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The Neuroprotective Effect of SENYDEM®: A New Therapeutic Approach for the Management of Cognitive Impairment in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative pathology characterized by the formation in the brain of β-amyloid-containing plaques and tau-containing neurofibrillary tangles (NFT). Today, the pharmacological treatments of AD are very limited and novel therapeutic strategies are required. The administration of natural based-products could prevent or alleviate the AD symptoms minimizing side effects. In vivo and ex vivo analysis were carried out on AD mouse model to evaluate the neuroprotective effect of an oral nutraceutical patented technology named SENYDEM®. Results on mnemonic tests and inflammation pathway demonstrated that SENYDEM® formulation could exert beneficial effects on neuro-degeneration and neuro-inflammation of cognitive system representing a promising nutraceutical composition to be used as potential adjuvant in the prevention and treatment of AD.

Keywords: Neuro-Inflammation; Senydem®; Alzheimer's Disease; Cognitive System

Abbreviations: AD: Alzheimer's Disease; NMDA: N-Methyl-D-Aspartate; CNS: Central Nervous System; PEA: Palmitoylethanolamide; ELISA: Enzyme-Linked Immunosorbent Assays

Introduction

Alzheimer's disease (AD) is a neurodegenerative pathology characterized by the formation in the brain of β-amyloid-containing plaques and tau-containing neurofibrillary tangles (NFT) responsible of amnestic or non-amnestic cognitive impairment [1]. Of all dementia cases, AD represents about 70% with an incidence increasing with age and doubling every five years. In particular, for people of age comprises between 65-69, 70-74, 75-79, 80-84, and 85 and older the incidence estimated is 0.6%, 1.0%, 2.0%, 3.3% and 8.4% respectively. Overall, the disease affects 25 million people all around the world [2]. The main risk factors, apart from age, include family history of dementia, head trauma, genetic alterations, being female, low education level, vascular disease and environmental factors. The β-amyloid-containing plaques are found in widespread distribution throughout the cerebral cortex and represent the earliest lesions in AD. They are composed by Aβ peptides which derive from APP (a single trans-membrane protein that is enriched in neuronal synapses) cleavage by β- secretases and γ-secretases [3]. These peptides are able to aggregate with high propensity in a concentration-dependent manner. Aβ aggregation is thought to be responsible of neurotoxicity. Furthermore, NTF are located mostly in large pyramidal neurons of Ammon's horn and cerebral neocortex. The main component of these cerebral lesions is the protein tau, a microtubule- associated protein, normally present in the cytoplasm of axons. Its main function is microtubule stabilization [4]. Tau tends to form aggregates, following post-translational modifications, and accumulates in a hyperphosphorylated form that appears histologically as neurofibrillary tangles. Pharmacological treatment of AD is very limited and based on the use of only two different classes of therapeutic agents: cholinesterase inhibitors and N-Methyl-D-Aspartate (NMDA) receptor antagonists [5].

The efficacy of pharmacological treatment of AD can be supported by para-pharmaceuticals able to improve drugs effects minimizing side effects; as known, it is important to study nutraceutical or medical devices efficacy and safety before proposing them as adjuvant agents [6-8]. *Salvia miltiorrhiza* is a medicinal plant used for the management of memory and cognitive impairment. This perennial plant is widely distributed in China and Japan, well known in the folk medicine. *In vitro* and *in vivo* studies, have demonstrated that the root extract of *S. miltiorrhiza* has several neuroprotective effects, especially for preventing or delaying the AD [9]. D-aspartate is found in high concentrations in human embryonic brain and its amount decreases during the post-natal phase. This amino acid is located on endocrine and central nervous system (CNS), as result of racemization process of L-aspartate [10]. In patients with AD, it has been reported very low levels of D-aspartate. For this reason, it is relevant restoring its neuronal concentration to preserve the cognitive functions. N-palmitoylethanolamide (PEA) is a non-endocannabinoid which represents a therapeutic molecule for treatment of AD. PEA is a lipid mediator biologically synthetized in different plant and mammal cells. From literature, it has been reported the ability of PEA to protect CNS from neuro-inflammation and neuro-degeneration [11]. The aim of this study was to evaluate the effect of a patented technology named SENYDEM® based on a specific formulation of *S. miltiorrhiza*, D-aspartate and PEA through *in vivo* and *ex-vivo* AD mouse model studying both behavioural aspects and effects on neuro-inflammation.

Materials and Methods

Reagents

The raw materials were supplied by Neilos S.r.l. In particular way, it was used *Salvia miltiorrhiza* 10% (*Salvia miltiorrhiza*; Arda Natura Srl, Piacenza, Italy), D-aspartic acid (D-aspartate; Barentz Service S.p.A., Milan, Italy) and PEA (Palmitoylethanolamide; Frau Pharma, Monza-Brianza, Italy). $A\beta_{1-42}$ peptide was purchased from Tocris (Milan, Italy). The mouse cytokine Array Kits were purchased from R&D System (Milan, Italy). All laboratory disposables were purchased from BioCell (Italy).

Animals

CD-1 male mice (10-14 weeks of age, 20-25 of weight) were purchased from Charles River (Milan, Italy) and kept in an animal care facility under controlled temperature, humidity, and light/dark cycle with food and water *ad libitum*. All animal procedures were performed according to the Declaration of Helsinki (European Union guidelines on the use of animals in scientific experiments), and following ARRIVE guidelines [12-13]. Experimental study groups were randomized and blinded. All procedures were carried out to minimize the number of animals used (N = 5-7 per group) and their suffering.

In Vivo Animal Model and Drug Administration

Mice were randomly separated into 6 experimental groups, as reported in Table 1, balancing body weight variation across groups. For the *in vivo* non-genetic model, we used a well-established AD [14] method consisting of a direct intracerebroventricular (i.c.v.) injection of $A\beta_{1-42}$ fragment. Briefly, before the injection, $A\beta_{1-42}$ protein was dissolved in PBS (1 µg/µl) in tubes that were sealed and incubated for 1 day at 37 °C to allow peptide assembly state. Anesthetized mice (mixture of N_2O and O_2 70:30 w/v containing 2% isoflurane) were then injected with aggregated $A\beta_{1-42}$ (3 µg/3 µl) into cerebral ventricle at a rate of 1 µl/min, using a micro-syringe (10 µl, Hamilton) according to the procedure previously [14]. The needle was removed after 3 min using three intermediate steps with 1 min interested delay to minimize backflow. Control group received the surgery procedure and Aβ peptide vehicle injection. After surgery and Aβ administration, mice were placed on a thermal pad until they recovered from the anesthetic. All procedures were performed under strictly aseptic conditions. To evaluate the protection profile of SENYDEM® formulation and of *S. miltiorrhiza*, D-aspartate and PEA alone against $A\beta_{1-42}$ peptide-induced neuro-inflammation, an oral (p.o.) administration of these compounds and SENYDEM® with respect to control for 21 days was performed (experimental endpoint; Figure 1).

Table 1: Experimental groups and relative dosages.

Sample	Dosage
CTRL (Control Group-Vehicle)	-
Beta (Aβ1-42 peptide)	3 µg/3 µl (ICV)
Salvia	Equivalent to 200 mg in man
PEA	Equivalent to 400 mg in man
Aspartate	Equivalent to 2000 mg in man
SENDEM®	Combo of Salvia + PEA +Aspartate

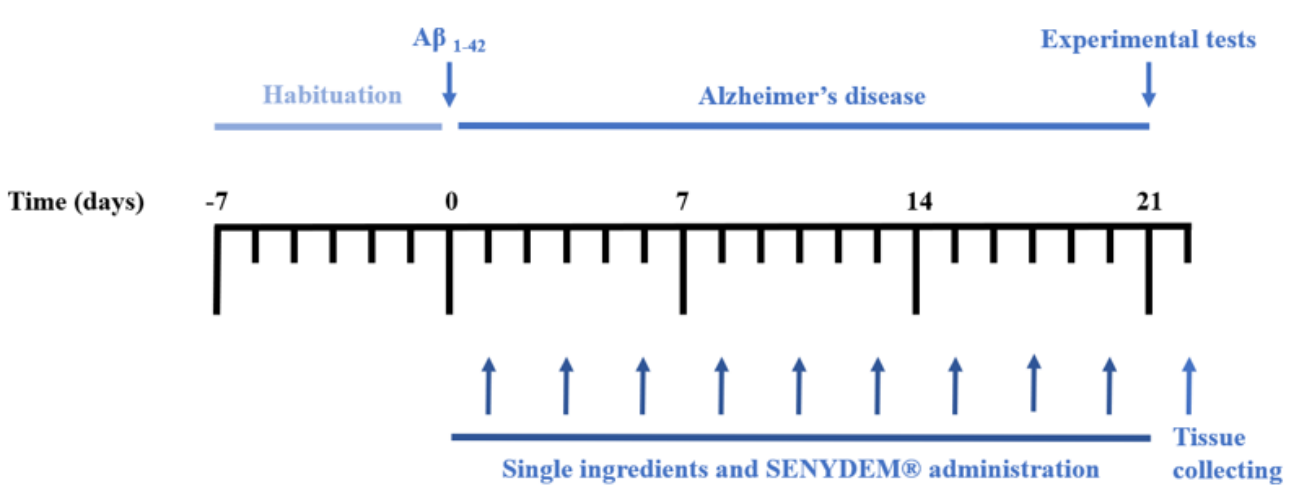

Figure 1: Schematic representation of experimental plan.

Behavioural Studies

21 days post $A\beta_{1-42}$ administration, mice were tested for novel object recognition (NOR) and Y-maze. All tests were performed between 9 a.m. and 2 p.m. in an experimental room with sound isolation. The animals were carried to the test room for, at least, 1 h for acclimation. Behaviour was monitored using a video camera positioned above the apparatus, and the videos analysed in a blinded fashion (two operators) using video tracking software (Any-maze, Stoelting, Wood Dale, IL, USA).

Novel Object Recognition (NOR)

The NOR task exploits a natural tendency of mice to explore a novel object after previous exposure to two identical ones. Mice were habituated for 10 min into the arena to reduce anxiety associated with the novel arena (plastic arena 30 x 30 x 50 cm). After his habituation stage, mice were ready to perform the task, which was conducted using a familiarization trial (T1) and a test trial (T2) with 30 minutes' pause. During T1, mice could explore for 10 min two identical objects (plastic screw-top tubes) secured to the floor using a small amount of Blu Tack in habituated arenas. For T2, one identical object from T1 was replaced with a novel one (small green flask), and mice could freely explore it for 5 min. T1 and T2 were recorded using a video camera and analysed for the time spent interacting with the novel object. All areas were cleaned with 80% ethanol before the test. Novel object exploration was calculated in T2 by (T novel x 100)/ (T novel + T identical) with exploration defined as the nose being less than 1 cm from the object when facing the object or actively engaging with the object by sniffing or paw touching. Climbing on the object was not considered exploratory.

Y-Maze Task

Spontaneous alternation is a measure of spatial working memory. Such short-term working memory was assessed by recording spontaneous alternation behaviour during a single session in the Y-maze (made with three arms, 40 cm long, 120° separate) positioned at the exact location for all procedures. Each mouse was placed at the end of one arm and allowed to move freely through the maze during a 5 min session. The series of arm entries were visually recorded. An arm choice was considered only when both forepaws and hind paws fully entered into the arm. The Y-maze was cleaned after each test with 80% ethanol to minimize odour cues. Alternation was defined as a successive entrance onto the three different arms. The number of correct entrance sequences (e.g., ABC and BCA) was defined as the number of actual alternations. The number of total possible alternations was, therefore, the total number of arm entries minus two, and the percentage of alternations was calculated as actual alternations/total alternations x 100 [15].

ELISA Assay

Enzyme-linked immunosorbent assays (ELISA) for $A\beta_{1-42}$ peptide, TNF-α, IL-1β e IL-6 were carried out on homogenized brains as previously described. Briefly, 100 µl of samples, diluted standards, quality controls and dilution buffer (blank) were added to a pre-coated plate with monoclonal anti-$A\beta_{1-42}$, TNF-α, IL-1β e IL-6 for 2 h. After washing, 100 µl of biotin labelled antibody was added for 1 h. The plate was washed and 100 µl of the streptavidin-HRP conjugate was added and plate was incubated for further 30 min period in the dark. The addition of 100 µl of the substrate and stop solution represented the last steps before the reading of the absorbance (measured at 450 nm) on a microplate reader. Antigen levels in the samples were determined by

using a standard curve and expressed as pg/pouch [16-17]. Dot plots were detected by using the enhanced chemiluminescence detection kit and Image Quant 400 GE Healthcare software (GE Healthcare, Italy) and successively quantified using GS 800 imaging densitometer software (Bio-Rad, Italy).

Data and Statistical Analysis

The data and statistical analysis in this study comply with the international recommendations on experimental design and analysis in pharmacology [18] and data sharing and presentation in preclinical pharmacology [19-20]. The results obtained were expressed as the mean ± SEM. Statistical analysis were performed by using one-way, or two-way ANOVA followed by Dunnett's or Bonferroni's for multiple comparisons. GraphPad Prism 8.0 software (San Diego, CA, USA) was used for analysis. Differences between means were considered statistically significant when $P \leq 0.05$ was achieved. Sample size was chosen to ensure alpha 0.05 and power 0.8. Animal weight was used for randomization and group allocation to reduce unwanted sources of variations by data normalization. No animals and related *ex vivo* samples were excluded from the analysis. *In vivo* and *in vitro* studies were carried out to generate groups of equal size (N = 5-7 of independent values), using randomization and blinded analysis.

Results

Improvement of the Vision Memory in Mice

After 3 weeks of treatment, it has been evaluated the tendency of mice to explore the different objects located on the arena, during the testing session. To describe the results, the object from the training session was defined as "obj A" while the new object added in the arena during the testing session it was defined as "obj B". For the control group (CTRL) it was reported that the interaction time with obj B was higher than obj A. As concerning the Beta group, the exploration time spent close to the obj B was similar to the obj A one, without any significant differences. About SENYDEM® formulation, its administration in mice implies an increased interaction time towards the obj B, thus obtaining the highest values in comparison with CTRL (**P < 0.01 vs obj A, Figure 2) and the single ingredients of the patented technology, as showed in Figure 2.

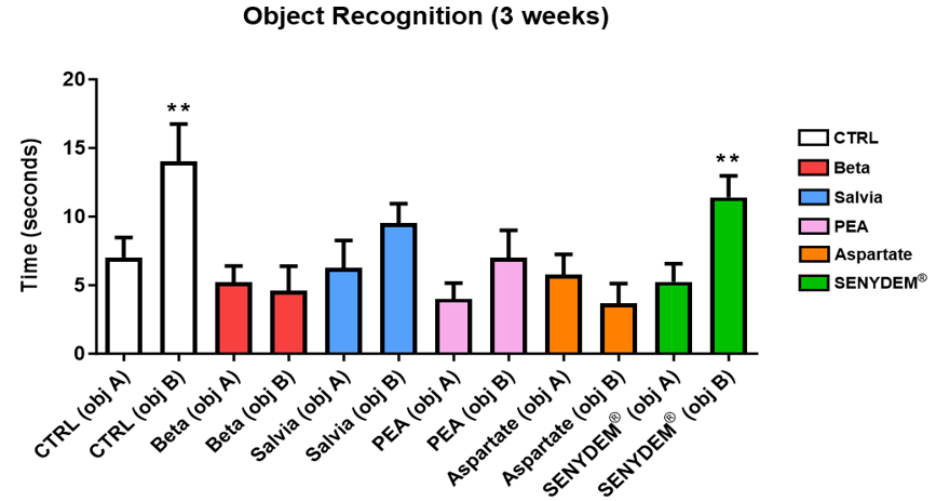

Figure 2: Neuroprotective effect of single ingredients and SENYDEM® formulation on object recognition test with obj A and obj B. Each ingredient and SENYDEM® formulation were orally administered in AD mice (**P<0.01 vs obj A of CTRL group). CTRL: Control group; Beta: Aβ1–42 peptide untreated group.

The Formula Increases the Spatial Memory of Mice

The results of Y-maze test were collected at the end of the treatment and expressed as percentage (%) of correct alternations. Low percentage of alternations can be considered as a marker of hippocampus damage [15]. In the Figure 3A, the administration of SENYDEM® formulation determined the best score of % correct alternations, related to the Beta group (*P < 0.05 vs Beta group, Figure 3A). Furthermore, the motor activity of mice was analysed after treatment with SENYDEM® formulation. No groups have reported alterations of mice motility, showing similar values of CTRL one, as indicated in Figure 3B.

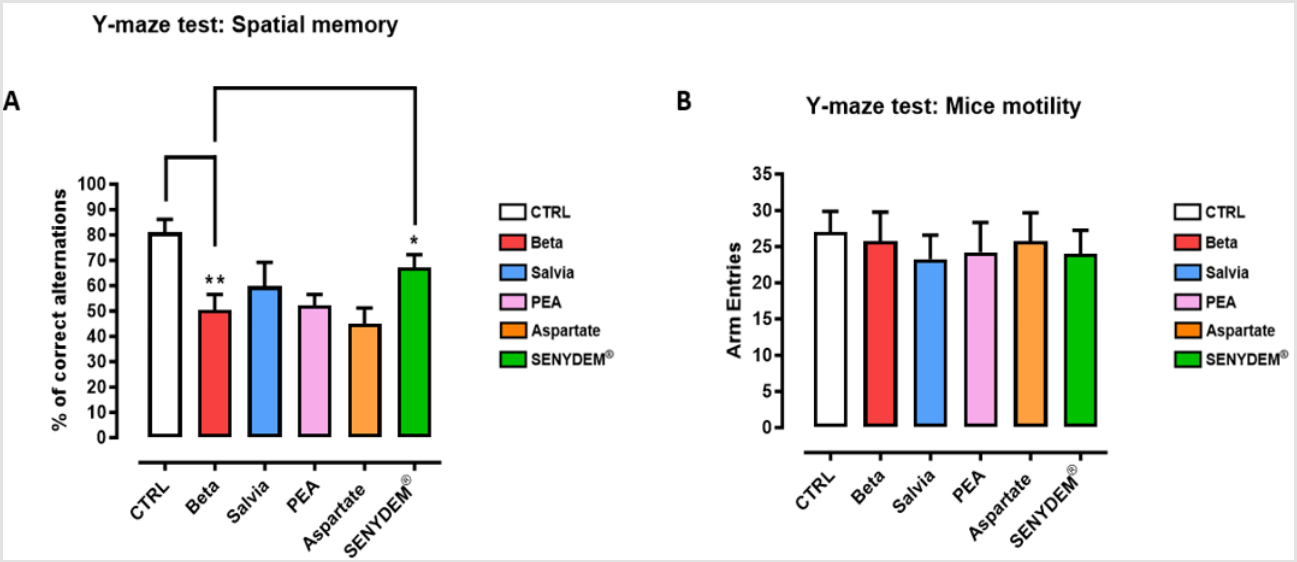

Figure 3: Neurodegeneration effect of single ingredients and SENYDEM® formulation on Aβ1-42-induced spontaneous alternation deficits in mice.
A. and for total number of arm entries in Y-maze test
B. Spatial memory and mice motility were determined after oral administration of single ingredients and SENYDEM® formulation (*P<0.05 vs Beta; **P < 0.01 vs CTRL). CTRL: Control group; Beta: Aβ1–42 peptide untreated group.

Changes in Neuro-Inflammation State after Administration of Formula

The ELISA assay contributed to determine the levels of different interleukins such as IL-1β, TNF-α and IL-6 in brain homogenates, expressed as ng per mouse (ng/mouse) in Figure 4. As expected, the CTRL group was characterized by the lowest levels of all interleukins analysed. Instead, the results of Beta group demonstrated that the formation of amyloid plaques in brain developed a marked inflammatory process. Indeed, the values of all tested cytokines of this group were the highest ones. After treatment with SENYDEM® formulation, the intracellular concentrations of IL-1β (Figure 4A; **P< 0.01 vs Beta group), TNF-α (Figure 4B; *P < 0.05 vs Beta group) and IL-6 (Figure 4c) were reduced by 64%, 35% and 50% respectively.

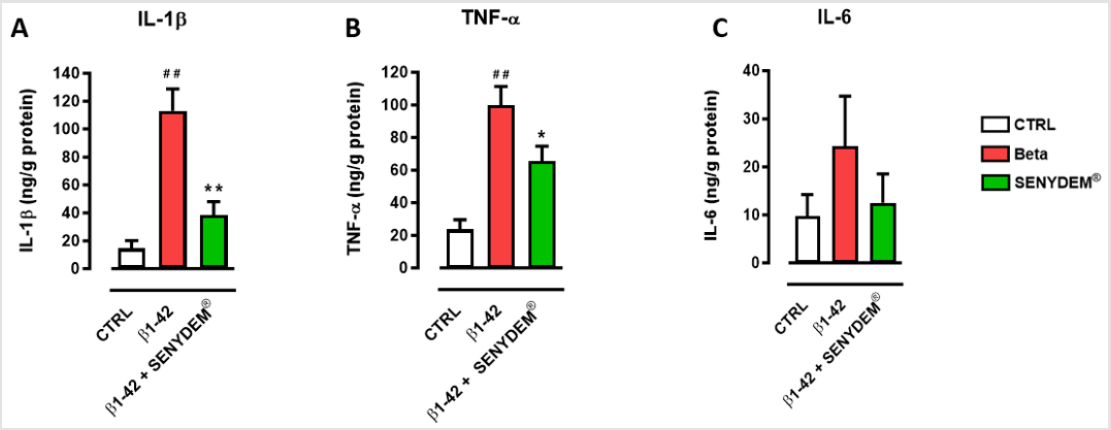

Figure 4: ELISA assay for the determination of IL-1β.
A. TNF-α
B. and IL-6
C. Levels expressed as ng/g protein (##P < 0.01 vs CTRL; *P < 0.05, **P < 0.01 vs β1–42) after the administration of SENYDEM® formulation. CTRL: Control group; β1–42: Aβ1–42 peptide untreated group.

Discussion

Alzheimer's disease is the most common neurodegenerative impairment that affects cognitive functions, thus becoming a relevant issue for human health. AD is characterized by neuronal tissue degeneration with onset of neuro-inflammation, which is attributed to accumulation of β-amyloid-containing plaques and tau-containing neurofibrillary tangles in brain. So far, the causes of AD are poorly known and the scientific research is focused on possible agents which can induce the cognitive decline. In this study, the patented technology named SENYDEM® based on a specific formulation of *S. miltiorrhiza*, D-aspartate and PEA has been examined in order to analyse its potential neuroprotective effect on cognitive system using *in vivo* and ex-vivo AD mouse model. After administration of SENYDEM® formulation, an improvement of vision and spatial memory was detected during the mnemonic tests, as reported in Figures 2 & 3. These findings could be associated to the reduction of Aβ-plaques and the inhibition of acetylcholinesterase activity, thanks to the specific composition of SENYDEM® formulation [21-22]. Furthermore, SENYDEM® formulation could probably counteract the astrogliosis, which is responsible for neuronal destruction and down-regulation of transcriptional factors, such as NF-kB and AP-1, able to stimulate Aβ-peptides synthesis [23]. The ingredients of this patented technology opportunely formulated in SENYDEM® could be also responsible of changes in synaptic plasticity [24]. It is hypothesized that SENYDEM® formulation could ameliorate the neurotransmitters flux by synthesis of novel branched synapses involved in memory, learning management and recognition processes. From experimental data, it should be noted that the single compounds and SENYDEM® formulation did not affect mice motility during the analysis carried out in the Y-maze. Based on these results, SENYDEM® formulation could be considered as safe for mice health. In addition, as reported in Figure 4, SENYDEM® formulation exerted an interesting effect on neuro- inflammation, reducing the intracellular concentrations of cytokines such as IL-1β, TNF- α and IL-6. SENYDEM® formulation could activate the peroxisome proliferator-activated α receptors (PPAR-α receptors) and so determine the decrease of inflammatory cytokines expression [25-26].

Conclusion

Experimental results demonstrated that the patented technology named SENYDEM® based on a specific formulation of *S. miltiorrhiza*, D-aspartate and PEA determines positive effects on behaviour and neuro-inflammation in an AD mouse model. Specifically, the oral administration of SENYDEM® formulation affects positively the vision and spatial memory of AD mice, maybe reducing the production of Aβ plaques and inhibiting the acetylcholinesterase activity. Furthermore, SENYDEM® formulation exerts an important anti-inflammatory activity on some cytokines involved in neuro-inflammation. These preliminary *in vivo* and *ex vivo* results of SENYDEM® formulation administrated in mice represent a starting point for further studies, aiming to better investigate the mechanism of action and clinical effect in neuro-degenerative disease, such as AD.

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