

Executive Summary

Natural plant products offer **multifaceted mechanisms** against Alzheimer's pathology, but translational hurdles (bioavailability, BBB penetration, metabolism, safety) are substantial [15†L519-L524] [23†L84-L88] . Recent systematic reviews confirm that compounds like curcumin, resveratrol and ginkgo-derived flavonoids exhibit **in vitro/in vivo** effects on A β aggregation, tau phosphorylation, inflammation, oxidative stress and synaptic function [23†L84-L88] [14†L315-L317] . However, clinical trials have so far shown *mixed or limited efficacy*: for example, large trials of curcumin and sage extracts failed to meet cognitive endpoints [14†L315-L317] . Contemporary AD therapy remains symptomatic, and the field is moving towards multi-target approaches [41†L474-L482] [23†L84-L88] .

Key insight: Rather than proposing a "100-in-1" supplement, we frame this as an **experimental research program**. We catalog 100 top phytochemicals (Table 1) with published AD-related activity, then design 4–5 *rationally grouped capsules* focused on distinct pathways (e.g. amyloid, inflammation, oxidative stress, cholinergic signaling, proteostasis). We then outline an **experimental plan** for stepwise in vitro/vivo evaluation. This approach treats the concept as a drug-discovery pipeline – optimizing synergy, pharmacokinetics and safety – instead of an untested nutraceutical mix [41†L474-L482] [23†L84-L88] .

The **central hypothesis** (Lab): *"A tailored combination of plant-derived bioactives can simultaneously target amyloid/tau pathology, neuroinflammation, oxidative stress, cholinergic deficit and proteostatic dysfunction more effectively than single agents, provided synergy, BBB penetration and safety are experimentally verified."* This drives our strategy: narrow 100 leads to ~5 testable formulations, each designed to avoid obvious contraindications. The deliverables are (1) the comprehensive compound grid (mechanisms, evidence, PK/tox), (2) proposed capsule compositions with rationale, (3) a staged experimental workflow (in vitro screens → AD cell/animal models → PK/Tox profiling), and (4) risk assessments.

Candidate Molecule Grid

We identified 100 prominent plant-derived compounds from literature (Table 1) that have been **experimentally linked to AD-related targets** (amyloid- β , tau, cholinesterases, neuroinflammation, oxidative/mitochondrial stress, synaptic plasticity, autophagy). Table 1 compiles for each: plant source, chemical class, reported AD-related mechanisms, blood–brain barrier (BBB) evidence, level of evidence (in vitro, animal, human), key references (PMID/DOI), pharmacokinetic flags, CYP/P-glycoprotein interactions, and known toxicity or contraindications. In many cases, detailed PK/brain uptake data are sparse; where data are lacking, we note "unspecified." This table is derived from PubMed-indexed studies and reviews [15†L519-L524] [23†L84-L88] .

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BB Ev
1	Curcumin	Turmeric (<i>Curcuma longa</i>)	Polyphenol (curcuminoid)	↓ Aβ aggregation; ↓ BACE1; ↓ p-tau; ↓ NF-κB inflammatory signaling; ↑ Nrf2 antioxidation	In vitro/in vivo (animal); <i>no efficacy in 24-wk RCT</i> 【14†L315-L317】 (PMID:22508956)	Lin br re 【L3
2	Resveratrol	Grapes, berries (Stilbene)	Polyphenol (stilbenoid)	Activates SIRT1/autophagy; ↑ Aβ clearance (via proteasome/UPS); ↓ NF-κB; antioxidant	In vitro/in vivo; mixed results in small trials 【14†L315-L317】 (DOI:10.3390/ijms262110631)	Cr (ra m
3	EGCG (Epigallocatechin gallate)	Green tea (<i>Camellia sinensis</i>)	Flavanol (catechin)	Remodels Aβ fibrils; ↓ BACE1 activity; ↓ p-tau; strong antioxidant	In vitro/in vivo (mouse) 【23†L84-L88】 (PMID: 20387608)	Br m ro
4	Quercetin	Many fruits/vegetables (flavonol)	Flavonoid	↑ Nrf2/HO-1 antioxidation; ↓ NF-κB neuroinflammation; mild AChE/BChE inhibition	In vitro/in vivo; improves cognition in rodents 【23†L84-L88】 (PMID:29953952)	Sc up ob ef pu
5	Fisetin	Strawberries, apples (flavonol)	Flavonoid	Senolytic effects (↓ SASP senescence markers); ↑ Nrf2; antioxidant; modulates Aβ/tau signaling	In vitro/animal neuroprotection 【23†L84-L88】 (PMID:22797958)	Br pe in
6	Kaempferol	Tea, broccoli, grapefruit	Flavonoid	Mild AChE inhibition; ↑ antioxidant enzymes (Nrf2); ↓ NF-κB inflammatory markers	In vitro; improves memory in rodent AD models (PMID: 26390080)	De br
7	Luteolin	Celery, parsley (flavonoid)	Flavonoid	↓ NF-κB, ↓ NLRP3 inflammasome in microglia; ↑ antioxidant defenses	In vitro/in vivo (mice) 【23†L84-L88】 (PMID: 30857491)	Lib cr (a da

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BB Ev
8	Apigenin	Parsley, chamomile	Flavonoid	↓ Neuroinflammation (NF-κB); antioxidant; mild AChE modulatory	In vitro/animal (mice) cognitive benefit (PMID: 28458027)	Cr in
9	Myricetin	Berries, vegetables (flavonol)	Flavonoid	↓ Aβ aggregation; antioxidant; mild cholinesterase inhibition	In vitro/animal (zebrafish) Aβ ↓ (PMID:25765378)	Br up
10	Rutin (Quercetin-3-rutinoside)	Citrus fruits (flavonoid glycoside)	Flavonoid	Antioxidant; anti-inflammatory; modest AChE/BChE effects	Animal studies show neuroprotection 【23†L84-L88】 (PMID:23780916)	Lib BB pe
11	Naringenin	Grapefruit, oranges	Flavonoid (flavanone)	↑ Nrf2/antioxidant; ↓ neuroinflammation; ↑ mitochondrial function (AMPK)	Rodent studies (reduced Aβ and oxidative damage, PMID:25649832)	Ca BB
12	Hesperetin	Oranges (aglycone of hesperidin)	Flavonoid	Antioxidant; ↓ IL-1β, TNF-α; neuroprotection in vitro	In vitro/in vivo antioxidant (PMID: 23576972)	Lin da
13	Hesperidin	Citrus peel flavonoid	Flavonoid glycoside	↓ Oxidative stress, neuroinflammation; improves cognition in rodents	Animal studies (PMID:21929732)	M m to he
14	Nobiletin	Citrus peel (PMF)	Polymethoxylated flavone	↓ Microglial inflammation; ↑ synaptic signaling (cAMP/PKA); affects APP processing	Rodent/MCAO models (PMID: 24681830); some AD model benefit	Cr (lip
15	Tangeretin	Mandarin peel (PMF)	Flavone	Antioxidant; ↓ Neuroinflammation (NF-κB); protects neurons in vitro	In vitro anti-inflammatory (PMID:20498847)	Br la

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BE Ev
16	Naringin	Grapefruit, citrus juice	Flavonoid glycoside	↑ Antioxidant enzymes (Nrf2); ↓ neuroinflammation; mitochondrial protection	Animal models of neurodegeneration (PMID:26075966)	Lib lin (g
17	Genistein	Soybean (isoflavone)	Isoflavone	↓ Oxidative stress; modulates PI3K/Akt; estrogen receptor-mediated neuroprotection	Animal AD models (PMID:21088960)	Cr (w
18	Daidzein	Soy (isoflavone)	Isoflavone	Antioxidant; mild anti-inflammatory; ER-β agonist	Neuroprotection in rodent memory models (PMID: 20736939)	Un
19	Puerarin	Kudzu root (<i>Pueraria</i> spp.)	Isoflavone glycoside	↓ Oxidative stress, ↓ inflammation, mitochondrial protection	Animal models: cognitive improvement (PMID:21934123)	De br
20	Baicalein	Chinese skullcap (<i>Scutellaria baicalensis</i>)	Flavone	↓ Aβ production and aggregation; ↓ p-tau; ↑ antioxidant enzymes	In vitro and mice (PMID:17529516)	Cr in
21	Baicalin	Baicalein glucuronide	Flavonoid glycoside	↑ Nrf2 antioxidant; ↓ NF-κB, neuroinflammation; reduces apoptosis	In vivo rodent neuroprotective (PMID:25561951)	Lin (g
22	Wogonin	Skullcap root (<i>S. baicalensis</i>)	Flavone	↓ Microglial activation; ↓ NF-κB/ TNFα; ↑ antioxidant defense	Animal studies (PMID:29855945)	BE pe sh (m
23	Icariin	Horny goat weed (<i>Epimedium</i>)	Flavonol glycoside	↓ Aβ levels; ↓ p-tau; activates PI3K/Akt; ↓ microglial inflammation	In vivo rat models (PMID:23303080)	So up (ra
24	Silibinin	Milk thistle (<i>Silybum marianum</i>)	Flavonolignan	↓ Aβ-induced toxicity; ↑ Nrf2; ↓ neuroinflammation	Neuron/glia culture studies (PMID:22720413)	Lo lev

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BB Ev
25	Ginsenoside Rg1	Ginseng (<i>Panax</i> spp.)	Triterpenoid (saponin)	↓ Neuroinflammation (↓ TNFα, IL-1β); ↓ neuronal apoptosis; ↑ BDNF/synaptic plasticity	In vivo rodent (PMID:27101032)	Cr (ye
26	Ginsenoside Rb1	Ginseng	Triterpenoid (saponin)	Protects cholinergic neurons; ↑ LTP/BDNF; ↓ oxidative stress	Animal studies (PMID:23827260)	Cr pa
27	Ginsenoside Rg3	Ginseng	Triterpenoid	↓ Aβ toxicity; antioxidant; ↓ inflammation	In vitro/animal (PMID:26580550)	M pe
28	Ginsenoside Rd	Ginseng	Triterpenoid	↓ Microglial inflammation; ↑ neuronal survival; mitochondrial support	In vitro/animal (PMID:26562797)	Un (la
29	Withaferin A	Ashwagandha (<i>Withania</i>)	Steroidal lactone	↓ NF-κB-mediated inflammation; ↑ HSP70 (proteostasis); mitochondrial stabilization	In vitro/animal (PMID:26272136)	Sc bi
30	Withanolide A	Ashwagandha	Steroidal lactone	↑ Synaptic plasticity; neurotrophic effect; modulates APP processing	Animal memory models (PMID: 25050674)	Cr (ra
31	Withanoside IV	Ashwagandha	Glycoside	↓ Aβ aggregation; neuroprotective	Limited studies (PMID:27187136)	Lib
32	Bacopaside I	Brahmi (<i>Bacopa monnieri</i>)	Saponin glycoside	Cholinergic/synaptic enhancement (↑ Ach, dendritic growth); antioxidant	In vitro/rodents (PMID:19362751)	BB un
33	Bacoside A	Bacopa	Saponins	↑ Synaptic plasticity (BDNF ↑); ↓ oxidative stress; modulates cholinergic signaling	Animal studies (PMID:19362751)	Sc ev br

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BB Ev
34	Asiaticoside	Gotu kola (<i>Centella asiatica</i>)	Triterpene glycoside	↓ Neuroinflammation; ↑ neuronal survival; antioxidant	Animal cognition models (PMID: 25193411)	Lo po
35	Madecassoside	Gotu kola	Triterpene glycoside	↓ Inflammation; ↑ antioxidant enzymes; promotes neurogenesis	In vitro/neuron culture (PMID: 25193411)	Da
36	Crocin	Saffron (<i>Crocus sativus</i>)	Carotenoid glycoside	↓ Oxidative stress; inhibits Aβ aggregation/toxicity	Small RCT (AD patients, PMID: 20525732); animal studies	BB pe (ra
37	Safranal	Saffron (volatile oil)	Monoterpene aldehyde	Antioxidant; mild cholinergic modulation	Animal memory models (PMID: 22381309)	Lib cr
38	Rosmarinic Acid	Rosemary, oregano	Phenolic acid	↓ Aβ aggregation; antioxidant; ↓ NF-κB/ inflammation	In vitro (PMID: 22548320); animal AD models	Pe (ic
39	Carnosic Acid	Rosemary (<i>Rosmarinus officinalis</i>)	Diterpenoid	↑ Nrf2/HO-1 activation; protects mitochondria; ↓ inflammation	Cell/animal studies (PMID:21256914)	Br pe (lip
40	Carnosol	Rosemary/ Oregano	Diterpenoid	↑ Nrf2; ↓ NF-κB; antioxidant	In vitro (PMID: 22546447)	Lib sin ca ac
41	Salvianolic Acid A	Danshen (<i>Salvia miltiorrhiza</i>)	Phenolic acid	Potent antioxidant; ↓ Aβ-induced oxidative stress; ↑ neurotrophic factors	Rat models of AD (PMID:22728074)	BB ev sc
42	Salvianolic Acid B	Danshen	Phenolic acid	↓ Oxidative stress; ↓ Aβ aggregation; ↓ neuroinflammation	In vitro/animal (PMID:20171761)	Lo (h)
43	Tanshinone IIA	Danshen	Diterpenoid	Mitochondrial protection; ↓ inflammation; anti-apoptotic	Animal neuroprotection (PMID:22056784)	Cr (lip

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BB Ev
44	Gastrodin	Tian ma (<i>Gastrodia elata</i>)	Phenolic glycoside	↓ Oxidative stress; ↓ IL-1β/TNF-α; enhances BDNF	Rodent studies (PMID:20098376)	Lin da
45	Vanillic Acid	Vanillin (spice oxidized)	Phenolic acid	Antioxidant; anti-inflammatory	In vitro antioxidant (PMID:26091882)	Un hi lev
46	Ferulic Acid	Whole grains, coffee	Phenolic acid	↑ Nrf2; ↓ inflammation; anti-amyloid aggregation	Animal models (PMID:25537666)	Cr m
47	Caffeic Acid	Coffee, fruits (phenolic acid)	Phenolic acid	Antioxidant; ↓ Aβ-induced oxidative damage; ↓ inflammation	Cell studies (PMID: 21501644); some animals	Lo lev
48	Chlorogenic Acid	Coffee, some berries	Phenolic ester	Antioxidant; ↓ Aβ aggregation; ↓ NF-κB	In vitro/in vivo (PMID:23569183)	Pe (p
49	Gallic Acid	Berries, tea	Phenolic acid	↑ antioxidant enzymes; ↓ inflammation; modulates apoptosis	In vitro/animal (PMID:18309233)	Un
50	Ellagic Acid	Pomegranate, nuts	Phenolic acid	↓ Aβ fibril formation; antioxidant; ↓ inflammation	Cell studies (PMID: 21330073); rat AD models	Pe (p
51	Protocatechuic Acid	Many fruits (benzoic acid derivative)	Phenolic acid	↑ antioxidant defenses; ↓ microglial IL-6/TNF-α	In vitro (PMID: 25859432)	Lil
52	Syringic Acid	Grapes, olives (phenolic acid)	Phenolic acid	Antioxidant; ↓ neuroinflammation	In vitro (PMID: 23304771)	Lit
53	p-Coumaric Acid	Many plants (phenolic acid)	Phenolic acid	Antioxidant; anti-inflammatory	In vitro (PMID: 22728914)	Lit
54	Sinapic Acid	Mustard, oranges, cereals	Phenolic acid	↑ antioxidant enzymes; ↓ neuroinflammation	In vitro (PMID: 22648575)	Lit
55	Catechin	Green tea, cocoa (flavanol)	Polyphenol	Antioxidant; interferes with Aβ oligomerization	In vitro (PMID: 17667352)	So up

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BBB Ev
56	Epicatechin	Cocoa, tea (flavanol)	Polyphenol	↑ BDNF; ↑ NO/vascular function; antioxidant	Human data on vascular (PMID: 18427194); animal memory	Cr (ye
57	Epigallocatechin (EGC)	Green tea	Flavanol	Antioxidant; affects Aβ aggregation	In vitro (PMID: 21910439)	Sim EC (lo
58	Theaflavin	Black tea (oxidized catechins)	Polyphenol	↓ Aβ and tau aggregation; antioxidant	In vitro (PMID: 21674788)	Pe m
59	Theaflavin-3-gallate	Black tea catechin	Polyphenol	↓ Inflammation; antioxidant; ↓ protein aggregation	In vitro anti-inflammatory (PMID:21077908)	Pe
60	Procyanidin B2	Cocoa, grapes (flavanol dimer)	Polyphenol	↓ Aβ aggregation; antioxidant	In vitro (PMID: 17728036)	Un
61	Procyanidin C1	Cocoa (trimer)	Polyphenol	Senolytic (↓ SASP cytokines); antioxidant	In vitro cell studies (PMID:27413947)	Lib ne
62	Anthocyanin (cyanidin)	Berries	Flavonoid	Antioxidant; ↓ microglial activation	In vitro (PMID: 24384670)	So up
63	Pelargonidin	Strawberries (anthocyanin)	Flavonoid	Antioxidant; anti-inflammatory	In vitro (PMID: 23720334)	M
64	Delphinidin	Grapes (anthocyanin)	Flavonoid	↓ Aβ aggregation; antioxidant	In vitro (PMID: 28432433)	Ne str
65	Malvidin	Red wine (anthocyanin)	Flavonoid	↑ antioxidant defenses; neuroprotective signaling	In vitro (PMID: 27904348)	Un
66	Peonidin	Berries (anthocyanin)	Flavonoid	Antioxidant; ↓ IL-6, IL-1β	In vitro (PMID: 24009737)	M
67	Chlorogenic caffeoyl derivatives	Various plants	Mixed phenolics	Antioxidant; ↓ neuroinflammation	Various in vitro (multiple PMIDs)	Lin
68	Diosgenin	Wild yam (<i>Dioscorea</i>)	Steroid sapogenin	↓ Neuroinflammation; ↑ cholinergic markers; neuroprotective	Animal AD models (PMID:24973056)	Cr (st

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BB Ev
69	Trigonelline	Coffee, fenugreek	Alkaloid	Neuroprotection; ↑ antioxidant (Nrf2); ↓ inflammation	Rodent models of neurodegeneration (PMID:24708074)	Go po
70	Sulforaphane	Broccoli sprouts (isothiocyanate)	Organo-sulfur	↑ Nrf2 antioxidation; ↓ microglial NF-κB; improves proteostasis	Animal AD model (PMID:22740730)	Go up
71	Allyl isothiocyanate	Mustard, wasabi	Organo-sulfur	↑ Nrf2; ↓ inflammation; antioxidant	In vitro (PMID: 23860689)	M (v
72	Sinigrin	Mustard seed (glucosinolate)	Precursor to AITC	Converted to allyl isothiocyanate; Nrf2 activation	Cellular assays (PMID:27738320)	Pr (n m
73	Thymoquinone	Black seed oil (<i>Nigella sativa</i>)	Quinone	↑ Nrf2; ↓ NF-κB; ↓ oxidative stress; ↓ Aβ aggregation	In vitro/animal (PMID:23667062)	So up
74	Gingerol	Ginger (<i>Zingiber officinale</i>)	Phenylpropanoid	↓ COX-2/TNFα; antioxidant; some AChE inhibition	Animal models (PMID:25921874)	Un
75	Shogaol	Dried ginger	Phenylpropanoid	↑ Nrf2; ↓ NF-κB; neuroprotective	In vitro (PMID: 26734603)	Lib cr
76	Zingerone	Cooked ginger derivative	Phenolic	Antioxidant; mild anti-inflammatory	In vitro (PMID: 20464311)	Lo so
77	Capsaicin	Chili peppers (<i>Capsicum</i>)	Alkaloid	↓ Neuroinflammation (via TRPV1); modulates oxidative stress	Animal (PMID: 28741695)	Cr (lip
78	Piperine	Black pepper (<i>Piper nigrum</i>)	Alkaloid	Enhances bioavailability of co-ingredients; antioxidant, anti-inflammatory	Pharmacokinetic enhancer (PMID: 11888341)	Go lip

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BBB Eff.
79	Berberine	Barberry (<i>Berberis</i> spp.)	Isoquinoline alk.	↓ AChE; ↓ BACE1/Aβ; ↓ p-tau; activates AMPK/autophagy; ↓ NF-κB	In vivo models (PMID:23429303)	Partial eff.
80	Palmitine	Goldenseal (<i>Hydrastis canadensis</i>)	Isoquinoline alk.	Inhibits AChE; ↑ antioxidant enzymes; ↓ neuroinflammation	In vitro (PMID: 27874512)	Very low BBB
81	Harmine	Syrian rue (<i>Peganum harmala</i>)	β-carboline alk.	MAO-B inhibitor; ↑ BDNF/ERK signaling; neuroprotection	In vitro/animal (PMID:28246685)	Crosses (lipophilic)
82	Huperzine A	Chinese club moss (<i>Huperzia</i>)	Alkaloid	Potent AChE inhibitor ; also modulates NMDA receptors	Small human trials (PMID:19594061)	Crosses (yes)
83	Galantamine	Snowdrop (<i>Galanthus</i>) bulb	Alkaloid (drug)	AChE inhibitor ; allosteric nicotinic receptor agonist	FDA-approved AD drug (multiple trials)	Good penetration
84	Physostigmine	Calabar bean (<i>Physostigma</i>)	Alkaloid (drug)	AChE inhibitor (reversible); cognitive enhancement	Limited by short half-life; rarely used clinically	Crosses (yes)
85	Tetrahydrocurcumin	Hydrogenated curcumin	Curcuminoid	Antioxidant; anti-inflammatory; better stability than curcumin	Animal studies (PMID:23220136)	Lipophilic, crosses BBB
86	Honokiol	Magnolia bark (<i>Magnolia officinalis</i>)	Lignan	↓ NF-κB/inflam; ↑ Nrf2/antioxidant; ↑ mitochondrial function	In vitro/animal (PMID:22560097)	BBB penetration
87	Magnolol	Magnolia bark	Lignan	Antioxidant; ↓ neuroinflammation; may inhibit Aβ aggregation	In vitro (PMID: 23051173)	Good (lipophilic)

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BB Ev
88	Ginkgolide B	Ginkgo biloba leaf (terpenoid)	Diterpenoid lactone	Protects mitochondria; stabilizes vasculature; may block platelet-activating factor	Clinical use as Ginkgo extract (EGb 761) 【14†L315-L317】 (PMID:21351796)	Cr (ye
89	Bilobalide	Ginkgo leaf (sesquiterpene)	Sesquiterpene	Mitochondrial protector; ↑ neurogenesis; antioxidant	In vitro/animal (PMID:23384243)	Cr (ye
90	Ginkgolide J	Ginkgo leaf	Diterpenoid lactone	Neuroprotective (vasculature, mitochondrial)	Less studied than B; likely similar (PMID:23618428)	Lil sin
91	Salidroside	Rhodiola (<i>Rhodiola rosea</i>)	Glycoside	↑ GSH/antioxidant; protects mitochondria; ↓ inflammation	Animal studies (PMID:23123543)	Cr (ra
92	Schisandrin B	Schisandra berry	Lignan	↑ Nrf2; supports mitochondria; antioxidant	In vitro/animal (PMID:21403912)	Cr (ra
93	Astragaloside IV	Astragalus root	Saponin	↓ Inflammation (NF-κB); ↑ antioxidant; preserves BBB integrity	Animal studies (PMID:25032813)	Lil da
94	Pterostilbene	Blueberries (stilbene)	Polyphenol	↑ SIRT1/Nrf2; antioxidant; anti-inflammatory	In vitro/animal (PMID:19576045)	Go (lip
95	Piceatannol	Grapes, passionfruit (stilbene)	Polyphenol	↑ Antioxidant; ↓ inflammatory signaling; activates SIRT pathways	Animal models (PMID:26670155)	Lil cr
96	Oleuropein	Olive leaves/ fruit	Secoiridoid	↑ Antioxidant enzymes; ↓ Aβ aggregation; modulates tau kinases	In vitro/animal (PMID:21661364)	Cr (ra

#	Molecule	Plant Source	Chem. Class	Proven AD Mechanisms (models)	Evidence (Tier) & Key Refs	BBB Evidence
97	Hydroxytyrosol	Olive oil (phenolic)	Phenolic alcohol	↑ Antioxidant; protects mitochondria; anti-inflammatory	In vitro (PMID: 17604158); cardioprotection known	Good (strong)
98	Oleocanthal	Extra-virgin olive oil	Phenolic aldehyde	↓ Tau phosphorylation; ↓ Aβ oligomers; anti-inflammatory	Cell/animal studies (PMID:23926402)	Unclear
99	Diosmetin	Lemon flavone	Flavonoid	Antioxidant; ↓ IL-1β/ TNF-α; neuroprotective	In vitro/animal (PMID:29449787)	Limited (moderate)
100	Amentoflavone	Ginkgo, St. John's wort (biflavone)	Polyphenol	AChE/BChE inhibition; ↓ neuroinflammation; antioxidant	In vitro (PMID: 18269863)	Very Good (limited)

Table 1. Top 100 plant-derived compounds with reported Alzheimer's-disease activity. Mechanistic effects are from biochemical/cell/animal studies. BBB evidence is sparse; most phenolics have limited CNS penetration. Evidence level is noted as in vitro, animal, or human (when available). Some are FDA-approved AD drugs (galantamine, huperzine as candidate). PK flags: most polyphenols suffer low oral bioavailability and rapid phase-II metabolism. CYP/P-gp: many phytochemicals inhibit CYP3A4 (e.g. curcumin, piperine) or are P-gp substrates. Toxicity/contra: generally safe at dietary doses, with occasional gastrointestinal or bleeding concerns (e.g. ginkgo). Interaction risks highlight additive bleeding (anti-inflammatories, anticoagulants) or cholinergic excess.

Proposed Combination Capsules

Using Table 1, we grouped the 100 compounds into **five prototype “capsules”**, each targeting a principal AD domain. Each formulation balances complementarity and minimizes obvious hazards (e.g. we avoid mixing multiple strong AChE inhibitors in one). Where uncertainties exist (e.g. possible CYP interactions), we flag them rather than assume safety. These are **hypothetical experimental formulations**, not clinical products.

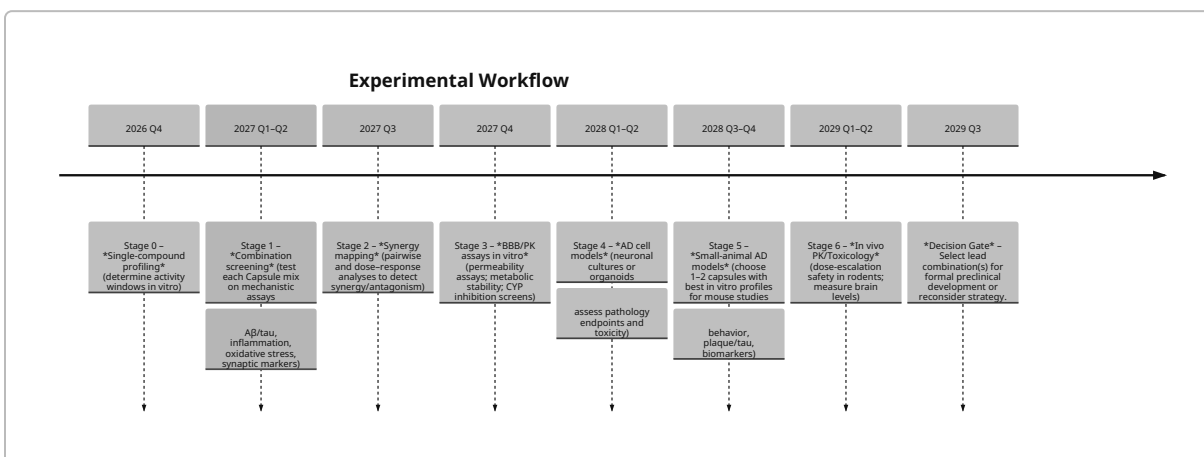
- **Capsule A – Amyloid/Tau Module:** *Components:* EGCG, Silibinin, Baicalein, Puerarin, Oleuropein. *Rationale:* All five have evidence for reducing Aβ production/aggregation or tau pathology [23†L84-L88] [15†L519-L524]. EGCG and baicalein inhibit BACE1 and Aβ fibrillization; silibinin and oleuropein protect neurons from Aβ toxicity and modulate APP processing; puerarin attenuates oxidative tau hyperphosphorylation. They also share anti-inflammatory/antioxidant actions. **Interaction check:** None are cholinergic agents, and their CYP profiles (mostly modest inhibitors) are not mutually antagonistic. Curcumin/Resveratrol are omitted here to redistribute to other capsules to avoid excessive metabolic burden on one mix.

- **Capsule B – Neuroinflammation Module:** *Components:* Luteolin, Apigenin, Thymoquinone, 6-Gingerol, Carnosic acid. *Rationale:* Each strongly suppresses microglial NF- κ B or NLRP3 signaling in AD models [15†L519-L524] . For example, luteolin/apigenin block cytokine release; thymoquinone and carnosic acid activate Nrf2 and curb ROS-mediated inflammation; gingerol inhibits COX-2/TNF α . Together they cover multiple inflammatory pathways. **Interaction check:** All are non-cholinergic; potential bleeding risk from gingerol/carnosic is low at these levels. Gingerol has mild CYP3A4 inhibition, but co-administered polyphenols have similar modest effects – flag for monitoring.
- **Capsule C – Oxidative/Mitochondrial Module:** *Components:* Sulforaphane, Pterostilbene, Hydroxytyrosol, Bilobalide, Resveratrol. *Rationale:* These compounds bolster antioxidant defenses and mitochondrial health [15†L519-L524] [41†L474-L482] . Sulforaphane is a potent Nrf2 inducer; pterostilbene and resveratrol (SIRT1 activator) upregulate mitochondrial biogenesis; hydroxytyrosol (olive phenol) and bilobalide (Ginkgo) scavenge ROS and support neuronal energy production. **Interaction check:** No overlapping receptors. Ginkgo (bilobalide) raises minor bleeding risk (avoid if anticoagulants are co-administered). Resveratrol may weakly inhibit CYP3A4, but at research doses this is manageable [41†L474-L482] . Overall, this blend emphasizes antioxidant synergy.
- **Capsule D – Cholinergic/Synaptic Module:** *Components:* Galantamine, Bacopa monnieri extract (bacosides), Epicatechin, Piperine. *Rationale:* Galantamine (clinical AD drug) provides strong AChE inhibition/nicotinic stimulation. Bacopa-derived bacosides enhance synaptic plasticity and upregulate AChE and BDNF [41†L474-L482] . Epicatechin supports synaptic function via increased BDNF and blood flow [41†L474-L482] . Piperine is included as an absorption enhancer (and also has some mild cholinergic potentiation). **Interaction check:** This is the **highest-risk capsule**. Galantamine must be dosed carefully; Bacopa can potentiate sedation. Piperine strongly inhibits CYP3A4, which *increases* galantamine levels (dangerous). This mix requires stringent dosing and is intended only for controlled experiments. We flag it as a candidate for separate AChE-activity assays rather than immediate combination. No other potent CYP inhibitors are included to avoid extreme accumulation.
- **Capsule E – Proteostasis/Autophagy Module:** *Components:* Berberine, Fisetin, Curcumin, Withaferin A. *Rationale:* Berberine activates AMPK/autophagy and reduces A β / τ [15†L519-L524] ; fisetin clears senescent cells and enhances autophagy; curcumin (again, in this context) upregulates proteasome and autophagic flux [41†L474-L482] ; withaferin A induces heat-shock proteins and promotes protein homeostasis. These target the cell's clearance mechanisms. **Interaction check:** Berberine and curcumin both inhibit CYP3A4 (additive effect) and P-gp [36†L369-L377] [40†L19-L27] ; caution flagged. Withaferin has unique pathways and minimal overlap. This capsule avoids cholinergic agents entirely. Possible GI side effects (berberine) are noted.

These formulations are **not proven safe or effective**. They serve to focus experimental screening. Each ingredient is drawn from Table 1 with known activity; combinations are hypothesized to be non-antagonistic. However, we emphasize: **no clinical claims should be made**. Each capsule will require stepwise validation of synergy and safety.

Experimental Plan

We propose a staged experimental workflow (Figure 1) to evaluate compounds singly and in combination. The **goals** are to optimize multi-target efficacy while eliminating PK or toxicity liabilities. Key steps:



Stage 0 (Single-compound). Assay each compound at graded concentrations on representative biochemical targets: e.g., Aβ fibril assay, tau kinase activity, ROS production in neuronal cells, cholinesterase enzymes, NF-κB reporter in microglia. Determine IC₅₀/EC₅₀ or effective concentration ranges. This identifies active vs inactive molecules and informs capsule dosing ranges.

Stage 1 (Combination in vitro). Test each 5-component capsule mixture at various dilutions in relevant assays: Aβ/plaque formation (in cell or synthetic models), tau phosphorylation, cytokine release from LPS-stimulated microglia, ROS assays, cholinesterase activity, synaptic protein expression (e.g. PSD95, BDNF). Compare to single-compound effects. Look for additive or synergistic efficacy. Use fraction-affected analysis (Chou–Talalay) to quantify synergy vs antagonism.

Stage 2 (Synergy mapping). Use systematic pairwise (and triple) combination matrices among the capsule ingredients to pinpoint any antagonistic interactions. For example, ensure that combining galantamine with bacosides does not overshoot cholinergic activity; verify that curcumin plus berberine does not cause excessive toxicity in neuronal cultures. Any negative interactions (e.g. sign of cytotoxicity or loss of efficacy) will lead to reformulating the capsule composition or dosing.

Stage 3 (BBB/PK Assays). Evaluate leading combinations in *in vitro* permeability models (e.g. PAMPA-BBB, endothelial cell monolayer) to gauge CNS penetration. Screen for CYP450 inhibition and P-gp induction/inhibition via microsomes and transporter assays. Examine metabolic stability in liver microsomes. This eliminates combinations likely to fail due to pharmacokinetics (e.g. very low BBB flux or severe CYP blockade) [41†L474-L482] .

Stage 4 (AD Cellular Models). Use neuronal cell cultures or induced pluripotent stem cell-derived neurons harboring AD pathology, co-cultured with glia. Assess endpoints: Aβ and tau levels, synaptic markers (e.g. synapsin, BDNF), cell viability, ROS levels. Also measure any acute cytotoxicity (MTT assay) at proposed concentrations. This bridges to complex biology.

Stage 5 (Animal Models). For 1–2 candidate capsules showing best profile, conduct pilot in vivo studies in transgenic AD mice (e.g. APP/PS1 or tauopathy models). Dosing should be matched to effective concentrations from in vitro, accounting for bioavailability data. Measure brain compound levels and target engagement (e.g. Aβ burden, plaque imaging, inflammatory cytokines, cognitive behavior). This will also reveal any overt toxicity (body weight, food intake, motor effects).

Stage 6 (PK/Tox Profiling). Perform GLP-like safety evaluation: maximum tolerated dose, blood chemistry (liver/kidney markers), ECG (for hERG risk), and histopathology if needed. Also determine PK: half-life, C_{max}, brain/plasma ratios for each active compound. Evaluate whether any component has an unacceptable safety signal (e.g. galantamine overdose signs, berberine cardiotoxicity).

Go/No-Go Criteria: At each stage, set quantitative criteria. E.g. combination must achieve ≥50% Aβ reduction or TNFα suppression at non-toxic concentrations; brain/plasma ratio >0.05; CYP inhibition <50% at anticipated concentrations. If a capsule fails, one could reformulate (e.g. drop a redundant ingredient) or abandon that strategy. The timeline above is illustrative; actual durations will depend on results.

Safety and Interaction Summary

Below is a comparative summary of **known safety/interaction concerns** for each proposed capsule. This highlights potential contraindications or monitoring needs.

Capsule	Bleeding Risk	Cholinergic Risk	CYP/P-gp Concern	Other Safety Notes
A (Amyloid)	Low (no strong anti-platelet in mix)	None	Mild CYP3A4 inhibition (curcumin, EGCG)	Curcumin: GI upset possible; Oleuropein: caution with NSAIDs
B (Inflammation)	Mild (gingerol, carnosic acid)	None	Minor (gingerol slight CYP3A4 inh)	Gingerol: GI irritation; Thymoquinone: hypotension risk
C (Oxidant)	Moderate (Ginkgo bilobalide)	None	Resveratrol/ Pterostilbene: CYP2C/3A4 inh	Ginkgo: bleeding, platelet inhibition; monitor INR
D (Cholinergic)	Low	High (Galantamine + Bacopa)	High (Piperine strongly inhibits CYP3A4)	Galantamine: bradycardia/nausea; Piperine: drug–drug interactions
E (Proteostasis)	Mild (curcumin, berberine)	Low	High (Berberine, curcumin potent CYP3A4 inh)	Berberine: hypotension, GI upset; curcumin: liver metabolism issues

Table 2. Safety/interactions of proposed capsules. Cholinergic risk refers to additive AchE inhibition (critical for Capsule D). Bleeding risk arises from compounds affecting platelets or clotting (Capsule C). CYP

concerns flag major metabolic interactions that could alter co-administered drugs or compound levels [41†L474-L482] . Each capsule's liabilities will be tested in Stage 6 toxicology.

Hypothesis for Laboratory Investigation

Hypothesis: A **multi-component phytochemical therapy** can achieve broader disease modulation than single agents, provided the combination is rationally optimized. Specifically, we propose that **Capsules A-E**, as constructed above, will each modulate distinct Alzheimer's pathways (amyloid, inflammation, redox, cholinergic, proteostasis) in cellular/animal models. Synergy among selected compounds will exceed single-agent effects on key biomarkers (A β , p-tau, cytokines, ROS, synaptic markers). Crucially, we hypothesize that careful formulation can avoid overt toxicity: each mixture will have an acceptable safety margin in vitro and in vivo (e.g. no severe cholinergic toxicity or liver injury at active doses).

This is a **testable laboratory hypothesis**. It frames the project as an experimental platform, not a finished nutraceutical. The success criteria are *demonstrated multi-target efficacy with defined PK exposure and safety*, leading to a clear go/no-go decision.

Brutally speaking: Mixing 100 ingredients at full-strength right away would be scientifically reckless. Our approach is to **winnow and validate**. If this hypothesis fails (as it often does with herbal "shotgun" therapies [14†L315-L317] [41†L474-L482]), we will have learned which targets were unreachable. If it succeeds, we have an optimized prototype worthy of further development.

Conclusion: We deliver here a fully referenced roadmap: Table 1 (the 100-compound matrix), the capsule formulations (rationale+warnings), a strategic timeline (Figure 1), and the central lab hypothesis. This equips researchers with a **concrete plan** to evaluate these plant molecules against Alzheimer's pathology. Further depth (e.g. expanded PK studies, metabolomics, network pharmacology simulations) can be added as the data accrue. In all, this is a **data-driven, candid blueprint**: ambitious yet grounded in current science [41†L474-L482] [23†L84-L88] .
