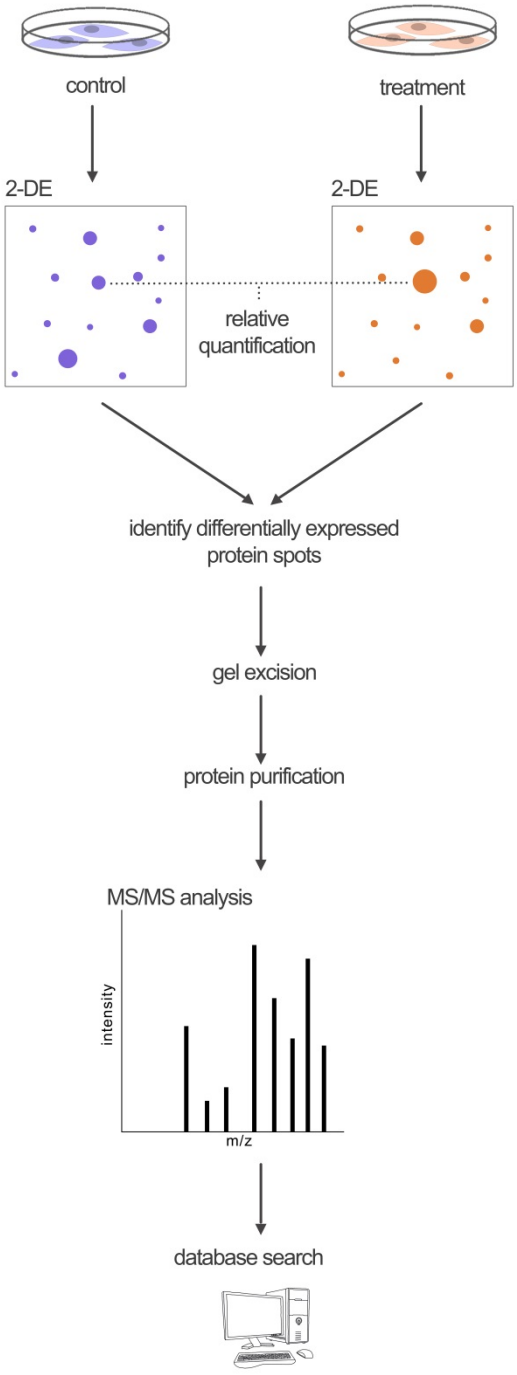
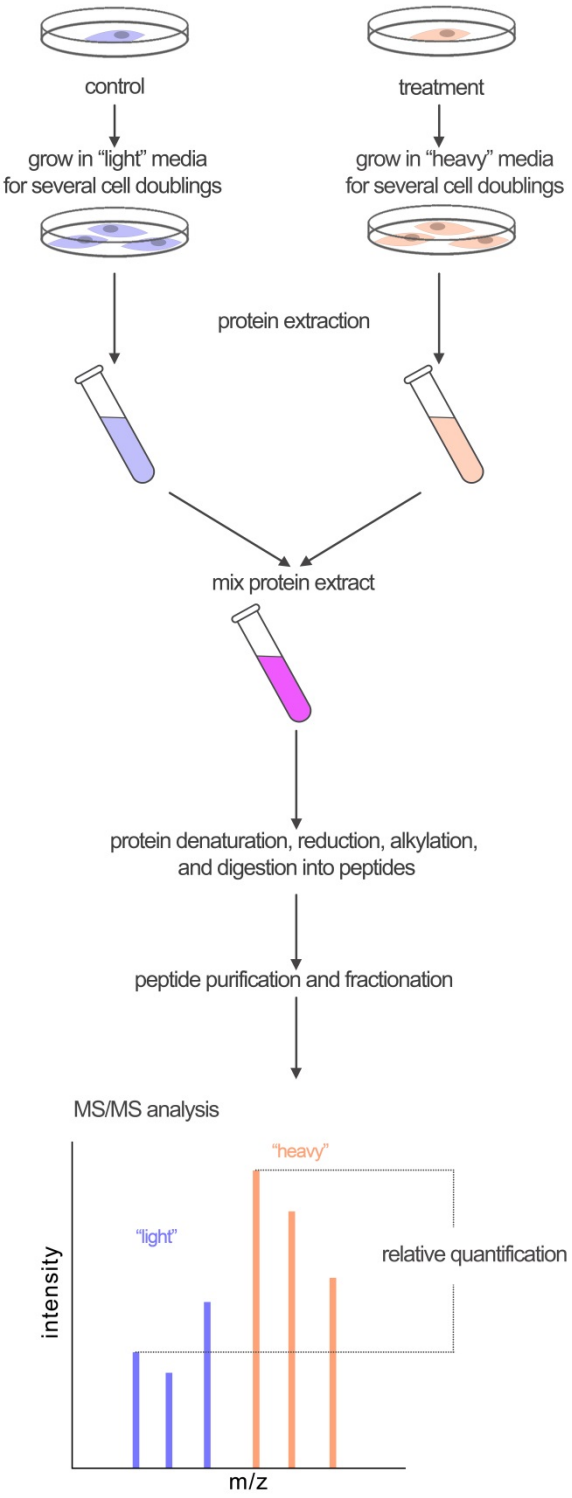
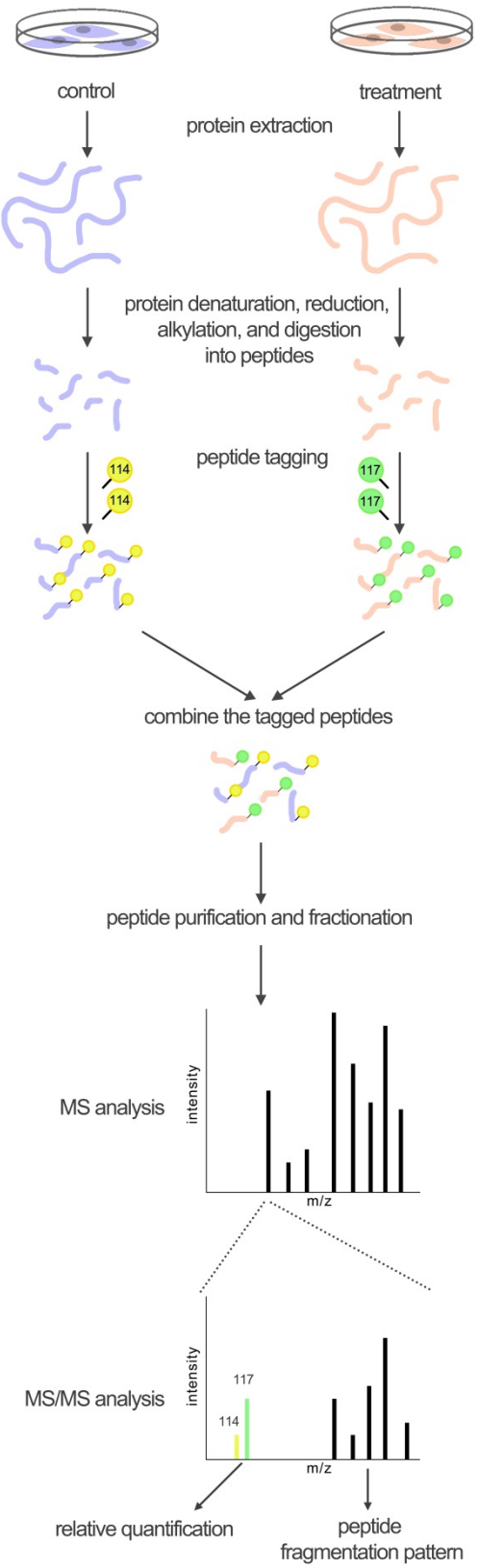


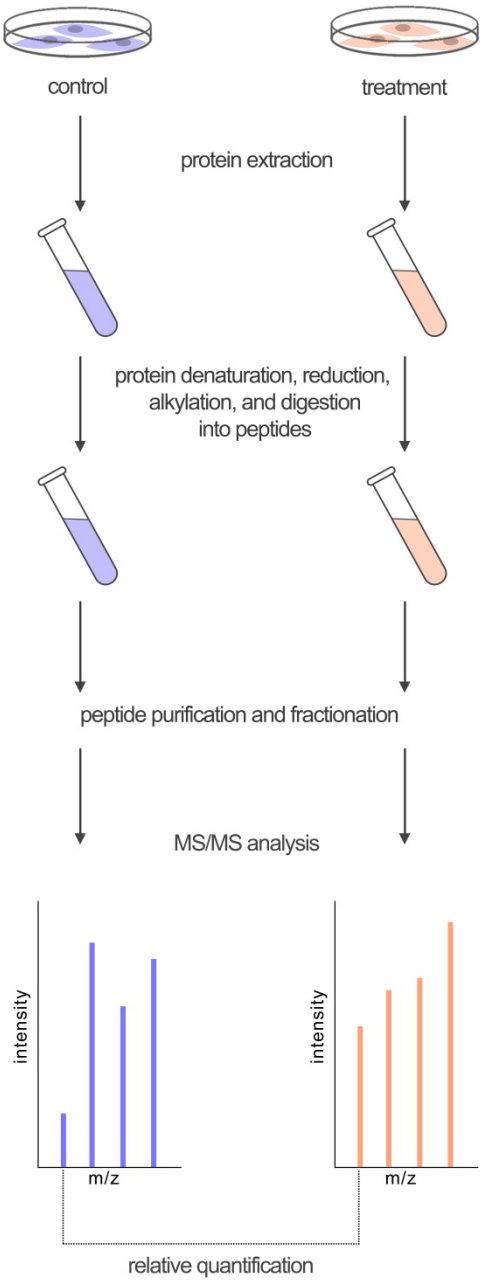

**Supplementary Figure S1.** Schematic diagram of 2DE proteomics. In this method, the proteins from treated cells and control proteins are extracted and separated using 2DE. The protein expression levels are compared by visualizing (e.g., by silver staining) and measuring the sizes of spots on the gel. The differentially expressed protein spots are then excised from the gel and purified (e.g., by HPLC) for MS/MS analysis.




**Supplementary Figure S2.** Schematic diagram of SILAC proteomics. Cells from treatment and control groups are grown in media containing "heavy" or "light" amino acids for several cell doublings (i.e., at least five doublings) to incorporate the amino acids into the cellular proteins. Subsequently, the proteins from both groups are extracted and combined for purification (e.g., by HPLC), and are then subjected to MS/MS analysis. The MS/MS spectra will produce peaks with higher m/z for the "heavy" labeled proteins, depending on the number and mass of the "heavy" amino acids. Comparison of the two groups is done by comparing the intensity of the peaks of the "light" and "heavy" pairs.




**Supplementary Figure S3.** Schematic diagram of iTRAQ or TMT proteomics. Cells from the treatment and control groups are extracted and digested into small peptides. These peptides then react with chemical labels (e.g., iTRAQ 114 and 117 tags for control and treatment groups, respectively). The tagged peptides are then combined and further purified (e.g., by HPLC) before undergoing MS/MS analysis. In the first MS spectrum, the peptides from both groups will produce a single peak. When the protein undergoes CID, however, the peptide will be fragmented, thereby releasing both the peptide and the balancer region from the tags. Ultimately, this process results in the production of peaks with discrete m/z measures according to the mass of the reporter region of the tag. Relative quantification of proteins is achieved by comparing the intensities of tags.




**Supplementary Figure S4.** Schematic diagram of label-free quantitative proteomics. In this method, protein extracts from the control and treatment groups are subjected to MS/MS analysis in parallel. The proteins from both groups are separately extracted, digested, purified (e.g., by HPLC), and analyzed using MS. Relative protein quantification is achieved by comparing the intensity of the identical peaks in respective samples.

**Table S1. AD-related studies using TCM or TCM-derived traditional medicines.**

| Title | Plant , TCM, or TCM-derived Material(s) | Testing Material(s) | Disease's model or assay | Effect of the TCM treatment | Ref |
|---|---|---|---|---|---|
| Neuroprotective effect of garlic compounds in amyloid-beta peptide-induced apoptosis in vitro | *Allium sativum* | Aged garlic extract and S-allylcysteine | PC12 cells; Aβ25– 35 | caspase-3 activation ↓, DNA fragmentation ↓, PARP cleavage ↓ | [1] |
| S-allyl-L-cysteine selectively protects cultured rat hippocampal neurons from amyloid beta-protein- and tunicamycin-induced neuronal death | *Allium sativum* | S-allylcysteine | Primary rat hippocampal and cerebral granule neurons treated with Aβ and tunicamycin | ROS↓, caspase-3 activation ↓ | [2] |

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| Effect of aged garlic extract on caspase-3 activity, in vitro | *Allium sativum* | Aged garlic extract | Caspase-3 *in vitro* assay | caspase-3 activity↓ | [3] |
| ESP-102, a standardized combined extract of Angelica gigas, Saururus chinensis and Schizandra chinensis, significantly improved scopolamine-induced memory impairment in mice | *Angelica gigas*, *Saururus chinensis*, and *Schizandra chinensis* in 8:1:1 ratio | ESP-102 (standarized extract) | Scopalamine treated mice, primary neuron treated with $A\beta_{25-35}$ and Glutamate | cognitive function↑, Aβ-induced toxicity↓ | [4] |
| Differentiating effects of anisodamine on cognitive amelioration and peripheral muscarinic side effects induced by pilocarpine in mice | *Anisodus tanguticus* | Anisodamine | Mice | cognitive function↑ | [5] |

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| Antioxidant activity of Bacopa monniera in rat frontal cortex, striatum and hippocampus | *Bacopa monniera* | *Bacopa monniera* standardized extract | Rat | SOD , catalase , GPX activities↑ | [6] |
| The green tea polyphenol (-)-epigallocatechin gallate attenuates beta-amyloid-induced neurotoxicity in cultured hippocampal neurons | *Camellia sinensis* (Green tea) | *Epigallocatechin gallate* (EGCG) | Primary neurons treated with Aβ | caspase-3 activation ↓, malondialdehyde↓ | [7] |
| Effects of green tea polyphenol on cognitive and acetylcholinesterase activities | *Camellia sinensis* (Green tea) | Green tea-derived polyphenol | Scopolamine treated mice | cognitive function↑, acetylcholinesterase activity↓ | [8] |
| Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats | *Centella asiatica* | *Centella asiatica extract* (asiaticoside) | Straptozotocin treated rats | cognitive function↑, malondialdehyde activity ↓, glutathione, catalase activity ↑ | [9] |
| Discovery of natural products from *Curcuma longa* that protect cells from beta-amyloid insult: a drug discovery effort against Alzheimer's disease | *Curcuma longa* | calebin-A, curcumin, demethoxycurcumin, bisdemethoxycurcumin, 1,7- | PC-12 cells treated with Aβ25– 35 or Aβ1–42 | Aβ-induced toxicity↓ | [10] |

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| | | bis(4-hydroxyphenyl)-1-heptene-3,5-dione | | | |
| Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro | *Curcuma longa* | Curcumin | Biochemical assay for Aβ1–40, Aβ1 – 42 | Aβ aggregation ↓ | [11] |
| Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo | *Curcuma longa* | Curcumin | Tg2576 mice | Aβ aggregation ↓ | [12] |
| A water extract of *Curcuma longa* L. (Zingiberaceae) rescues PC12 cell death caused by pyrogallol or ypoxia/reoxygenation and attenuates hydrogen peroxide induced injury in PC12 cells | *Curcuma longa* | Water extract | PC12 cells treated with Pyrogallol or H2O2 | antioxidant activities↑ | [13] |

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| The herbal medicine *Dipsacus asper Wall* extract reduces the cognitive deficits and overexpression of β-amyloid protein induced by aluminum exposure | *Dipsacus asper* | Crude extract | Aluminum chloride-induced AD rats | cognitive function↑, Aβ accumulation↓ | [14] |
| Inhibitory effect of zeatin, isolated from *Fiatoua villosa*, on acetylcholinesterase activity from PC12 cells | *Fiatoua villosa* | Zeatin | Biochemical assay | acetylcholinesterase activity↓ | [15] |
| Ginkgo biloba extract EGb 761 increases stress resistance and extends life span of Caenorhabditis elegans | *Ginkgo biloba* | EGb761 | *C. elegans* | increase life span, ROS↓, apoptosis↓ | [16] |

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| Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment | *Ginkgo biloba* | Commercial extract (similar to EGb761) | Tg2576 mice | cognitive function↑ | [17] |
| Amyloid precursor protein metabolism is regulated toward alpha-secretase pathway by Ginkgo biloba extracts | *Ginkgo biloba* | EGb761 | Rats | non-amyloidogenic APP processing↑ | [18] |
| Effects of EGb 761 Ginkgo biloba extract on mitochondrial function and oxidative stress | *Ginkgo biloba* | EGb761 | PC12 cells treated with Aβ | oxidative stress ↓, ROS↓, apoptosis↓ , Aβ-induced toxicity↓ | [19] |
| Antiapoptotic properties of Ginkgo biloba extract EGb 761 in differentiated PC12 cells | *Ginkgo biloba* | EGb761 | PC12 cells | caspase-3 activation ↓ | [20] |

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| The Ginkgo biloba extract Egb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands | *Ginkgo biloba* | EGb761 | PC12 cells treated with Aβ | Aβ aggregation ↓ | [21] |
| Reactive oxygen species-induced apoptosis in PC12 cells and protective effect of bilobalide | *Ginkgo biloba* | EGb761 | PC12 cells treated with ROS | p53 and caspase-3 activation ↓ | [22] |
| EGb 761 is a neuroprotective agent against beta-amyloid toxicity | *Ginkgo biloba* | EGb761 | Rats primary hippocampal neurons treated with Aβ | Oxidative stress ↓, ROS↓, apoptosis↓, Aβ-induced toxicity↓. | [23] |

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| The Ginkgo biloba extract (EGb 761) protects and rescues hippocampal cells against nitric oxide-induced toxicity: involvement of its flavonoid constituents and protein kinase C | *Ginkgo biloba* | EGb761 | Rat primary mixed hippocampal cell cultures | NO-induced toxicity↓, PKC activity ↓ | [24] |
| The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid | *Ginkgo biloba* | EGb761 | Rats primary hippocampal neurons treated wih Aβ | ROS↓, apoptosis↓ | [25] |
| Ginkgolide B inhibits the neurotoxicity of prions or amyloid-beta1-42 | *Ginkgo biloba* | Ginkgolide B | SH-SY5Y treated with Aβ or prion proteins sPrP106 | E2 prostalglandin production ↓, caspase-3 activation ↓, microglia activation ↓ | [26] |

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| Inhibition of amyloid-beta aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761 | *Ginkgo biloba* | EGb761 | N2a cells treated with Aβ | Aβ aggregation ↓, caspase-3 activation ↓ | [27] |
| Oxidative damage and protection by antioxidants in the frontal cortex of Alzheimer's disease is related to the apolipoprotein E genotype | *Ginkgo biloba* | EGb762 | brain tissues from AD patients | lipid oxidation for patients with APO ε3/ ε3 and ε3/ ε4 allele↓ no effect on patients with ε4/ ε4 allele | [28] |
| Structure-activity studies with Ginkgo biloba extract constituents as receptor-gated chloride channel blockers and modulators | *Ginkgo biloba* | EGb 761 | hippocampal and cerebellar neurons | blocks glycine-activated chloride channels | [29] |

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| Self-assembly of Abeta(1– 42) into<br>globular neurotoxins | *Ginkgo biloba* | Ginkgo bilobaextract | PC12 cells treated with Aβ | Aβ aggregation ↓ | [30] |
| Huperzine A enhances the level of<br>secretory amyloid precursor protein and protein kinase C-alpha in<br>intracerebroventricular beta-amyloid-(1– 40) infused rats and human<br>embryonic kidney 293 Swedish mutant cells | *Huperzia serrata* | Huperzine A | Sprague–Dawley rats; APPsw-expressing HEK293 cells | APP expression ↑, PKC activity ↑ | [31] |
| Acetylcholinesterase complexed with<br>bivalent ligands related to huperzine A: experimental evidence for<br>species-dependent protein-ligand complementarity | *Huperzia serrata* | Huperzine A | *In vitro* cholinesterase inhibition assay | acetylcholinesterase activity↓ | [32] |
| Huperzine A, a nootropic alkaloid, inhibits Nmethyl-d-aspartate-induced current in rat dissociated hippocampal neurons | *Huperzia serrata* | Huperzine A | Rats primary hippocampal neurons | NMDA-induced current ↓ | [33] |

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| Comparative effects of huperzine A, donepezil and rivastigmine on cortical acetylcholine level and acetylcholinesterase activity in rats | *Huperzia serrata* | Huperzine A | Rats | acetylcholinesterase activity↓ | [34] |
| Indirubins inhibit glycogen synthase kinase-3 beta and CDK5/p25, two protein kinases involved in abnormal tau phosphorylation in Alzheimer's disease. A property common to most cyclindependent kinase inhibitors | *Indigo naturalis* | Indirubins | Insect Sf9 cells and tau phosphorylation in vitro; slices from adult mouse brain striatum | Tau protein phosphorylation↓, various kinases activities↓ | [35] |
| Nicotine Enhances the Biosynthesis and Secretion of Transthyretin from the Choroid Plexus in Rats: Implications for β-Amyloid Formation | *Nicotiana tabaccum* | Nicotine | Rats | transthyretin (Aβ aggregation inhibitor) expression↑ | [36] |

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| Nicotine reduces Aβ in the brain and cerebral vessels of APPsw mice | *Nicotiana tabaccum* | Nicotine | APPsw-mutant mice | Aβ aggregation ↓ | [37] |
| Nicotine increases the expression of high affinity nerve growth factor receptors in both in vitro and in vivo | *Nicotiana tabaccum* | Nicotine | Rats | TrkA expression ↑ | [38] |
| Effect of combination of extracts of ginseng and *Ginkgo biloba* on acetylcholine in amyloid beta-protein-treated rats determined by an improved HPLC | *Panax ginseng* (Ginsenosides Rg1 and Re, 35%), *Ginkgo biloba* (Ginkgolides, 20%), and *Ginkgoflavones* (16%). | Naoweikang (Chinese traditional medicine) | Rats treated with Aβ | ACh level ↑ | [39] |
| $A\beta_{25\text{-}35}$-induced memory impairment, axonal atrophy, and synaptic loss are ameliorated by M1, A metabolite of protopanaxadiol-type saponins | *Panax vietnamensis* | 20-O-beta-D-glucopyranosyl-20(S)-protopanaxadiol and Ginsenoside Rb1 | $A\beta_{25–35}$-injected mice and primary rat cortical neurons | Spatial memory↑, Neurite extension↑ | [40] |

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| Effect of kami-untan-to on the impairment of learning and memory induced by thiamine-deficient feeding in mice | *Pinellia ternate Breit* (3.0 g of tuber), *Poria cocos* (3.0 g of fungus), *Citrus unshiu* (3.0 g of peel), *Phyllostachys nigra* (3.0 g of stalk), *Zizyphus jujuba* (2.0 g of seed), *Scrophularia ningpoensis* (2.0 g of root), *Polygala tenuifolia* (2.0 g of root), *Panax ginseng* (2.0 g of root), *Rehmanii glutinosa* (2.0 g of root), *Zizyphus jujuba* (2.0 g of fruit), *Citrus aurantium* (2.0 g of immature fruit), *Glycyrrhiza glabra* (2.0 g of root), and *Zingiber officinable* (0.5 g of rhizome). | Kami-untan-to (Traditional Chinese and Japanese medicine) | Male ddY mice; Thiamine-deficient (TD) feeding | Choline acetyltransferase expression ↑ | [41] |

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| Tenuigenin treatment decreases secretion of the Alzheimer's disease amyloid beta-protein in cultured cells | *Polygala tenuifolia* | Tenuigenin | Neuroblastoma cells | β-secretase activity↓ | [42] |
| Ptychopetalum olacoides, a traditional Amazonian ‘‘nerve tonic’’, possesses anticholinesterase activity | *Ptychopetalum olacoides* | *Ptychopetalum olacoides* ethanol extract | Frontal cortex, hippocampus, and striatal primary neurons of male Wistar rats (in vitro) and of male Swiss albino mice (ex vivo | acetylcholinesterase activity↓ | [43] |
| Effects of Yukmijihwangtang derivatives (YMJd), a memory enhancing herbal extract, on the gene-expression profile in the rat hippocampus | *Rehmannia radix* (19.83%), *Discoreae radix* (20.05%), *Corni fructus* (41.64%), *Hoelen* (1.11%), *Mountain cortex radicis* (21.45%), and *Alismatis radix* (20.92%). | Yukmijihwang-tang (Chinese herbal medicine) | Rats | transthyretin, PEP-19 expression↑, apoptosis↓ | [44] |

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| Rhizoma acori graminei and its active principles protect PC-12 cells from the toxic effect of amyloid-beta peptide | *Acori graminei* | Eugenol and h-asarone | PC12 cells; Aβ1 – 40 | Aβ-induced $Ca^{2+}$ uptake↓ | [45] |
| Protection against 1-methyl-4-phenylpyridinium ion (MPP+)-induced apoptosis by water extract of ginseng (*Panax ginseng* C.A. Meyer) in SH-SY5Y cells | *Panax ginseng* | Water extract of *Panax ginseng* | SH-SY5Y cells | ROS↓, apoptosis↓ | [46] |
| *Panax ginseng* enhances cognitive performance in Alzheimer disease | *Panax ginseng* | *Panax ginseng* powder | AD patients | cognitive function ↑ | [47] |

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| An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. | *Panax ginseng* | Korean red ginseng (KRG) | AD patients | cognitive function↑ | [48] |
| Long-term ginsenoside consumption prevents memory loss in aged SAMP8 mice by decreasing oxidative stress and upregulating the plasticity-related proteins in hippocampus | *Panax ginseng* | Crude ginsensodide | senescence-accelerated mouse | Aβ↓, anti-oxidant enzymes expression↑, neuronal plasticity-related proteins↑ | [49] |

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| The neuroprotective effects of ginsenosides on calcineurin activity and tau phosphorylation in SY5Y cells | *Panax ginseng* | Ginsenoside extracts from stems and leaves of *Panax ginseng* | SH-SY5Y cells | tau phosphorylation↓, anti-oxidant enzymes↑ | [50] |
| Protective effect of ginsenoside Rb1 on beta-amyloid protein(1-42)-induced neurotoxicity in cortical neurons. | *Panax ginseng* | Ginsenoside Rb1 | primary cortical neurons treated with Aβ | LDH, malonyldialdehyde, and SOD activity↓ | [51] |
| Ginsenoside Rb1 protects PC12 cells against β-amyloid-induced cell injury | *Panax ginseng* | Ginsenoside Rb1 | PC12 cells treated with Aβ | ROS↓, lipid peroxidation ↓, Bcl-2/Bax ratio↑ | [52] |

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| Involvement of calpain and p25 of CDK5 pathway in ginsenoside Rb1's attenuation of beta-amyloid peptide25-35-induced tau hyperphosphorylation in cortical neurons | *Panax ginseng* | Ginsenoside Rb1 | Primary rat cortical neurons | p25 (CDK5 activator)↓, calpain activity↓, intracellular $Ca^{2+}$↓ | [53] |
| Anti-neuroinfl ammation effect of ginsenoside Rbl in a rat model of Alzheimer disease. | *Panax ginseng* | Ginsenoside Rb1 | Rat injected with $A\beta_{1-42}$ | cognitive function↓, neuroinflammation↓ | [54] |
| Ginsenoside-Rg1 inhibits cell apoptosis induced by beta amyloid | *Panax ginseng* | Ginsenoside Rg1 | PS1M146L/APP751 mutant CHO cells | $A\beta_{42}$↓, caspase-3 activation↓ | [55] |

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| Ginsenoside Rg1 protects against hydrogen peroxide-induced cell death in PC12 cells via inhibiting NF-κB activation | *Panax ginseng* | Ginsenoside Rg1 | PC12 cells treated with $H_2O_2$ | NF-κB ↓, Akt and ERK1/2 ↑ | [56] |
| Ginsenoside Rg1 attenuates amyloid-beta content, regulates PKA/CREB activity, and improves cognitive performance in SAMP8 mice | *Panax ginseng* | Ginsenoside Rg1 | senescence-accelerated mouse | Aβ↓, PKA activity↓, pCREB↑, BDNF↑ | [57] |
| Reductions in levels of the Alzheimer's amyloid beta peptide after oral administration of ginsenosides | *Panax ginseng* | Ginsenoside Rg1, Rg3, and Re | CHO cell line, Tg2576 mice | Aβ↓ (*in vitro* and in mouse brain) | [58] |

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| Ginsenoside Rg1 inhibits betasecretase activity in vitro and protects against Abeta-induced cytotoxicity in PC12 cells | *Panax ginseng* | Ginsenoside Rg1 | PC12 cells induced with Aβ | β-secretase activity↓, apoptosis↓ | [59] |
| Ginsenoside Rg3 promotes beta-amyloid peptide degradation by enhancing gene expression of neprilysin | *Panax ginseng* | Ginsengoside Rg3 | $APP_{sw}$ SK-N-SH cells | neprylisin (Aβ-degrading enzyme) expression↑, Aβ↓ | [60] |
| Gintonin, a ginseng-derived lysophosphatidic acid receptor ligand, attenuates Alzheimer's disease-related neuropathies: involvement of non-amyloidogenic processing | *Panax ginseng* | Gintonin | wt or mutant APP-expressing SH-SY5Y cells, various AD-phenotype mice | sAPPα release↑, $Aβ_{42}$↓, $Aβ_{40}$-mediated toxicity↓, AP formation↓ (*in vivo)*, cognitive function↑ (*in vivo*) | [61] |

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| Protective effect of resveratrol on beta-amyloid induced oxidative PC12 cell death | *Vitis vinifera* | Resveratrol | PC12 cells treated with Aβ | ROS↓, apoptosis↓ | [62] |

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