Clinical evidence: 300 milligrams of *B. monniera* powder taken once, which contains 55% of the total amount of bacosides A and B didn't significantly alter cognitive function at 2 hours in a double blind, placebo controlled trial involving 38 healthy volunteers (ages 18–60). However, a randomised, placebo controlled, a double blind trial found that the giving healthy adults aged 40 to 65 the herb *Bacopa* for six weeks (For people under 90 kilograms, the dosage is 300 milligrams, and for those over 90 kg, it is 450 milligrams, which is comparable to six grams and 9 grams of dried out roots, accordingly) significantly improved their ability to remember new information. Despite the fact that there was no variation in the rate of information collection. With the placebo controlled, a double blind trial involving 46 participants in good health (aged 18 to 60), Stough et al., found that taking Bacopa (which contains 55% total bacosides) at an amount of 300 milligrams each day for 12 weeks. Significantly improved verbal learning, memory consolidation, and the speed of early information processing. The gradual beginning of action could linked to *Bacopa's* antioxidant capabilities either is impact on systems acetylcholine because the effects were not noticed until five weeks into treatment. Additional 54 senior people, randomly allocated, double blind in placebo controlled trial (mean age 73.5 years) who did not exhibit any clinical symptoms of dementia found that a *Bacopa* treatment similar to this one improved a comparison with the untreated group on a stroop test, an extended words memory test, and an auditory language acquisition testing. Standardized herbal extract of *Bacopa* with the dose 125 mili gram was administered twice each day for a period of 12 weeks in a double blind, placebo controlled study to subjects older than 55 who had memory impairment. Logic memory, mental control, and paired related learning were significantly improved. *Bacopa* extract, given daily for 12 weeks at a dose of 300 mg/kg, also improved memory acquisition and retention in the population of healthy older Australians. When given daily for a period of three months, every day to youngsters (age 6 to 8), 350 mg of *Bacopa* powder, *Bacopa* syrup produced a substantial improvement compared to the placebo. However there was no blinding in this study. An attention deficit disorder with hyperactivity diagnosis was present in 36 kids, Negi et al., conducted a double blind, randomized, placebo controlled experiment (age range 8.3 to 9.3 years). 19 kids was given 50 mg of herb extract of *Bacopa* twice daily for 12 weeks. The extract was standardized to contain 20% bacosides. Children receiving *Bacopa* showed a significant improvement in cognitive function compared to placebo at 12 weeks, which was supported by improvements in tasks requiring repetition of sentences, logical memory, and learning with paired associates. This improvement persisted the 16^{th} week (after 4 weeks of placebo administration).

Curcuma longa

Description of the plant: The herb turmeric (*C. longa*) is perennial from Zingiberaceae family. Southeast and South Asia are where it is cultivated for commercial use. Turmeric, also known as curcumin, is a common food flavoring and coloring ingredient in India. It is produced from the plant's rhizome. The Ayurveda medical system has been using various plant based treatments for ages.

The primary chemical components of turmeric are curcuminoids, which are mostly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin. Curlone, zingiberene, alpha- and beta-tumerone, artumerone, alpha- and gamma atlantone, and curcumol are additional chemical substances found in this plant.

Curcuminoids have a wide range of pharmacological effects, including analgesic, anti-inflammatory, anti-cancer, hypocholesterolemic, antithrombotic, anti-hepatotoxic, anti-diarrheal, carminative, diuretic, anti-rheumatic, hypotensive, larvicidal, insecticidal, antivenomous, and anti-tyrosinase effects, according to previous studies.

Pre-clinical studies: It is also among the plants that have been thoroughly examined for a variety of disorders in preclinical scenarios 133. In numerous experimental studies, it has been claimed to have a wide range antioxidant, anti-inflammatory, and cholesterol lowering properties all of which are significant pathophysiological processes in the development of AD among other biological and pharmaceutical effects.

Curcumin's inability to dissolve in water is a significant drawback, but it has been partially solved by the creation of curcumin nanoparticles coated with biodegradable Poly (Lactic-co-Glycolic Acid, or PLGA). These nanoparticles were reported to have antioxidative activity and the ability to inhibit amyloid aggregation without having any harmful effects. Curcumin Nano liposomes have been discovered to suppress the synthesis of oligomeric fibrils an *in vitro* due

to their strong affinity for A1-42 fibrils.

Curcumin containing poly (butyl) cyanoacrylate nanoparticles delivered by apolipoprotein E3 (ApoE3-C-PBCA) offered photo stability, improved cellular absorption, and increased curcumin's effectiveness prevent the cytotoxicity caused by Aβ. Additionally, turmeric demonstrated that it protects over Aβ neurodegeneration by accelerating the transformation of Aβ into fibrils and lowering the production of Aβ by reducing the expression of Presenilin 1 (PS1) and GSK- 3β.

Aβ plaque can form in both *in vivo* and *in vitro* conditions have been demonstrated to be reduced by curcumin. In cerebral cortex of the transgenic APPSw mouse (Tg2576), curcumin administration within a six month period dramatically reduced increased amount of oxidized amino acids and inflammatory interleukin-1141. Curcumin was also found to reduce plaque development and levels of both soluble and insoluble Aβ in the same study. In the sporadic AD model in mice, Turmeric (10, 20 and 50 mg/kg, p.o. for a period of 21 days) pretreated reduced memory deterioration. Moreover, curcumin supplementation enhanced synaptophysin loss, oxidative stress, and spatial memory by lowering Aβ deposits. Significant cognitive improvement was observed at low (160 ppm) and high (1000 ppm) doses of curcumin after administration for six months in the twin transgenic AD mouse (APP/PS1). Curcumin may defend against beta amyloid assault and consequent Cell death brought on by the effects of oxidative stress *in vivo*. At low doses, curcumin can prevent Aβ from aggregating or encourage it to do so (IC50=0.81-1) sence of curcumin, monomeric Aβ generated fewer aggregates, whereas increasing doses of curcumin encouraged disassembly of preformed A aggregates. Curcumin shares structural similarities with Congo red, which, when bound to plaques, can prevent the development of oligomers and reveal secondary structure in fibrillar and oligomeric Aβ. A low dose of curcumin lowered the levels of soluble c, insoluble amyloid, and plaque burden by around 40%. In the APPswe/PS1dE9 mouse model of AD, curcumin therapy for 7 days reduced the load of plaques and restored structural alterations in dystrophic dendrites.

AD is linked to insulin or the Insulin like Growth Factor-1 (IGF-1) signaling dysfunction. It causes mitochondrial malfunction, oxidative stress, necrosis, hyperphosphorylation of the tau protein, and cognitive impairment. In the sporadic Alzheimer model using Intracerebroventricular (ICV)-Streptozotocin (STZ), curcumin markedly increased cognitive performance *via* raising the IGF-1 level. Moreover, it reduced plaque load and oxidative damage, decreased levels of insoluble amyloid, glial fibrillary acidic protein, and IL-1. A second research examination showed that turmeric treatment enhanced memory and cognitive function in the STZ model of Alzheimer by reducing oxidative damage, enhancing ChAT activity, and restoring insulin receptor protein.

Curcumin considerably boosted microgliosis immediately close to plaques while dramatically decreasing microgliosis in neuronal layers, supporting the notion that it may drive microglial phagocytosis of amyloid. Alpha-1-Antichymotrypsin (1ACT) suppression and NF-B mediated transcription of apolipoprotein E are two additional potential pathways for Curcumin's neuroprotective benefits (ApoE). In APP transgenic mice, 1ACT and ApoE have both been demonstrated to be proamyloidogenic. In addition, oxidative stress and elevated cholesterol levels, two additional proamyloidogenic variables, can be decreased by curcumin. The protective impact of the turmeric blend and each of its parts on 163 and apoptosis gene expression in Dementia was investigated using an Aβ plus ibotenic acid-infused rat model. According to Ahmed and colleagues, treatment of a curcuminoids in mixture (bisdemethoxycurcumin, demethoxycurcumin, and curcumin) enhanced retention of information in rat models of AD created by amyloid fragments. Nevertheless, curcumin therapy given repeatedly also protected mice from cognitive damage brought on by colchicine by lowering oxidative stress.

Due to a rise in serum corticosterone levels, chronic stress causes aberrant neuroendocrine and plasticity processes that impair spatial cognition. By restoring normal corticosterone response, curcumin reduces levels glutamate receptor, calcium/calmodulin kinase II, and (NMDA-2B), which has neuroprotective effect. According to Wang et al. and Yin et al., therapy Turmeric 300 mg per kilogram improved spatial retention and learning deficits along with hippocampus regeneration in an Aβ1–40 AD model. There is evidence that the AD brain has high levels of metals, and turmeric chelates copper and iron attached to beta amyloid (but not zinc), which may help reduce amyloid. McClure et al., used a different strategy, treating young 5XFAD mice with curcumin through aerosol in a manner that

prevented Aβ accumulation compared to untreated mice, mature animals have cognitive and memory issues. Such multi target substances are potentially effective treatment of Alzheimer's and the resulting cognitive deterioration. There are, however, little clinical studies on the effectiveness of curcumin in treating AD despite extensive study on the drug's effects on a number of disorders.

Clitoria ternatea

Tropical annual climbing herb *Clitoria ternatea* (*C. ternatea*) has a thin, downy consistency branch that can be grown in gardens and in the wild across tropical India. It has white or blue blooms. *C. ternatea* is a member of the Fabaceae, also known as the "butterfly" family. It is an Ayurvedic drug that is frequently utilized. In Indian traditional medicine, *C. ternatea* is known by the names Aparajit (Hindi), Aparajita (Bengali), and Kakkattan. Ayurveda has employed *C. ternatea* extracts as a component of "Medhya-rasayana."

The principal chemical substances are: Numerous phytochemicals are isolated from *C. ternatea*, including taraxerol, teraxerone, ternatins, delphinidin-3, delphinidin-3ß-glucoside, malvidin-3ß-glucoside, 3-monoglucoside, 3-rutinoside, 3-neohisperidoside, 3-o-rhamnosyl Glycoside, kaempferol-3-o-rhamnosyl 172.

Medicinal techniques: Earlier investigations have shown that *C. ternatea* has a wide range of biological properties, including nootropic, anticonvulsant, antidepressant, antianxiety, antistress, antioxidant, anti-inflammatory, antihyperlipidemic, antidiabetic, antiasthmatic, analgesic, immunomodulatory, cytotoxicity, platelet aggregation inhibitory, antimicrobial, gastroprotective, and hepatoprotective properties.

Pre-clinical studies: The nootropic effect of methanol derived extracts of apical parts of *C. ternatea* (100 mg/kg, p.o.) has been noted, using elevated plus maze and the object recognition test using rats. Taranalli and Cheeramkuzhy studied the effects of ethanolic extracts of the roots and apical parts of *C. ternatea* at doses of 300 and 500 mg/kg, per oral. on dementia induced by submaximal electroshock. Also, they calculated the Ach levels throughout the entire brain and various regions of it. Better memory retention and more Ach were found in the brain when the aerial parts extract was given as compared to 500 milligrams per kilogram, and 300 mg/kg.

Comparable yet greater pronounced impacts that are practically comparable at both doses were seen in the root extract. In rats going through a growth spurt, Rai, et al., demonstrated how the *C. ternatea* root extract improved learning and memory. Neonatal rats who were 7 days old were intubated for 30 days, they gave them doses of 50 and 100 mg/kg of *C. ternatea's* aqueous root extract. The extract enhanced spatial performance in the T-maze test and retention in the passive avoidance task. A 30 day post-treatment evaluation revealed that the behavioral modifications were long lasting. In a previous study, it was also demonstrated that the aqueous root extract (50 and 100 mg/kg, p.o. for 30 days) improved the neuronal dendritic arbor in the rat amygdala. The presence of growth factors like nerve growth factor or brain derived neurotrophic factor was speculated to be the cause of this effect on cognition. One of the causes of the nootropic action of *C. ternatea* root may be an increase in hippocampal acetylcholine content. Additionally, Rai reported that 3 promoting consequence on the *C. ternatea* root extrac showed up in the anterior subventricular zone of brain stem cells. In a previous study, it was also demonstrated that the aqueous root extract (50 and 100 mg/kg, p.o. for 30 days) enhanced dendritic arborization of rat amygdala neurons. Its effect on cognition was thought to be caused by the presence of growth factors such as brain derived neurotrophic factor or nerve growth factor. One of the potential causes of the nootropic effects of *C. ternatea* root is a rise in the choline level of the cerebral cortex. In addition, Rai noted that 3 encouraging sequel on the *C. ternatea* extract of root was found in the brain stem cells' anterior subventricular zone. Recently, Damodaran et al., reported the brain protective properties of the *C. ternatea* roots extract in correcting continuous brain function hypoperfusion induced neuronal injury and loss of memory at doses of 200 and 300 mg/kg. In a different investigation, Mehla and associates showed that *C. ternatea* has anti-AD effects in ICV-STZ. Rats were subjected to circumstances resembling AD. These results suggest that C. *ternatea* extract's positive benefits are brought about through slowing the progression of AD's mental loss. However, a thorough assessment of *C. ternatea* extract has potential for human use is still required.

The *Withania somnifera* plant (*W. somnifera*) is a small, woody shrub from the Solanaceae family that is widely cultivated in India. It goes by the name's Indian ginseng, winter cherry, and ashwagandha. Approximately one centimeter long, greenish or yellowish, are its flowers. Old Indian Sanskrit writings refer to ashwagandha as a "Medhya rasayana." It is frequently used in Ayurveda and goes by the name Indian ginseng. It is a component of numerous formulations recommended as a general tonic to boost energy, enhance all around health, and lengthen life.

The main phytoconstituents of (*W. somnifera*) are its main chemical ingredients. Examples of somnifera include isopellertierine, anferine, withanolides, withaferins, sitoindosides VII and VIII, and withanoloides. Other substances include withanine, somniferine, 3-a-gloyloxytropane, choline, cuscohygrine, withanine, pseudo-withanine, tropine, and pseudo-tropine.

Pharmacological actions: Wide ranging biological effects of *W. somnifera* include anti-inflammatory, antioxidant, neuroprotective, anti-ischemic, anti-parkinson's, antiepileptic, anxiolytic, antidepressant, antiarthritic, cardioprotective, antidiabetic, anticancer, antistress, nephroprotective, hepatoprotective, antihypoxic, immunomodulatory, hypolipidemic, and antimicrobial effects.

Pre-clinical investigations: The effects of *W. somnifera's* root whole an alkaloid derivative (ashwagandholine, AG) on the central nervous system have been researched. By acting as an antioxidant, W. somnifera reduced the lack of remembering resulting from STZ. By halting stress induced degeneration in the rat brain's hippocampus, the preparation of root systems has been demonstrated to be capable of preventing neurological conditions. The extract of a herb comprising sitoindosides VII-X and withaferin A was given to rats with ibotenic acid induced dementia and a decline in acetylcholine indications (such as Ach and ChAT) for a period of two weeks. Differentially, but favourably, Withaferin and stoindosides VII–X (40 milligram per kilogram for a period of seven days) changed Several regions of the brain exhibit increased M1 and M2 muscarinic receptor binding and the AchE activity. In BV-2 microglial cells, withaferin A and withanolide A may has a strong impact immune system modulation by activating the Nrf2 pathway, which results in the synthesis of neuroprotective proteins such heme oxygenase-1.

Withanoside IV, an alternative chemical constituent for withania, lessened dementia of the brain in an animal model of Alzheimer when administered orally at a level of 10 micromol/kg. Axonal and dendritic regeneration as well as synaptic rebuilding were stimulated Amyloid peptide A (25–35) damaged rat neurons in the cortex was cultivated, and with Withanoside IV metabolite sominone (1 microM). Using sominone as the active ingredient, withanoside IV might function being a prodrug. Semitone's ability to improve spatial memory might linked to A RET transmitter for Neurotrophic Factor (NF) is a mediator of neuritic expansion. Human neuroblastoma cells' ability to generate *in-vitro* dendrites was improved by methanolic root extract. According to a study of Jayaprakasam et al., withanamides found in *W. somnifera* fruit shield pheochromocytoma (PC-12) against toxicity caused by β-amyloid. The same study found that the two withanamide molecules contain a serotonin molecule inhibited the production of β -amyloid fibrils.

Through increasing the protein linked to a low density lipoprotein receptor, *Withania* root extract treatment 1 g/kg, orally for 30 days changed the pathogenesis of Alzheimer and lifted the cognitive deficit in APP/PS1 mice that were elderly and old. Withanone, an ingredient in the Ethanol *Withania* herb extract, proved neuroprotective against alterations in the brain caused by scopalmine. Aβ peptide has also been shown to have an inhibitory effect on fibril production *in vitro*. The effects of withania on cognition and memory may be partially explained by the ability of cortical muscarinic cholinergic receptors was raised. Anxiolytic, depressive, anti-inflammatory, and antioxidant properties of the rhizome herbal extract and its chemicals, like glycowithanolides, may be important in the treatment of AD. Moreover, withanone, a chemical component found in *W. somnifera* root extract, improved cognitive abilities by preventing the processing of amyloid and lowering increased proinflammatory cytokine concentrations and signs of oxidative damage. *W. somnifera* (20 mg/mL) was used for treating D. melanogaster, an Alzheimer model, which decreased the toxic effects of Aβ and improved lifespan.

Clinical evidence: Using ashwagandha an extract of roots during treatment (300 mg twice daily for eight weeks).

Improved executive function, focus, and data processing speed in people with mild cognitive impairment, as well as improved short and long term memory, according to a hypothetical, randomized, double blinded placebo controlled research. Ng and his colleagues reported herbal extract from *W. somnifera* improved executive functions and reduced cognitive impairment of people possessing a slight mental disorder in a systematic study. There is not much information available about using *Withania* for cognitive impairment in therapeutic settings.

Celastrus paniculatus

Botanical description: *Celastrus paniculatus* (*C. paniculatus*) is a large climbing plant in the Euonymaceae family. It grows throughout India, on the slopes of the Sub-Himalayas, in the foothills in Punjab and south part of India. The term "Jyothismati" is derived from the Sanskrit phrases "Jyoti Teja" (spirit fire) and "Mati" (fire). (intelligence). The tree's bark and nuts have historically been employed as an energy booster and expectorant, as a cerebral tonic, to heighten cognition and enhance digestion. His *C. paniculatus* has been utilised in Ayurveda for the treatment of a wide range of illnesses, including anxiety, the leprosy, paralysis in humans, high temperatures, and gout. Because of their calming, relaxing, and wound-healing qualities, fruits and seed derived oils are frequently employed.

Chemical constituents: Sequiterpenoid polyalcohols including ester compounds, among other plant elements, are present in *C. paniculatus*. (markanniol, marcangunin, polyalcohol AD and serapnin). Paniculatin and celastrin is alkaline compounds. Celastrol and paniculatadiol are phenol triterpenoids. Oleic, linoleic, linolenic, palmitic, stearic and lignoceric acids.

Pharmacological activity: pharmacology of *C. paniculatus* including hypolipidemic, neuroprotective, antifertility, Analgesic, anti-bacterial, anti-inflammatory, antibacterial, anti-malarial, with wound healing and antifungal activities Activity has been reported.

Preclinical studies: Several research models of dementia, including sodium nitrite induced amnesia with scopolamine, have been tested on *Celastrus* seed extract and oil. Rats cognitive abilities were examined after being exposed to *C. paniculatus* seed extracts in methanolic, chloroform solution, petroleum based ether, and water. The aqueous extract significantly enhanced cognitive function when administered orally for 14 days at doses of 200 and 300 mg/kg. Methanolic extract was found to improve memory in rats when administered at dosages of 100, 200, and 400 mg/kg in another study. *C. paniculatus's* antioxidant activity may have a role in boosting cognitive function. The ability to learn and recall information in the radial arm maze were enhanced when Wistar rodents were fed 400 milligrams per kilogram of *C. paniculatus* oil from seeds every day for 14 days, and the production of the AchE enzyme in the brain regions of the hypothalamus, frontal lobe, and hippocampal was decreased. With a dose of 400 mg/kg for 3 days, Karanth et al., similarly showed that *C. paniculatus* had a comparable impact. Rats were given 850 mg/kg of *C. paniculatus* oiled to eat for a period of fifteen days in a different trial, and the rats memory in two passive avoidance tasks significantly increased. The morris water maze spatial memory impairment caused by scopolamine was reversed and enhanced locomotor activity Rats action on AchE was unaffected by the use of seed oil therapy for 14 days at doses of 50, 200, and 400 milligrams per kilogram, orally. The watery extract of seeds enhanced memory capacity in the raised plus maze and in sodium nitrite induced dementia *via* reducing AchE activity. Furthermore, scopolamine induced amnesia in rats was improved by *C. paniculatus* seed oil therapy. Clinical investigations for the safety and effectiveness of *C. paniculatus* have not been conducted.

Evolvulus alsinoides

Evolvulus alsinoides L., often known as the dwarf morning glory and a member of the Convolvulaceae family, possesses a small, branched, wooden root and is an annual plant. A weed called *E. alsionoides* is primarily present in swampy areas of worldwide tropical and subtropical areas. Possess several, beyond 30 centimeters long, hairy branches. Flower is blue in color, while the leaves are tiny, sharp, and elliptic. It is widely used in Ayurveda and is known locally as Shankhpushpi. The bulk compounds from the Medhya Rasayana sold at India contain this as a primary component. It has historically been used to treat neurological conditions including epilepsy and to improve memory in youngsters and the elderly.

Chemical components: The primary chemical constituents are cholesterol, n-hexadecanoic acid, piperine, squalene, as well as ethyl oleate.

Pharmacological activities: *Evolvulus alsionoides* (*E. alsionoides*) has been shown to have *in-vitro* antioxidant, immunomodulatory, adaptogenic, anti-amnesic, with antiulcer actions.

Pre-clinical studies: In rats, Nahata et al., observed that its water based, ethanolic, and extractive portions improved learning and memory. Rats exposed to scopolamine induced dementia were likewise protected by 100 milligrams per kilogram of the ethanol based extract, orally. *E. alsionoides* (100 mg/kg) oral therapy for three days was successful in reducing the deficit caused by scopolamine in adult male Swiss mice. The preliminary treatment with hydro-alcoholic extracts at dosages of 100, 300, and 500 milligrams per kilogram, p.o. decreased oxidative stress and rho kinase (ROCK II) activity in the rat brain's activity, which improved memory deficit brought on with ICV-STZ. Aqueous and hydroalcoholic extracts of *E. alsinoides* demonstrated anti-inflammatory, free radical scavenging, and enzyme inhibitory activity *in vitro*. These enzymes include cholinesterase, catechol-o-methyl transferase, prolyl endopeptidase, glycogen synthase kinase-3-, Rho kinases (ROCKI I), along with monoglycerol protease. In the experimental paradigm of amnesia, other investigations have shown that *E. alsionoides* improves memory. The acetylcholinesterase activity of the *E. alsinoides* methanol and water extract supports the plant's potential to reverse neuronal dysfunctions and hence aid in the treatment of AD.

CONCLUSION

In this paper we learn more detail about the pathophysiology and disease progression of AD and an insight into the potential therapeutic targets. Despite of the bulk of knowledge regarding this complex disease, only a fistful options are available for its management. Currently available drugs (AChEIs and memantine) for the treatment unfortunately target symptoms only and not the cause of the disease. So, the hope is now raised for the novel therapies that act at the root of the disease process.

REFERENCES

[1] Amor S, et al. *Immunology*. **2010**;129(2):154-169.
[2] Kumar Gp, et al. *Pharmacognosy Reviews*. **2012**;6(12):81.
[3] Scott A. *Neuron*. **2008**;60(4):534-542.
[4] Huang HC, et al. *J Alzheimers Dis.* **2009**;16(1):15-27.
[5] Ferri CP, et al. *Lancet*. **2005**;366:2112-2117.
[6] Fox NC, et al. *Lancet*. **2001**;358:201-205.
[7] Kaye JA, et al. *Neurology*. **1997**;48:1297-1304.
[8] Forstl H, et al. *Br J Psychiatry*. **1995**;167:737-746.
[9] Craig LA, et al. *Neurosci Biobehav Rev*. **2011**;35:1397-1409.
[10] Greig NH, et al. *Int Psychogeriatrics*. **2002**;14:77-91.
[11] Jing L, et al. *Drug Discov*. **2019**;24:629-635.
[12] Sussman JL, et al. *Science*. **1991**;253:872-879.
[13] Dinamarca MC, et al. *Mol Neurodegener*. **2010**;5.
[14] Ferrari GV, et al. *Biochemistry*. **2001**;40:10447-10457.
[15] Wang Y, et al. *Curr Neuropharmacol*. **2016**;14:364-375.
[16] Hartmann J, et al. *J Neurochem*. **2007**;100:1421-1429.
[17] Guillozet AL, et al. *Ann Neurol*. **1997**;42:909-918.
[18] Hardy JA, et al. *Science*. **1992**;256:184-185.
[19] Chu D, et al. *ACS Chem Neurosci*. **2019**;10:931-944.
[20] O'Brien RJ, et al. *Annu Rev Neurosci*. **2011**;34:185-204.