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Review Article

Natural Product-Inspired Multi-Target Directed Ligands for Alzheimer's Disease: Current Status, Design Strategies and Critical Translational Gaps

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ABSTRACT

Amyloid-β buildup, tau hyperphosphorylation, cholinergic dysfunction, oxidative stress, and neuroinflammation are some of the pathogenic pathways linked to Alzheimer's disease (AD), a progressive neurodegenerative condition. While disease-modifying therapies have few advantages and raise safety issues, current treatments mostly relieve symptoms. The necessity for treatment strategies that can concurrently target several disease-associated pathways is highlighted by the multifaceted character of AD. Because of their wide range of pharmacological effects, multi-target-directed ligands (MTDLs), especially those derived from natural products, have become attractive options. The potential of MTDLs inspired by natural products in the treatment of AD is examined in this review, with particular attention paid to their pharmacological characteristics, molecular design approaches, and translational difficulties. The cholinesterase-inhibitory, antioxidant, anti-inflammatory, and anti-amyloid properties of major natural product classes, such as alkaloids, flavonoids, curcuminoids, stilbenes, coumarins, and terpenoids, are reviewed. Additionally, representative hybrids made from curcumin, resveratrol, berberine, coumarin, and donepezil are used to investigate linked, fused, and merged pharmacophore methods. Additionally emphasised are the functions of network pharmacology, quantitative structure–activity relationship analysis, molecular docking, and molecular dynamics in MTDL development. Clinical translation is still difficult despite promising preclinical results because to low blood–brain barrier penetration, weak pharmacokinetic characteristics, uneven target potency, toxicity, and inadequate experimental validation. Crucially, no authorised natural product-inspired MTDL for AD was found in the examined literature, and the majority of reported NP-inspired MTDLs are still in the computational or preclinical stages. CNS drug-likeness, experimentally verified multi-target action, early safety evaluation,

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quantifiable brain exposure, and disease-relevant animal models should be given top priority in future research. All things considered, well-thought-out natural product-inspired MTDLs are a promising area of study; nonetheless, a systematic translational approach and more robust experimental validation are needed to fully realise their therapeutic promise.

INTRODUCTION –

The most frequent cause of dementia is Alzheimer's disease, an irreversible, progressive neurological illness .[1] According to global burden figures, the number of people with AD is expected to increase from 26.6 million in 2006 to approximately 107 million by 2050, making it one of the fastest-growing causes of death [2]. The histopathological features of AD include intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated tau, extracellular deposits of aggregated amyloid-β (Aβ) peptides, and loss of neurones and synapses [3] . Cholinergic failure, glutamatergic excitotoxicity, metal-ion dyshomeostasis, oxidative stress, autophagy dysfunction, neuroinflammation, and gut-microbiota-brain signalling have all been linked in addition to amyloid and tau [4] .

1.2 Current therapy's limitations

The NMDA-receptor antagonist memantine, the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and a fixed-dose donepezil–memantine combination that was licensed in 2014 are the only five alternatives available in the traditional symptomatic arsenal [5] . These medications alleviate symptoms but do not change how the illness progresses [6] . Since then, it has been demonstrated that decreasing amyloid can somewhat halt clinical decline with the anti-Aβ antibodies lecanemab [7] and donanemab [8] . However, their benefit is limited, and they pose a risk of amyloid-related imaging abnormalities. Aβ accumulation may be an initial factor rather than the only cause of disease, according to new clinical evidence that refines the original amyloid cascade concept [9] and shows that removing Aβ alone does not significantly enhance cognition [10] .

One-molecule, one-target to multiple-target-directed ligands

Cavalli, Melchiorre, and associates coined the phrase "multi-target-directed ligands" in 2008 to characterise substances that work well in complicated illnesses because they interact with many targets believed to be involved in pathogenesis [11 ,12] . Since then, the idea has developed into a continuum that falls under the broader category of "designed multiple ligands" [13] and extends from medication combinations to single hybrid molecules [14] . One molecule with the necessary functions or a combination of drugs can be used in polypharmacological treatment; the latter is known as the MTDL approach [15] .

Pharmacological and practical considerations support the use of a single multifunctional molecule as opposed to a mixture. A single chemical entity reduces total polypharmacy and associated adverse-effect burden, minimises drug-drug interactions between the components, and streamlines dosing, all of which can enhance adherence [16] . Combination therapy is constrained by poor compliance, interaction risk, dose-limiting toxicity, and complex pharmacokinetic/pharmacodynamic profiles, despite its synergy and possibility for lower dosages [17] [18] . Crucially, the MTDL benefit is contingent upon the molecule maintaining sufficient potency at each target and fulfilling the strict property requirements for exposure to the central nervous system (Section 5.5).

1.4 Why use natural products?

Galantamine, an alkaloid from the Amaryllidaceae family, and physostigmine from Physostigma venenosum, which served as the model for later cholinesterase inhibitors, are two examples of how NPs and their derivatives continue to be a significant source of authorised medications [19] [20] . Key brain enzymes and receptors are activated by alkaloids, flavonoids, terpenoids, and other phenolics; many of these compounds combine antioxidant, anti-inflammatory, anti-aggregation, metal-chelating, and cholinesterase-inhibitory activities in a single scaffold [2] [21]. Because they provide special structures with inherent polypharmacology and some have been specifically suggested as scaffolding for multi-target ligands, NPs are

therefore ideal places to start when designing MTDLs [22] [23].

The parent NPs, however, seldom make excellent clinical prospects. Many are promiscuous in assays, bioavailability and BBB penetration are low, and potency is frequently minimal. To overcome these limitations, "NP-inspired" MTDLs have been created that preserve, simplify, hybridise, or optimise an NP pharmacophore. The main topic of this review is whether they have truly solved them.

1.5 Extent

This narrative review: (i) describes the pathogenic network that guides target combinations; (ii) summarises late-stage multi-target agents and current therapy; (iii) surveys NP families used as MTDL templates; (iv) analyses design strategies; and (v) identifies critical translational gaps with a suggested roadmap.

2. The pathogenic network and logical choice of targets

The amyloid pathway –

β-secretase (BACE1) and γ-secretase sequentially cleave the amyloid precursor protein (APP) to produce 38–43 residue Aβ peptides. Aβ42 is the more fibrillogenic species and the primary constituent of plaques, whereas Aβ40 predominates in healthy individuals, accounting for around 5–15% of the pool [24] . According to the amyloid hypothesis, abnormal Aβ processing and the development of hazardous oligomers are linked to mutations in APP, PSEN1, and PSEN2 [4] [9] . For over ten years, BACE1, an aspartyl protease and the rate-limiting enzyme in amyloidogenic processing, has been targeted [25].

Tau pathway –

Under kinase/phosphatase regulation, tau stabilises microtubules; improper post-translational modification in AD causes aggregation into oligomers and NFTs [4] . Only the tau aggregation inhibitor TRx0237 made it to Phase 3, and tau-directed treatments have so far failed in clinical trials [4] .

cholinergic pathway –

According to the cholinergic theory, which was put forth by Bartus and associates in 1982 [26] , cognitive impairment is directly caused by the degeneration of basal forebrain cholinergic neurones and the decrease in acetylcholine synthesis [4] . AChE inhibition is still the mainstay of symptomatic treatment and a common anchor pharmacophore in MTDLs since decreased choline acetyltransferase activity decreases acetylcholine [27] .

calcium dysregulation and glutamatergic excitotoxicity –

When NMDA receptors are overstimulated, postsynaptic Ca2+ influx rises and downstream enzymes are activated, disrupting normal cellular function and promoting cell death [4] [27] . In AD, increased intracellular Ca2+ enters through L-type voltage-gated channels, disrupting calcium homeostasis, which is tightly regulated in healthy neurones. This leads to impaired synaptic function, mitochondrial disruption, inflammation, and activation of Ca2+-dependent kinases like protein kinase C and GSK-3β that promote NFT formation [28] . As a result, it has been suggested that MTDL design include calcium channel blockers (CCBs) [28] .

Metal ions, MAO, and oxidative stress –

Reactive oxygen species (ROS) are increased in AD due to mitochondrial dysfunction, glutathione depletion, and decreased antioxidant enzymes; Aβ buildup in mitochondria further increases ROS formation [4] . When amines are oxidatively deaminated by monoamine oxidase (MAO), $H2O_2$ is produced. When Fe2+ is present, this $H2O_2$ enters Fenton chemistry and produces harmful radicals [27] . Zn^{2+} binds Aβ's histidine residues and encourages oligomerisation, whilst Cu^{2+} and Fe^{3+} catalyse the production of hydroxyl radicals, connecting metal dyshomeostasis to oxidative damage and Aβ toxicity [4] [15] .

Neuroinflammation –

Aβ is first cleared by microglia, but prolonged exposure results in dysfunctional, pro-inflammatory cells that emit mediators such as TNF-α, IL-1β, and IL-6 [4] . A vicious loop is created when persistent stimulation leads to aberrant synaptic pruning and neuronal death [10] . NPs have been shown to inhibit cytokine release and microglial activation [21] , and treatments

that restrict tau hyperphosphorylation and Aβ accumulation while controlling neuroinflammation are thought to be especially promising MTDL candidates [29] .

The gut-brain axis and autophagy –

The microbiota–gut–brain axis connects gut microorganisms, immunological signalling, and the central nervous system [4] . Autophagy failure reduces Aβ clearance, increases intraneuronal tau accumulation, and increases neuroinflammation.

BBB and Vascular dysfunction –

BBB integrity supports synaptic and neuronal function and is dependent on vascular cell cooperation [30] . Certain tau species can cross the BBB in both directions, exacerbating barrier degradation, and BBB dysfunction interacts with tau disease by causing tau hyperphosphorylation [31] . As we revisit in Section 7, the BBB is the primary pharmacokinetic barrier to medication delivery.

Table None: (I). Pathogenic Theories and Related Therapeutic Targets

Hypothesis / pathway	Core mechanism	Representative targets for MTDL design	Refs
Amyloid cascade	APP → Aβ by BACE1/γ-secretase; Aβ42 oligomers and fibrils	BACE1, γ-secretase, Aβ aggregation	[4,9,24,25]
Tau	Hyperphosphorylation, NFT formation, microtubule destabilisation	GSK-3β, tau aggregation	[4]
Cholinergic	Loss of basal forebrain cholinergic neurons and ACh	AChE (catalytic and peripheral sites), BuChE	[4,26,27]
Glutamatergic / Ca^{2+}	NMDA over-activation, Ca^{2+} overload	NMDA receptor, L-type Ca^{2+} channels	[4,27,28]
Oxidative stress / MAO	ROS, mitochondrial dysfunction, MAO-derived H_2O_2	MAO-A/B, Nrf2, radical scavenging	[4]
Metal ions	Zn/Cu/Fe–Aβ binding, Fenton chemistry	Metal chelation	[4]
Neuroinflammation	Chronic microglial activation, cytokine release	NF-κB, NLRP3, TNF-α, IL-1β	[4,10,21,29]
Autophagy / gut–brain	Impaired clearance; dysbiosis	Autophagy regulators	[4]
BBB dysfunction	Barrier breakdown, altered Aβ/tau transport	Barrier-protective agents	[30,31]

3. Late-stage multi-target agents and current pharmacotherapy

3.1 Approved treatments

A highly selective, reversible, non-competitive AChE inhibitor with a lengthy half-life of 50–70 hours, donepezil is considered first-line therapy [6] Galantamine functions as a positive allosteric modulator of nicotinic receptors and reversible AChE inhibitor; in a three - year research including 280 patients, therapy was linked to cognitive scores declining more slowly than the anticipated drop in untreated patients [6] . The Amaryllidaceae alkaloid galantamine was initially isolated from the Caucasian snowdrop and subsequently from a number of related taxa [32,33] .

Table None: (Ii). AD Medications That Have Been Approved and Their Significance for Multi-Target Design.

Drug	Mechanism	Origin	Key notes	Refs
Donepezil	Selective, reversible AChE inhibitor	Synthetic	First-line; t½ 50–70 h; N-benzylpiperidine is a frequent MTDL anchor	[6,34]
Galantamine	Reversible AChE inhibitor + nicotinic allosteric modulator	Amaryllidaceae alkaloid	Dual mechanism; natural-product drug	[6,32,33]

Drug	Mechanism	Origin	Key notes	Refs
Rivastigmine	AChE and BuChE inhibitor	Physostigmine-derived carbamate	Transdermal patch reduces side effects	[6,34,35]
Memantine	NMDA-receptor antagonist	Synthetic	Low-micromolar IC_{50}; poor subtype selectivity	[5,34]
Memantine + donepezil (fixed-dose)	Combination of two mechanisms	Synthetic	Approved 2014 for moderate–severe AD	[5]
Lecanemab, donanemab	Anti-Aβ monoclonal antibodies	Biologic	Modest slowing of decline; ARIA risk	[7,8]

3.2 Multi - target ligands versus combination therapy

Single-molecule hybrids of the same pharmacophores are encouraged by the approval of a fixed-dose donepezil–memantine product [5] , which demonstrated the viability of merging two established mechanisms [36] . Strategies based on expertise (medicinal chemistry), biological screening, or virtual screening can produce polypharmacological ligands [6] . Additionally, it has been suggested that a ligand that targets multiple proteins is less susceptible to resistance resulting from a single active-site mutation [6] . This reasoning primarily stems from infectious diseases and cancer, and its applicability to AD is theoretical rather than proven.

3.3 Late-stage polypharmacological and multi-target candidates

Repurposed medications and fixed combinations are among the treatments with pleiotropic mechanisms that have advanced to Phase 3 [37] . Combinations like losartan, amlodipine, and atorvastatin may lower the incidence of AD, potentially through synergistic effects on vascular and cholesterol-related pathology, according to epidemiological and clinical-association research [37] . The agents listed in the primary literature are updated to October 2026 in Table (iii).

Table None: (Iii): Current Status and Reported Mechanism of Late-Stage Multi-Target / Polypharmacological Drugs.

Agent	Reported mechanism	Current status (Oct 2026)	Refs
Simufilam	Binds altered filamin A, restoring its interaction with receptors incl. α7 nAChR	Two Phase 3 trials (RETHINK-ALZ, REFOCUS-ALZ) missed co-primary cognitive and functional endpoints; AD programme discontinued in 2025	[37,38]
Blarcamesine (ANAVEX2-73)	Sigma-1 agonist/muscarinic modulator; effects on oxidative stress, misfolding, mitochondria, inflammation	EMA CHMP negative opinion (Dec 2025); applicant withdrew the marketing application on 25 Mar 2026	[37,39]
Valiltramiprosate (ALZ-801)	Blocks formation of neurotoxic soluble Aβ oligomers	Phase 3 APOLLOE4 (APOE4/4 homozygotes, n = 325) missed the primary ADAS-Cog13 endpoint in the overall population; nominal benefit reported in a prespecified MCI subgroup	[37,40]
AXS-05 (dextromethorphan–bupropion)	NMDA antagonist/sigma-1 agonist with CYP2D6 inhibition by bupropion	FDA approved (30 Apr 2026) for agitation associated with AD dementia	[36,41]
AVP-786 (d6-dextromethorphan/quinidine)	Sigma-1 agonist, NMDA antagonist; quinidine raises dextromethorphan exposure via CYP inhibition	Mixed Phase 3 results; Otsuka terminated development in May 2024	[37,42]

Agent	Reported mechanism	Current status (Oct 2026)	Refs
Nilotinib (BE formulation)	BCR-ABL and other kinase inhibition; enhanced autophagy and clearance of Aβ/tau	Phase 3 NILEAD registered (NCT05143528); no results located, registry record last updated in 2021	[37,43]

Here are two observations. First, while the disease-modifying multi-target prospects have failed or delayed, the single recent regulatory success in this group, AXS-05, addresses a neuropsychiatric symptom (agitation) instead of altering the disease. Second, none of the agents in Table 3 are hybrids developed from natural products; according to the literature reviewed here, NP-inspired MTDLs are still in the preclinical stage. The rest of the review focuses on this gap.

4. Families of natural products as MTDL models

Metabolites from plants, fungi, and marine organisms provide scaffolds with inherent polypharmacology. Commonly used medicinal herbs have components with AChE inhibition, antioxidant, anti-inflammatory, neuroprotective, and Aβ-modulating activity, according to several in vitro and in vivo investigations [2] . We classify the major families according to chemotype and indicate the translation-related evidence for each.

4.1 Alkaloids

A strong, short-acting, reversible AChE inhibitor is physostigmine, an indole (pyrroloindole) alkaloid from Physostigma venenosum. Isoquinoline alkaloids from Colchicum, Coptis, and Corydalis species inhibit AChE and BuChE in vitro, whereas rutaecarpine and dehydroevodiamine from Evodia rutaecarpa have been used as templates for novel AChE inhibitors [35] .

Huperzine A, The tetrameric (G4) form of AChE, which is predominant in the mammalian brain, is selectively inhibited by Huperzine A, which is derived from Huperzia serrata [44] . It is a natural dual-target drug since it is more powerful than tacrine, physostigmine, and galantamine on a per-concentration basis and also lessens glutamate-induced cytotoxicity through NMDA-receptor antagonism [45] . While meta-analyses of randomised trials report improvements in cognition, daily living, and global assessment [46] , with primarily mild and transient adverse effects [47] , a Phase II trial in mild-to-moderate AD showed a modest, dose-dependent signal rather than a clear sustained benefit [48] . The modest size and brief length of the underlying studies limit the conclusions drawn from these meta-analyses.

Berberine, by controlling kinases like GSK-3β, dampening NF-κB, TLR4, MAPK, and NLRP3 signaling, and activating Nrf2-dependent antioxidant defences, the isoquinoline alkaloid berberine from Coptis chinensis may reduce tau hyperphosphorylation [49]. In neuroinflammation models, it also affects autophagy, ferroptosis, gut microbiota, and microglial polarisation (M1→M2) [21] . A berberine derivative with metal-chelating and antioxidant activity, as well as significantly increased solubility and cell survival in comparison to the original, was produced via a straightforward chemical alteration that introduced free phenolic hydroxyls [49] . Although some of them lost their ability to inhibit AChE, berberine-benzenediol, -melatonin, and -ferulic acid conjugates were more antioxidant and stronger inhibitors of Aβ aggregation than berberine [50] , demonstrating a recurrent theme: acquiring one function by hybridization might corrode another.

4.2 Curcuminoids, stilbenes, and polyphenols

Numerous natural substances inhibit Aβ aggregation. Curcumin reduced soluble and insoluble Aβ and plaque burden in Tg2576 mice; resveratrol acts through BACE-1 inhibition, proteasomal degradation, and AMPK-driven autophagy; and flavonols like myricetin prevent the conformational switch to β-sheet [51] . EGCG, the main green-tea polyphenol, promotes the formation of unstructured, non-toxic Aβ aggregates. The unifying structural lesson is that Aβ can be redirected into non-toxic assemblies by binding at the β-sheet interface with tiny, planar molecules that can adopt an extended linear shape [51] . This view is supported by molecular-dynamics research on phenolics like okanin and rhapontigenin, which are anticipated to disturb the structure of Aβ fibrils and have better binding stability than apigenin [52] .

Resveratrol, the most popular stilbene template is resveratrol. It may help AD through effects on cognition, Aβ accumulation, BBB protection, mitochondrial function, tau stabilisation, oxidative stress, and neuroinflammation, according to a comprehensive review of systematic evidence [53] . In vitro and in vivo studies also support curcumin and resveratrol's anti-amyloidogenic properties [54] . Its low bioavailability and restricted BBB penetration have prompted the development of nanoparticle, liposomal, and prodrug formulations [16] , whereas the analogue pterostilbene has higher oral bioavailability and BBB permeability [31] . Preclinical effectiveness has been documented at moderate dosages (e.g., 10–20 mg/kg in a streptozotocin rat model), such as curcumin (50 mg/kg i.p. in mice), nobiletin, fisetin, and berberine [55] .

This hope is tempered by human testing. No clinical or biochemical effect was seen in a 24-week placebo-controlled study with curcumin (2 or 4 g/day), and the authors noted low bioavailability [56] . The compound and its metabolites were detectable in plasma and CSF during a 52-week resveratrol trial; Aβ40 levels decreased less in the resveratrol arm than in the placebo arm, but brain volume loss was higher with resveratrol [57] . The authors' safety and biomarker results serve as a reminder that target engagement in an assay does not guarantee benefit. MTDL potential is supported by in silico studies that show EGCG to be a powerful dual inhibitor of BACE1 and MAO-B [58] , but this is still computational.

4.3 Flavonoids –

Flavonoids are polyphenolic secondary metabolites that are frequently used in MTDL design because of their antioxidant, anti-inflammatory, AChE-inhibitory, anti-aggregation, MAO-inhibitory, and metal-chelating properties [36] . AChE, Aβ aggregation, and the AChE –Aβ interaction are inhibited by quercetin and apigenin, and suitably decorated flavonoids have been suggested as co-adjuvants or as components of multi-target compounds [59] . Didymin, a flavanone glycoside, decreases Aβ aggregation and inhibits BACE1 and cholinesterase [60] . 4′-OH improves flavonol activity while 4′-methylation decreases it, and 3′-O-methylation boosts antioxidant capacity, according to QSAR and in vitro research on BACE1; isorhamnetin and taxifolin appeared as moderate dual-activity scaffolds [61] . There have also been reports of curcumin and flavonoid derivatives developed in silico against AChE and BACE-1[44]. Sugar-bearing flavanones are more effective BACE1 inhibitors than aglycones, according to structure-activity studies, and hydrogen bonding to the catalytic aspartates Asp32 and Asp228 is crucial . Docking scores, as covered in Section 5.4, do not indicate activity, however flavonoids from Millettia brandisiana [62] and flavonoids rated by docking against AChE and BACE-1 [63] provide further in silico leads.

4.4 Coumarins

Numerous plants and fungi contain coumarins (2H-chromen-2-ones), and naturally inspired derivatives are being investigated against AChE, MAO, and, more recently, human carbonic anhydrase, a target for which acetazolamide has decreased Aβ accumulation and enhanced cognition in a transgenic mouse model [64] . Clinical-stage drugs like ensaculin and AP2469 combine anti-AChE, anti-aggregation, and radical-scavenging characteristics; coumarins bind the peripheral anionic site (PAS) of AChE through π–π stacking, suppress Aβ formation, and are well-established MAO inhibitors [65] . Naturally occurring fungal and plant metabolites with coumarin-like nuclei have been suggested as scaffolds for novel multi-target ligands [22] , and coumarin-linked heterocyclic hybrids have been examined as a broad MTDL platform [66] . In the Y-maze and Morris water maze tests, a coumarin–eugenol hybrid (LD • 300 mg/kg) enhanced memory in scopolamine-treated mice in a manner similar to that of conventional anti-AD medications [67] . Although the coumarin nucleus is tiny and lipophilic, which is sufficient for CNS penetration, hybrids may be forced outside Lipinski and Veber space [67] (Section 5.5) if large triazole, piperazine, or tacrine units are attached.

4.5 Glycosides, terpenoids, essential oils, and other sources

The broadest and most varied class of NPs used in AD research is terpenoids. Inula britannica's seco-eudesmane OABL is a powerful anti-inflammatory with significant BBB permeability; in 5xFAD mice, it

enhanced cognition, decreased plaque, Aβ, tau hyperphosphorylation, and BACE1 expression, and attenuated microglial and astrocytic activation [21] . Tectochrysin, verbascoside, and Schisandra chinensis essential oil mostly affect oxidative and inflammatory pathways [21] . Additional NP building blocks for hybrids include the hydroxycinnamic acids ferulic and caffeic acid, as well as α-lipoic acid, one of the few antioxidants that easily penetrate the brain [36] .

There is conflicting clinical data for complete NP products. Several natural compounds, such as sesame oil cake extract, saffron, and some citrus phytochemicals, were found to have cognitive benefits in people with MCI (improved verbal learning and lower plasma Aβ), but curcumin and Melissa officinalis showed limited benefits; inconsistent formulation and reporting prevented definitive conclusions, and mechanisms like autophagy and neurogenesis were understudied [68] . As demonstrated by tacrine-template MTDLs made from cashew nutshell liquid, a food waste stream, which provided sub-nanomolar, selective AChE/BuChE inhibition after prioritising hepatic, neuronal, and microglial toxicity, sustainable source is becoming a design focus [69] . In the extensive GEM study, the most extensively researched standardised product, ginkgo biloba extract, did not lower the risk of dementia [70] .

Table None: (iv). Lists Representative Natural Materials and Their Translational Status as MTDL Templates.

Natural product (class)	Multi-target profile reported	Main limitation / clinical status	Refs
Galantamine (alkaloid)	AChE inhibition + nicotinic allosteric modulation	Approved; symptomatic only	[6,32]
Huperzine A (alkaloid)	G4 AChE inhibition; NMDA antagonism	Phase II modest/dose-dependent; small meta-analyses	[47,71]
Berberine (alkaloid)	GSK-3β, NF-κB/NLRP3, Nrf2, autophagy, microbiota	Preclinical; translational barriers; hybridization may lower AChE activity	[21,48,50]
Resveratrol (stilbene)	Anti-Aβ, BACE-1, SIRT1/AMPK, antioxidant, anti-inflammatory	Low bioavailability/BBB; 52-week trial showed greater brain volume loss	[16,51,53,57]
Curcumin (curcuminoid)	Anti-Aβ aggregation, anti-inflammatory, metal chelation	No efficacy at 2–4 g/day in 24-week trial; bioavailability	[51,55,56]
EGCG (flavan-3-ol)	Aβ remodelling; BACE1/MAO-B (in silico)	Computational dual-target evidence	[51,58]
Quercetin, apigenin (flavonoids)	AChE, Aβ aggregation, AChE–Aβ interaction	In vitro/in silico evidence	[59,61]
Coumarins	AChE (PAS), MAO, Aβ, antioxidant	Hybrids often exceed CNS property limits	[65,67]
OABL (terpenoid)	Anti-inflammatory, BBB-permeable; anti-Aβ/tau in 5xFAD	Preclinical	[21]
Ginkgo biloba extract	Antioxidant, multi-modal	No dementia-prevention effect in GEM	[35,70]
Sesame, saffron, citrus extracts	Antioxidant, anti-aggregation	Small, heterogeneous trials	[68]

5. Design techniques for MTDLs inspired by natural products

5.1 Strategies for combining pharmacophores

In order to preserve the primary interaction and maintain compatibility with the second target, the fundamental design principle of an MTDL is to incorporate a second pharmacophore while maintaining the original activity of the first [17] . Depending on how much the pharmacophores overlap, three designs are typically identified: fused (directly attached), linked (joined by a linker), and merged (overlapping so that

both exploit shared structural features) [13] . According to a related classification that uses the terms linkage, fusion, and incorporation, incorporation (integration) is thought to be the optimal pathway to drug-like MTDLs because linkage and fusion expand the ligand and so tend to decrease BBB permeability and bioavailability [27] . There are two types of linked designs: cleavable linkers, which hydrolyse to release two distinct pharmacophores, and non-cleavable linkers, which maintain the hybrid intact in vivo [17] [18] .

Table None: (V) : MTDL Pharmacophore-Combination Methods.

Strategy	Definition	Preferred when	Advantages	Drawbacks	Refs
Linked, non-cleavable	Two pharmacophores joined by a metabolically stable linker	Binding regions are small and deep in the protein	Each pharmacophore keeps its original activity; modular, synthetically convenient	Larger, more lipophilic molecules; risk to BBB penetration and bioavailability	[17,18,27]
Linked, cleavable	Linker hydrolysed in vivo, releasing both pharmacophores	Targets are best engaged separately	Prodrug-like; each fragment can reach its own target	Becomes combination therapy in vivo; PK of fragments must be matched	[17,18]
Fused	Pharmacophores directly attached without a linker	Both targets have large binding sites	Smaller than linked hybrids; partial overlap	Requires compatible geometry; activity at one target may be lost	[17,27]
Merged / incorporated	Functional groups of lead compounds integrated into one scaffold	Binding sites are similar	Lowest molecular weight; best chance of CNS drug-likeness	Hardest to design; requires strong SAR and structural knowledge	[16,17,27]

5.2 Typical hybrids influenced by NP

Coumarin and tacrine have been mixed together several times. Click chemistry-prepared triazole-linked tacrine-coumarin hybrids demonstrated multifunctional activity against cholinesterases, MAOs, and Aβ aggregation [72] . An in silico campaign of 500 tacrine-coumarin hybrids, assessed by docking and protein-ligand interaction fingerprints against AChE, BuChE, and BACE-1, prioritised 34 ligands as synthetic candidates [73] . Methylene-linked tacrine-coumarin hybrids functioned as dual-site AChE inhibitors with activity against BuChE, Aβ aggregation, and BACE1 [74] . Natural analogues of memoquin, tacrine–caffeic acid hybrids that were effective metal chelators with antioxidant capacity (ORAC values of 2.75–9.37) higher than caffeic acid, and resveratrol-based MTDLs are examples of related coumarin-based study [75] . Coumarin–lipoic acid and coumarin–chalcone hybrids enhance antioxidant and additional enzymatic activity, while coumarin–dithiocarbamate hybrids take use of dual-site binding (coumarin at the PAS, dithiocarbamate at the catalytic site) [65] . Compound 12d, a lead based on caffeic acid, inhibited both AChE and BuChE with IC^{2}_{0} values of 3.72 ± 0.34 μM and 9.65 ± 0.08 μM, respectively [76] .

Stilbene hybrids demonstrate the variety of strategies: resveratrol–clioquinol hybrids inhibited self- and Cu (II)-induced Aβ aggregation, chelated metals, and demonstrated antioxidant capacity (ORAC-FL 0.9–3.2 Trolox equivalents) [77] ; tacrine–resveratrol fused hybrids inhibited human AChE at micromolar concentrations and modulated Aβ self-aggregation [78] . Tacrine's hepatotoxicity [27] , a known clinical side effect of the parent medication [79] , was the driving force behind tacrine–resveratrol hybrids.

The N-benzylpiperidine fragment, a crucial AChE pharmacophore with strong water solubility, serves as an anchor in donepezil-based hybrids. AChE inhibitors that were also metal chelators, antioxidants, and Aβ-aggregation inhibitors were produced by fusing donepezil with curcumin; the optimised compound was assessed in a PAMPA-BBB permeability assay [80] ; chalcone–vitamin E–donepezil hybrids were created for multifunctional potency and drug-like properties [81] ; and donepezil–arylsulfonamide hybrids sought to enhance AChE binding and prevent Aβ aggregation

[82] . Chalcone derivatives with a N-arylpiperazine [83] , indole-based agents with anti-neuroinflammatory activity [84] , BACE-1/Nrf2 dual agents [85] , and hybrids of curcumin analogues with cinnamic acid derivatives—all but one of which were mutagenic in the Ames test [86] —are additional NP-inspired chemotypes. A more comprehensive study of natural compounds and their derivatives as multifunctional ligands has been conducted [87] . All of these examples exhibit multi-target action in vitro, but balanced potency, BBB penetration, and in vivo efficacy in the same molecule are much less common. The clinical outcome of the early hybrid ladostigil (rivastigmine–rasagiline, a dual cholinesterase/MAO inhibitor) is instructive: memoquin, a flagship MTDL of the 2000s [11] , has not advanced to approval, and it failed clinical trials due to safety and efficacy concerns [66] .

Table None: (Vi) : Evidence for Representative MTDLs Inspired by NPs.

Hybrid / template	Targets reported	Key reported outcome	Caveat	Refs
Tacrine–coumarin (triazole, click)	ChE, MAO, Aβ aggregation	Compounds 17 and 18 multifunctional	In vitro; tacrine hepatotoxicity	[72,79]
Tacrine–coumarin (methylene linker)	AChE (dual-site), BuChE, Aβ, BACE1	Dual-site AChE inhibition	In vitro	[88]
Tacrine–coumarin (virtual library)	AChE, BuChE, BACE-1	34 of 500 designs with favourable docking	Computational only	[89]
Coumarin–dithiocarbamate	AChE (CAS + PAS), Aβ	Good-to-moderate anti-Aβ activity vs curcumin	Did not follow linker-length trends	[65]
Caffeic acid-based lead 12d	AChE, BuChE	IC_{50} 3.72 µM (AChE), 9.65 µM (BuChE)	Micromolar potency	[76]
Tacrine–caffeic acid	Antioxidant, metal chelation	ORAC 2.75–9.37, above caffeic acid	In vitro	[75]
Tacrine–resveratrol (fused)	hAChE, Aβ self-aggregation	Micromolar hAChE inhibition	In vitro	[90]
Resveratrol–clioquinol	Aβ aggregation, Cu(II), antioxidant	Strong anti-aggregation, chelation	In vitro	[77]
Resveratrol–maltol	$Aβ_{1–42}$, antioxidant, chelation	Triple function in vitro	In vitro	[78]
Donepezil–curcumin (fusion)	AChE, Aβ, chelation, antioxidant	Compound 11b tested in PAMPA-BBB	In vitro/permeability only	[80]
Chalcone–vitamin E–donepezil	Multifunctional	Designed for drug-like properties	Early stage	[81]
Donepezil–arylsulfonamide	AChE, Aβ aggregation	Improved AChE binding intended	Early stage	[82]
Berberine–benzenediol/melatonin/ferulic	Antioxidant, Aβ aggregation	Better than berberine on both	Some lost AChE inhibition	[50]
Curcumin analogue–cinnamic acid	Multiple AD targets	Multi-target in vitro	Ames-positive (all but 3d)	[86]
Coumarin–eugenol	Cognition (scopolamine model)	Y-maze/MWM improvement; LD_{50} 300 mg/kg	Mechanism not resolved	[67]

5.3 Recurring structure–activity correlations

NP-inspired MTDLs exhibit a number of recurring SAR patterns. A polar group on the aromatic moiety is necessary for AChE inhibition, which is dependent on spacer length [23] . Aβ40-aggregation inhibition in stilbenes is dependent on a meta-OH on ring A and a para-OH on ring B [23] . A strong electron-donating group (7-OCH_3) in coumarins favours activity against both AChE and BuChE, while electron-withdrawing replacement favours BuChE selectivity [65] , while substitution at C3/C4 modifies MAO selectivity [74] . A chlorine at position 6 in tacrine–resveratrol hybrids improves van der Waals interactions with hydrophobic residues in the AChE gorge and boosts efficacy in

comparison to tacrine [27] . For flavonoids, hydrogen bonding to Asp32/Asp228 is necessary, and 4′-OH and glycosylation promote BACE1 inhibition [61,91] . Although these guidelines are consistent, they have not been verified against brain exposure and were primarily developed from small series examined in biochemical experiments.

5.4 Computational and integrative research

Since it is very difficult, time-consuming, and costly to examine ligand-protein interactions experimentally in AD, in silico methods have become essential. They are classified as either structure-based drug design (docking and molecular dynamics) or ligand-based drug design (e.g., QSAR) [92] . Molecular dynamics to phenolic Aβ-fibril disruptors [52] , virtual screening with ADMET prediction, docking, and dynamic simulation to NP BACE1 inhibitors [25] , and docking to 59 selected phytochemicals revealed verazine-type alkaloids with anticipated dual-site (CAS–PAS) AChE binding similar to donepezil [93] . Experimental follow-up is less common: BACE1 was inhibited by lupeol and lupenone from Pueraria lobata, with IC^{2}_{0} values of 5.12 and 62.98 μmol/L, respectively, compared to 21.28 μmol/L for quercetin [94] . With 107 potential AD-related targets, a new integrative pipeline that integrated ligand fishing from turmeric by UHPLC-ESI-HRMS, molecular dynamics, SH-SY5Y cell tests, and network pharmacology confirmed binding of eight curcuminoids to $Aβ_{1–42}$ and protection against oligomer toxicity [95] .

Authors in the discipline are open about their limitations. Epicatechin demonstrated more persistent hydrogen bonding to AChE than donepezil in one dual-action phytochemical study; however, the authors presented (+)-boldine and epicatechin as candidates for additional validation rather than verified multi-target leads because dynamic validation was only carried out for AChE and two free-energy methods disagreed [96] . We reiterate that warning: a predicted dual-target profile for EGCG [58] or a docking score like −10.4 kcal/mol for epicatechin gallate at AChE [97] are hypotheses. At the very least, orthogonal biophysical or cellular proof of Aβ/tau regulation, counter-screens for assay interference, and enzymatic confirmation at each claimed target are necessary for credible MTDL claims (Section 7.4).

5.5 CNS property-guided design

MTDLs must meet more stringent physicochemical requirements than peripheral medications because AD is a CNS illness. Molecular weight should not be more than 430–450 Da, logP should be less than 4, and hydrogen-bond donor and acceptor counts should be low for CNS drugs; topological polar surface area (TPSA) should normally be less than 70 $Å^2$ logD at pH 7.4 below about 3, and pKa should be between 7 and 9 [16] . These trade-offs are formalised by surveys of CNS-drug properties [98] and multiparameter scoring systems like the CNS MPO method [99] , which align with the broader oral drug-likeness norms of Lipinski [100] and Veber [101] . All of them are simultaneously harmed by hybridisation. The Lipinski and Veber requirements are often violated when large triazole, piperazine, or tacrine units are attached to a small, CNS-compatible NP fragment like coumarin [67] . The design implication is that property filters should be used during the design phase rather than after potency has been established, and merged or included NP-inspired structures should be favoured over connected ones.

6. What is the current status of MTDLs inspired by NP? A ladder of evidence

Despite the identification of several MTDLs with intriguing in vitro and in vivo characteristics, none of them have been authorised for AD, indicating the significant obstacles that lie ahead [28] . The majority of the 126 ligands that were reported to be in AD clinical trials in 2021 (82.5%) focused on disease biology, with the remaining ligands targeting neuropsychiatric symptoms (7.1%) or improving cognition (10.3%) [27] . Annual pipeline analyses reveal that synthetic small molecules, biologics, and repurposed agents continue to dominate the pipeline [102] . In late-stage development, NP-inspired MTDLs are virtually nonexistent.

Placing the data produced for a typical NP-inspired MTDL on a ladder of increasing translational stringency is a useful method to understand. Only the lowest rungs are reached by the majority of compounds in Table (vi).

Table None: (Vii) Shows the Evidence Ladder for MTDLs Inspired by NPs and the End of the Available Data.

Rung	Evidence required	Typical status in the literature reviewed	Refs
1	In silico prediction (docking, QSAR, MD, network pharmacology)	Very common; frequently the only evidence offered	[25,73,93,95,97]
2	Enzymatic or biophysical confirmation at each claimed target	Common, usually at micromolar potency	[65,74,75,88]
3	Cell-based neuroprotection and counter-screens	Sometimes; interference and toxicity checks rarely complete	[72,86]
4	BBB permeability (PAMPA or cell model) and measured brain exposure	PAMPA in a minority; measured brain exposure rare	[80]
5	Efficacy in disease-relevant animal models	Mostly symptomatic (scopolamine) models; transgenic data mainly for parent NPs	[21,67]
6	Formal safety and toxicology	Sparse (e.g. a single LD_{50}); some hybrids Ames-positive	[67,86]
7	Human target engagement and biomarkers	Largely limited to parent NPs (resveratrol, curcumin)	[56,57]
8	Randomised clinical efficacy	Parent NPs only, with negative or inconclusive results	[10,45,56]

7. Important translational gaps

7.1 BBB penetration and expansion of molecular properties

There are several difficulties because of the BBB's thick structure. Approximately 98% of small-molecule medications, including curcumin, are unable to pass through the barrier due to inadequate lipophilicity or excessive molecular weight; compounds that do pass through are actively eliminated by efflux pumps; increasing the systemic dose to compensate runs the risk of peripheral toxicity, such as gastrointestinal reactions or liver damage [10] . The practice of adding big heterocycles to tiny NP fragments results in molecules beyond Lipinski and Veber space [67] , and hybridisation by linkage or fusion enlarges the ligand and degrades precisely the qualities that dictate brain exposure [27] . Permeability evaluated in healthy-barrier models may not accurately predict exposure in patients because tau pathology in AD is bidirectionally related to reduced BBB integrity [30,31] . Although they increase formulation complexity and regulatory load, delivery-side treatments such as nanoplatforms for brain-targeted co-delivery of phytochemicals [10] , nanoparticle formulations that boost brain concentrations of resveratrol [16] , and NP modulation of BBB function [31] are being investigated.

7.2 Parent natural products' poor pharmacokinetics

MTDLs are frequently inspired by pharmacophores that have failed in humans due to pharmacokinetic issues. Resveratrol has low bioavailability and limited BBB penetration [16] , and while it and its metabolites were detected in plasma and CSF in a 52-week trial, the biomarker and imaging signals were unfavourable [57] . Curcumin demonstrated no efficacy in a 24-week trial, and the authors cited limited bioavailability [56] . Medicinal chemistry can be helpful in improving permeability and oral bioavailability, as demonstrated by structural analogues like pterostilbene [31] . However, a hybrid based on a poorly absorbed NP inherits the issue unless it is specifically engineered out. Furthermore, it is impossible to draw clear conclusions due to formulation and reporting variation across NP trials [68] .

7.3 Balanced potency, synergy, and target selection

Developing an appropriate pharmacokinetic and toxicological profile and determining the best combination of targets and their compatibility to elicit synergy are the two main difficulties in medicinal chemistry [28] . Rarely is synergy shown; most research indicate that a hybrid maintains some activity at each target, not that engaging them jointly is preferable to engaging them

separately. Additionally, a developed multiple ligand must have balanced potency, with each target's actions falling within a brain-achievable exposure window [13] . Since many of the NP-inspired hybrids in Table 6 exhibit low micromolar activity at one target and weaker activity at others, therapeutic brain concentrations would need to be unreasonably high in order to engage all targets at once.

Additionally, the selection of targets is ambiguous. Simufilam, blarcamesine, valiltramiprosate, and AVP-786 have recently failed in Table 3, demonstrating that multi-target mechanisms are not immune to the issue [40] [42] . Clearing Aβ alone has not significantly improved cognition [10] , and tau-directed agents have so far failed, with only TRx0237 reaching Phase 3 [4] . It is made worse by patient heterogeneity: target combinations that make sense on average could not be meaningful for specific individuals because various mechanisms predominate in different patients [3] . The data already show genotype-defined subgroups, such as SIGMAR1 status in the blarcamesine review [39] and APOE4/4 homozygotes in the valiltramiprosate trial [40] .

7.4 Promiscuity, assay interference, and overinterpretation of calculations

Numerous NP templates are polyphenols, catechols, or enones that often show up as hits in biochemical and biophysical tests for reasons unrelated to target engagement. These pan-assay interference chemicals (PAINS) are widely known [103] , and curcumin in particular has been studied as an example where apparent efficacy is compromised by chemical instability and reactivity [104] . The likelihood of false positives increases since MTDLs are purposefully assessed across numerous assays. A second source of overinterpretation is introduced by computation: anticipated dual-target profiles [58,95] , docking scores, and conflicting free-energy estimations are not indicators of function. Before a drug is classified as a multi-target lead, the field would benefit from implementing a common minimum dataset (orthogonal assays, aggregation/redox counter-screens, compound-identity and purity data).

7.5 Toxicology and safety

Tacrine, a common MTDL template, is hepatotoxic [27] , a risk that has been clinically established [79] . Unless the hybridisation clearly reduces it, it is a concerning anchor for novel hybrids. The Ames test has shown that a number of hybrids constructed from NP motifs are mutagenic [86] , and toxicological information for NP hybrids is usually restricted to a single acute LD_{50} value [67] . Even natural products are not inherently safe: curcumin caused gastrointestinal withdrawals in a trial [56] , resveratrol caused nausea, diarrhoea, and weight loss [57] , and ginkgo biloba extract EGb 761 can cause a disulfiram-like reaction with alcohol [21] . The cashew-nutshell-liquid program's early hepatic, neuronal, and microglial toxicity filtration [69] should be the norm.

7.6 Clinical trial design and preclinical models

While the more disease-relevant transgenic models (such as 5xFAD mice) have primarily been utilised for parent NPs [21] , the majority of NP-MTDL efficacy claims rely on scopolamine-induced amnesia, which simulates cholinergic symptoms but not progressive neurodegeneration [67] . NP product clinical trials are brief, modest, and include a variety of formulations [46,68] . Regulations are strict: the valiltramiprosate trial missed its primary endpoint with benefit limited to a prespecified subgroup [40] , and the EMA concluded that the main blarcamesine study failed to demonstrate efficacy and raised concerns about methodological issues, subgroup analysis, and tolerability [39] . AXS-05, the only recent clearance, used a four-trial design to treat a symptom domain [41] . A symptom-only main endpoint may underestimate the predicted disease-modifying benefit for a multi-target mechanism, whereas a disease-modification claim necessitates lengthier, stratified, biomarker-supported studies.

7.7 Manufacturing, standardization, and supply

While the complete synthesis of structurally complicated NPs, such as galantamine, has required significant synthetic effort [32] , natural source raises issues about batch variability and standardization [68] . A prospective countertrend is the use of sustainable chemical techniques that produce MTDL scaffolds from plentiful waste streams [69] .

Table 8: Strategies for Mitigating Translational Gaps.

Gap	Evidence from the literature reviewed	Proposed mitigation	Refs
BBB penetration, molecular-weight inflation	~98% of small molecules fail to cross; hybrids exceed Lipinski/Veber	Merged/incorporated designs; CNS MPO gating; nanocarriers; prodrug (cleavable) linkers	[10,17,27,67]
Poor parent-NP pharmacokinetics	Curcumin and resveratrol trials negative or unfavourable	Select analogues with proven exposure (e.g. pterostilbene); measure brain/CSF levels early	[16,31,56]
Unproven synergy; unbalanced potency	Micromolar potency at some targets only	Demonstrate synergy versus single-target controls; match potencies to exposure	[13,28]
Assay interference; over-reliance on docking	PAINS-type chemotypes; discordant free-energy methods	Orthogonal assays, counter-screens, experimental validation at every target	[103,104]
Safety liabilities	Tacrine hepatotoxicity; Ames-positive hybrids	Early toxicity panels; avoid liability-bearing anchors	[27,69,79,105]
Weak models and trial design	Scopolamine models; small NP trials; failed multi-target Phase 3s	Transgenic and complementary models; biomarker-stratified, adequately powered trials	[68]
Supply and standardization	Batch variability; complex total syntheses	Standardised extracts/reference materials; sustainable sourcing	[68]

8. Prospects for the future: a phased translational pathway

In order to reduce translational risk early and affordably, we suggest that NP-inspired MTDL programs implement explicit stage-gates.

1. Use property constraints when designing. Apply CNS MPO and physicochemical windows prior to potency optimisation, and favour combined or integrated designs [16,17] [27] .
2. Specify the potency window and target set. Use single-target comparators to test for synergy, establish target-specific potency requirements based on anticipated brain exposure, and support each target with a pathogenic hypothesis [13] [28] . Calcium handling [28] , human carbonic anhydrase (64) , Nrf2 [80] , and autophagy [4] are understudied but mechanistically appealing nodes.
3. Retire toxicity and interference hazards. Use orthogonal tests, PAINS and reactivity filters, and early genotoxicity/hepatotoxicity screens [86,104] [103] .
4. Show that you were exposed. Consider delivery-enabled strategies for lead series that would normally achieve potency targets, and go beyond PAMPA to measured brain and CSF concentrations [10,80] .
5. Use complementary models for testing. Report poor outcomes by combining transgenic or disease-modifying models with symptomatic models [21,67] .
6. Measure and stratify. Plan trial endpoints that represent a multi-target mechanism and make use of genotype and biomarker enrichment [3,39,40] .
7. Adhere to a standard. To enable comparison and pooling of data, document extract composition, formulation, and compound identity [68] .

CONCLUSION

The multifactorial biology of AD necessitates an MTDL strategy, and natural products provide chemically rich, polypharmacological starting points. Hybrids of tacrine, donepezil, coumarin, resveratrol, curcumin, berberine, and flavonoid scaffolds with impressive multi-target action in vitro are currently described in a vast and inventive body of research. However, no NP-inspired MTDL has been approved, and repurposed synthetics—many of which have recently failed—populate the late-stage multi-target pipeline. Molecular-weight inflation against the BBB,

parent compounds with poor pharmacokinetics, unbalanced potencies, assay artefacts and unvalidated computation, safety liabilities, and clinical programs poorly matched to a multi-target mechanism are all factors that contribute to the explanation, rather than the multi-target concept itself. Stage-gated, property-first design, thorough exposure and safety data, and biomarker-guided trials are necessary to close these gaps. NP-inspired MTDLs continue to be one of the most logical approaches to Alzheimer's disease disease-modifying therapy assuming.

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