. As a consequence, the disease progression may be halted as well as the cholinergic deficiency – mediated cognitive decline and dementia may be ameliorated.

When a ligand binds to the active site of a receptor with higher docking scores, i.e., more negative docking score values, better inhibition of the receptor takes place. Thus, more negative docking scores indicate more stable ligand-receptor complex [16–22]. Against all the receptors, the polyphenols were found to show highest docking scores with best conformations at the active site where the co-crystallized ligand binds, despite the fact that a larger sphere was considered for docking. This indicates that all the ligands have identical binding site (Fig. 2).

The molecular docking shows that against β-secretase, the known inhibitor Elenbecestat shows highest MolDoc score (−146.205), while among the tea polyphenols EGCG shows the maximum score (−141.686), which is comparable to the former. On the other hand, CAT shows maximum hydrogen bond score (−22.858), and the same for EGCG was found to be −14.664. The hydrogen bonding scores of all

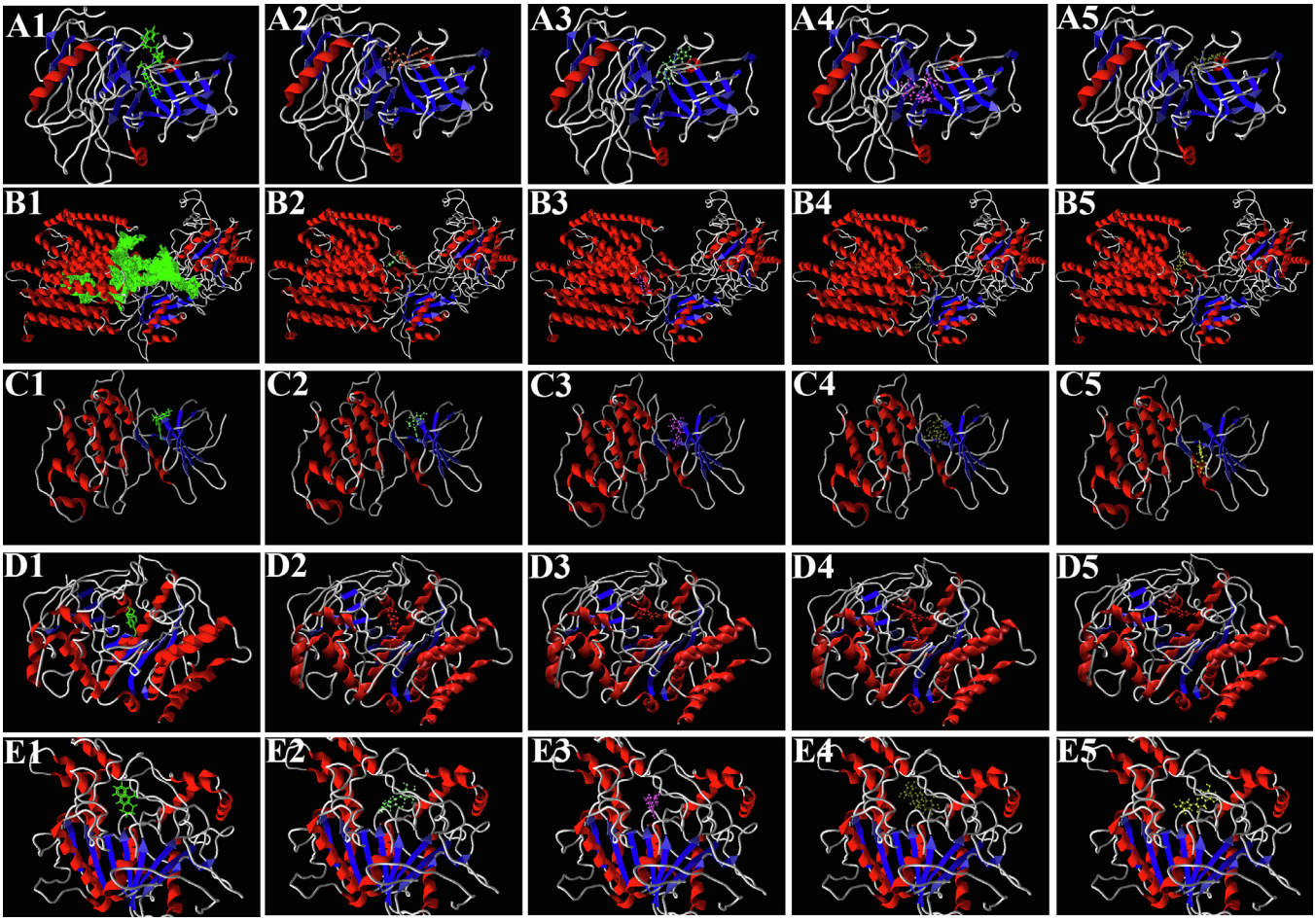

Fig. 2. Docking poses of different ligands with their respective receptors. (A) β- secretase, (B) γ-secretase, (C) GSK-3β, (D) AChE and (E) BuChE. A1, C1, D1 and E1 represent the docking poses of the bound or co-crystallized ligands at the active site of the receptors. The docking poses of the tea polyphenols EGC (A2, B2, C2, D2, E2), EPC (A3, B3, C3, D3, E3), EGCG (A4, B4, C4, D4, E4) and CAT (A5, B5, C5, D5, E5) are shown. For γ-Secretase (B), the docking was performed at the largest available cavity of the receptor (cavity shown in green in B1). The poses were generated following docking using MVD.

the ligands were found to be quite comparable, which shows that the inhibition of the receptor is largely brought about by the hydrogen bonding interactions (Table 3).

Against γ-secretase, EGCG shows highest MolDoc score (−128.822), with hydrogen bond score of −14.4365, while EPC shows highest hydrogen bond score (−17.828). Although, the MolDoc score of the known inhibitor (−79.525) is although comparable to EGC (−83.671) and EPC (−75.590), it has quite lesser hydrogen bonding score (−5.109). The hydrogen bond scores of EPC and EGCG were thus found to be 3.49-fold and 2.83-fold higher respectively, compared to the known inhibitor (Table 3). The lesser hydrogen bond scores and MolDoc scores of the inhibitor may be attributed to lesser numbers of hydrogen bond donor and hydrogen bond acceptor groups present in it, compared to the polyphenols (Table 2). Thus, it reveals that the inhibition of the receptor by the polyphenols is largely due to more hydrogen bond interactions, compared to the known inhibitor Segamacestat.

In case of GSK-3β, EGCG shows highest MolDoc score (−114.384) with hydrogen bond score of −11.110, both of which are higher among all the ligands studied, including the known inhibitor AR-A014418. While hydrogen bond score of the known inhibitor was found to be −4.857, the same is 2.29-fold higher in case of EGCG. EGC (−6.697) and EPC (−5.516) have hydrogen bond scores comparable to the known inhibitor (−4.856) (Table 3). The higher scores for the EGCG may be attributed to the more numbers of hydrogen bond acceptor and hydrogen bond donor groups in the polyphenol (Table 2).

Against AChE, although EGCG shows highest MolDoc score (−176.664), the hydrogen bond score is quite lesser (−0.986), which suggests that the MolDoc score is largely due to weaker interactions. On the other hand, EPC shows highest hydrogen bond score (−19.606), which is 2.61-fold higher than the known inhibitor Galantamine (−7.510). The other polyphenols also show good hydrogen bonding scores, viz. −18.826 and −17.790 for EGC and CAT respectively (Table 3). Considering the hydrogen bond scores, CAT, EPC and EGC are better inhibitors of the enzyme, compared to EGCG as well as the known inhibitor.

At the active site of BuChE, EGCG was found to have the highest MolDoc score (−150.744), with hydrogen bond score of −22.608. However, CAT shows highest hydrogen bond score (−24.775) among all ligands. The hydrogen bond scores of EGCG and CAT were found to be 9.04-fold and 9.91-fold higher than the known inhibitor Tacrine (Table 3). Thus, inhibition of BuChE by the polyphenols was found to be largely affected by hydrogen bond interactions, and may be attributed to the fact that Tacrine has only 3 groups which can form hydrogen bonds (Table 2).

Taken together, the present findings indicate that all the tea polyphenols have significant inhibitory potentials at the active sites of γ-secretase, β-secretase, GSK-3β, AChE and BuChE. Further, EGCG was found to have the best docking scores, which may be attributed to the fact that EGCG, and also the other polyphenols, have more phenolic groups which may form hydrogen bonds with active site amino acid residues of the receptors. Inhibition of these receptors by the

Table 3
Table showing docking scores (MolDock score and hydrogen bond score) of different ligands with the respective receptors. Elenbecestat, Segamacestat, AR-A014418, Galantamine and Tacrine are the known inhibitors of the respective receptor, and have been used as reference ligands for binding sites of the receptors as well as comparison of docking scores. The scores were determined using MVD software, following docking of the ligands at the active site of the receptors.

Sl. No.	Receptor	Ligands	MolDock Score	H-bond score
1	β-Secretase	Elenbecestat	−146.205	−17.721
		EGC	−91.720	−16.618
		EPC	−99.986	−17.818
		EGCG	−141.686	−14.664
		CAT	−108.556	−22.858
2	γ-Secretase	Segamacestat	−79.525	−5.109
		EGC	−83.671	−11.337
		EPC	−75.590	−17.828
		EGCG	−128.822	−14.436
		CAT	−104.630	−13.088
3	GSK-3β	AR-A014418	−103.617	−4.856
		EGC	−79.114	−6.697
		EPC	−87.606	−5.516
		EGCG	−114.384	−11.110
		CAT	−90.040	−10.434
4	AChE	Galantamine	−125.778	−7.510
		EGC	−128.042	−18.826
		EPC	−123.617	−19.606
		EGCG	−176.664	−0.986
		CAT	−132.426	−17.790
5	BuChE	Tacrine	−82.874	−2.500
		EGC	−121.804	−22.770
		EPC	−104.442	−10.209
		EGCG	−150.744	−22.608
		CAT	−124.505	−24.775

polyphenols may inhibit the progression of the AD pathophysiologies, as well as ameliorate the symptoms by elevating the levels of ACh. Further, the polyphenols have been reported to confer neuroprotection through metal chelation, anti-oxidant and anti-inflammatory properties [38], which are among pathophysiologies underlying the progressiveness of AD. Thus, the tea polyphenols may provide significant neuroprotection in AD through different pathways (Fig. 3).

Conclusion

The present study was based on the hypothesis that tea polyphenols, viz. CAT, EPC, EGC and EGCG, may potentially interact with the active sites of key drug targets of AD. Molecular docking was employed as a tool to validate the hypothesis. The polyphenols have been found to potentially inhibit the enzymes AChE, BuChE, β-secretase, γ-secretase and GSK-3β. Thus, it is speculated that this inhibition will bring about elevation in the level of ACh in the brain and thereby ameliorate the behavioural abnormalities associated with AD (Fig. 3). Further, inhibition of GSK-3β, β-secretase and γ-secretase will ameliorate the deposition of Aβ plaques and neurofibrillary tangles of hyperphosphorylated tau proteins, thereby serving as disease modifying therapy (Fig. 3). Thus, these tea polyphenols may emerge as alternatives to the currently used drugs for the treatment of AD. Nevertheless, further *in vivo* and *in vitro* studies are warranted to establish the efficacy of the tea polyphenols in the treatment of AD.

Conflict of interest

None declared.

Source of funding

None.

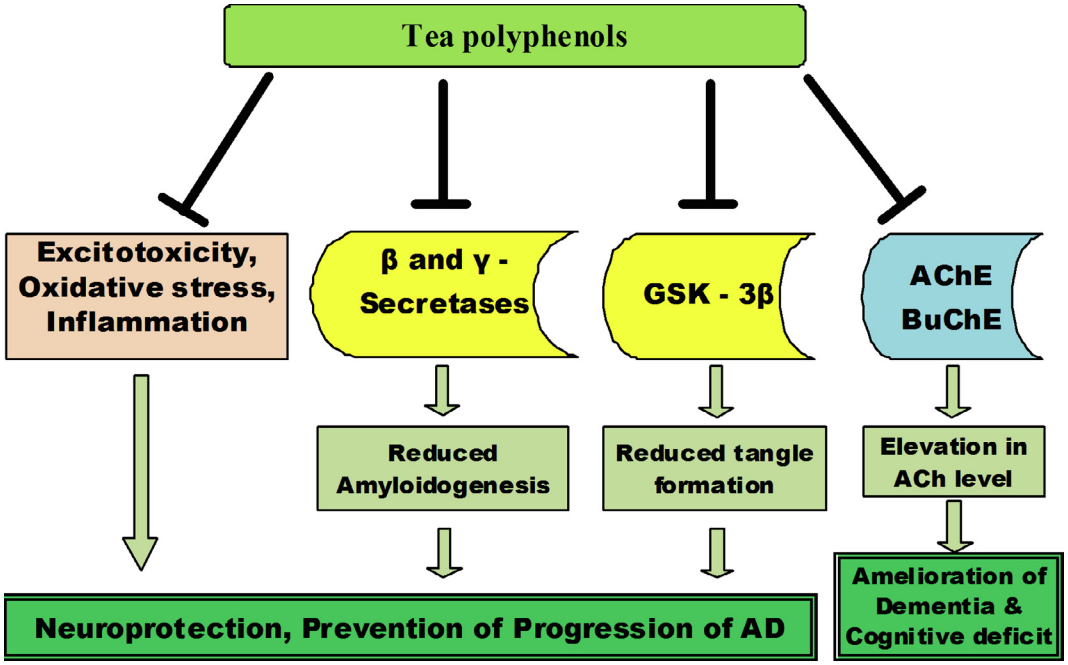

Fig. 3. The mechanism of neuroprotection by tea polyphenols in AD. While tea polyphenols have been reported extensively to possess antioxidant, anti-inflammatory and anti-excitotoxicity role, the present findings indicate their potential as inhibitors of β-Secretase, γ-Secretase, GSK-3β, AChE and BuChE. While inhibition of secretases prevent formation of Amyloid plaques, inhibition of GSK-3β prevent formation of neurofibrillary tangles. These processes may halt progression of AD. Further, through inhibition of AChE and BuChE, the polyphenols may elevate the levels of ACh at the synaptic cleft, and thereby ameliorate dementia and cognitive decline in AD.

Author contribution

The work is the outcome of equal contribution of all the authors.

References

[1] Avrahami L, Farfara D, Shaham-Kol M, Vassar R, Frenkel D, Eldar-Finkelman H. Inhibition of glycogen synthase kinase-3 ameliorates-amyloid pathology and restores lysosomal acidification and mammalian target of rapamycin activity in the Alzheimer disease mouse model. J Biol Chem 2013;288(2):1295–306.

[2] Bai XC, Rajendra E, Yang G, Shi Y, Scheres SH. Sampling the conformational space of the catalytic subunit of human γ-secretase. Elife 2015;4:e11182https://doi.org/10.7554/eLife. 11182.

[3] Bhat R, Xue Y, Berg S, Hellberg S, Ormo M, Nilsson Y, et al. Structural insights and biological effects of glycogen synthase kinase 3-specific inhibitor AR-A014418. J Biol Chem 2003;278:45937–45.

[4] Bohnen NI, Kaufer DI, Hendrickson R, Ivanco LS, Lopresti B, Davis JG, et al. Cognitive correlates of alterations in acetylcholinesterase in Alzheimer's disease. Neurosci Lett 2005;380:127–32.

[5] Braak H, Del Tredici K. Alzheimer's pathogenesis: is there neuron-to-neuron propagation? Acta Neuropathol 2011;121(5):589–95.

[6] Butterfield D, Castegna A, Pocernich C, Drake J, Scapagnini G, Calabrese V. Nutritional approaches to combat oxidative stress in Alzheimer's disease. J Nutr Biochem 2002;13:444–61.

[7] Cheung J, Rudolph MJ, Burshteyn F, Cassidy MS, Gary EN, Love J, et al. Structures of human acetylcholinesterase in complex with pharmacologically important ligands. J Med Chem 2012;55:10282–6.

[8] Gandhi S, Abramov AY. Mechanism of oxidative stress in neurodegeneration. Oxid Med Cell Longevity 2012;2012:428010.

[9] Ghosh AK, Hong L, Tang J. β-Secretase as a therapeutic target for inhibitor drugs. Curr Med Chem 2002;9:1135–44.

[10] Greig NH, Lahiri DK, Sambamurti K. Butyrylcholinesterase: an important new target in Alzheimer's disease therapy. Int Psychogeriatr 2002;14(1):77–91.

[11] Hardy J. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. J Neurochem 2009;110(4):1129–34.

[12] Higdon JV, Frei B. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. Crit Rev Food Sci Nutr 2003;43:89–143.

[13] Hong L, Koelsch G, Lin X, Wu S, Terzyan S, Ghosh AK, et al. Structure of the protease domain of memapsin 2 (beta-secretase) complexed with inhibitor. Science 2000;290:150–3.

[14] Kolaj I, Liyanage SI, Weaver DF. Phenylpropanoids and Alzheimer's disease: a potential therapeutic platform. Neurochem Int 2018;120:99–111.

[15] Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006;443:787–95.

[16] Mazumder MK, Bhattacharjee N, Borah A. Garcinol prevents hyperhomocysteinemia and enhances bioavailability of L-DOPA by inhibiting catechol-o-methyltransferase: an in silico approach. Med Chem Res 2015;25(1):116–22.

[17] Mazumder MK, Bhattacharya P, Borah A. Inhibition of matrix metalloproteinase-2 and 9 by Piroxicam confer neuroprotection in cerebral ischemia: an in silico evaluation of the hypothesis. Med Hypotheses 2014;83:697–701.

[18] Mazumder MK, Borah A. Piroxicam confer neuroprotection in Cerebral Ischemia by inhibiting cyclooxygenases, acid-sensing ion channel-1a and aquaporin-4: an in silico elucidation of a novel mechanism. Bioinformation 2015;11(4):217–22.

[19] Mazumder MK, Borah A. Piroxicam inhibits NMDA receptor-mediated excitotoxicity through allosteric inhibition of the GluN2B subunit: an in silico study elucidating a novel mechanism of action of the drug. Med Hypotheses 2014;83:740–6.

[20] Mazumder MK, Paul R, Borah A. β-phenethylamine – a phenylalanine derivate in brain – contributes to oxidative stress by inhibiting mitochondrial complexes and DT-diaphorase: an in silico study. CNS Neurosci Ther 2013;19(8):596–602.

[21] Mazumder MK, Paul R, Phukan BC, Dutta A, Chakrabarty J, Bhattacharya P, et al. Garcinol, an effective monoamine oxidase-B inhibitor for the treatment of Parkinson's disease. Med Hypotheses 2018;117:54–8.

[22] Mazumder MK, Phukan BC, Bhattacharjee A, Borah A. Disturbed purine nucleotide metabolism in chronic kidney disease is a risk factor for cognitive impairment. Med Hypotheses 2018;111:36–9.

[23] Nachon F, Carletti E, Ronco C, Trovaslet M, Nicolet Y, Jean L, et al. Crystal structures of human cholinesterases in complex with huprine W and tacrine: elements of specificity for anti-Alzheimer's drugs targeting acetyl- and butyrylcholinesterase. Biochem J 2013;453:393.

[24] Parameshwaran K, Dhanasekaran M, Suppiramaniam V. Amyloid beta peptides and glutamatergic synaptic dysregulation. Exp Neurol 2008;210:7–13.

[25] Perry E, Walker M, Grace J, Perry R. Acetylcholine in mind: a neurotransmitter correlate of consciousness? Trends Neurosci 1999;22:273–80.

[26] Perry EK, Perry RH, Blessed G, Tomlinson BE. Changes in brain cholinesterase in senile dementia of Alzheimer's type. Neuropathol Appl Neurobiol 1978;4:273–7.

[27] Prince MWA, Guerchet M, Ali G, Wu Y, Prina M. The global impact of Dementia: An analysis of prevalence, Incidence, Costs and trends. Alzheimer's Disease Int. https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf.

[28] Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, et al. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science 2007;316:750–4.

[29] Sanabria-Castro A, Alvarado-Echeverría I, Monge-Bonilla C. Molecular pathogenesis of Alzheimer's disease: an update. Ann Neurosci 2017;24:46–54.

[30] Santacruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, et al. Tau suppression in a neurodegenerative mouse model improves memory function. Science 2005;309:476–81.

[31] Savelieff MG, Lee S, Liu Y, Lim MH. Untangling amyloid-β, tau, and metals in Alzheimer's disease. ACS Chem Biol 2013;8:856–65.

[32] Scheltens P, Blennow K, Breteler MMB, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet 2016;388(10043):505–17.

[33] Thomsen R, Christensen MH. MolDock: a new technique for high-accuracy molecular docking. J Med Chem 2006;49:3315–21.

[34] Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. The importance of neuritic plaques and tangles to the development and evolution of AD. Neurology 2004;62:1984–9.

[35] Tuppo EE, Arias HR. The role of inflammation in Alzheimer's disease. Int J Biochem Cell Biol 2005;37(2):289–305.

[36] van der Kant R, Goldstein LS. Cellular functions of the amyloid precursor protein from development to dementia. Dev Cell 2015;32:502–15.

[37] Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, et al. β-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 1999;286:735–41.

[38] Weinreb O, Mandel S, Amit T, Youdim MBH. Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's disease. J Nutr Biochem 2004;15:506–16.

[39] Wenk GL. Neuropathologic changes in Alzheimer's disease. J Clin Psychiatry 2003;64:7–10.

[40] Wischik CM, Harrington CR, Storey J. Tau-aggregation inhibitor therapy for Alzheimer's disease. Biomed Pharmacol 2014;88:529–39.

[41] Association Alzheimer's. Alzheimer's disease facts and figures. Alzheimers Dement 2014;10(2014):e47–92.

[42] Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry 1999;66:137–47.

[43] Ono K, Yoshiike Y, Takashima A, Hasegawa K, Naiki H, Yamada M. Potent anti-amyloidogenic and fibril-destabilizing effects of polyphenols in vitro: implications for the prevention and therapeutics of Alzheimer's disease. J Neurochem 2003;87:172–81.