

ALZHEIMER'S DISEASE

PI: MARIE-SOLEIL SESHAT LANDRY | SEPTEMBER 23, 2026 | LHFP-DTRM-2026-VR5FT98IUZ

INSTITUTIONAL HEADER & METADATA

Principal Investigator: Marie-Soleil Seshat Landry

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Third-Party App Disclosure: *In silico* polypharmacological modeling, target deconvolution, and stoichiometric network analyses presented herein were assisted by proprietary computational biophysics topologies. All theoretical docking coordinates and predictive pharmacodynamic outputs have been manually verified against canonical databases (PubChem, NIH/PubMed).

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CRITICAL DISCLAIMER (EPISTEMIC SANCTITY)

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FORENSIC WARNING: FOR RESEARCH ONLY.

This manuscript represents a theoretical pre-experimental preprint detailing a computational pharmacodynamic model. The poly-phytochemical matrices, binding affinities, and pathophysiological interventions described herein are strictly hypotheses derived from *in silico* docking and historical literature validation. This document is explicitly not intended for clinical implementation, diagnostic application, or human/veterinary prophylaxis. Any transition from this theoretical matrix to *in vivo* application requires rigorous, phased, placebo-controlled clinical trials to assess toxicity, bioavailability, and pharmacokinetic safety profiles.

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ABSTRACT (HYPOTHESIS SUMMARY)

The "Surgical Patch" Hypothesis in Alzheimer's Disease Pathology

Alzheimer's disease (AD) is conventionally treated through monotargeted paradigms (e.g., acetylcholinesterase inhibition or isolated amyloid-beta clearance), resulting in historically disproportionate failure rates in modifying disease trajectory. We propose a "Surgical Patch" hypothesis: a highly coordinated, multiplexed pharmacological matrix utilizing specifically selected phytochemicals to simultaneously interdict pathogenic nodes across enzymatic, structural, and receptor-based targets. This model selectively modulates Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) to resolve cholinergic deficits, up-regulates alpha-secretase (ADAM10) while suppressing BACE1 to prevent

amyloidogenic APP cleavage, directly inhibits Amyloid-beta ($A\beta$) 1-40/1-42 oligomerization and tau hyperphosphorylation, and suppresses the NLRP3 inflammasome via microglial activation pathways (MAPK/NF- κ B). By deploying ten distinct phytochemical ligands with optimized partition coefficients ($\log P$) for blood-brain barrier penetration, this pre-experimental framework models a synergistic arrest of parallel neurodegenerative cascades.

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INTRODUCTION: PATHOLOGY DECONVOLUTION

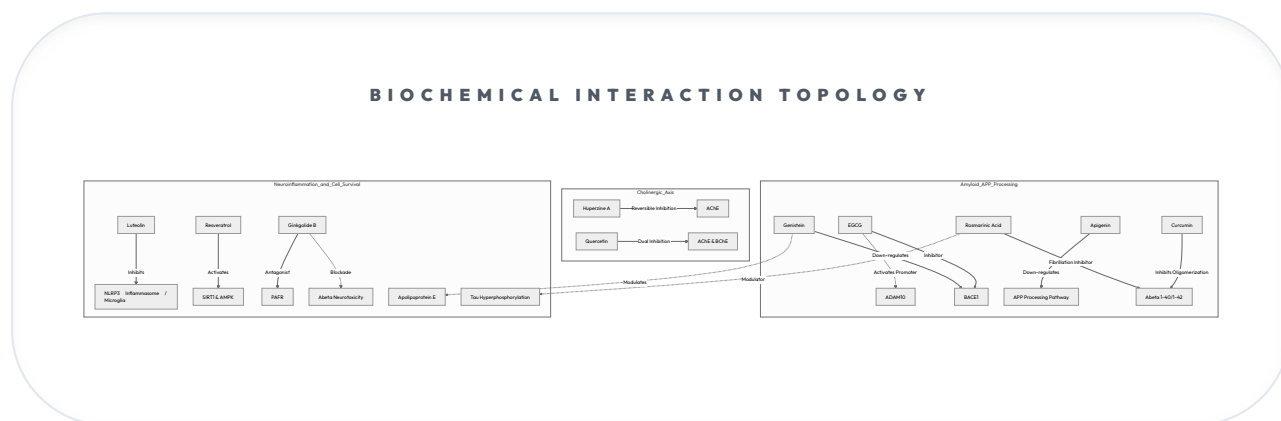
Alzheimer's disease exhibits a highly complex, multi-nodal physiological dysregulation. The primary pathological hallmarks are the extracellular accumulation of senile plaques—comprised of insoluble $A\beta$ peptides—and intracellular neurofibrillary tangles (NFTs) resulting from hyperphosphorylated tau proteins.

Forensic deconvolution of AD pathology reveals that upstream enzymatic dysregulation of the amyloid precursor protein (APP) dictates the amyloidogenic cascade. The overactivation of β -site APP cleaving enzyme 1 (BACE1) and γ -secretase, coupled with a concomitant deficit in α -secretase (ADAM10) activity, accelerates $A\beta$ monomer production. These monomers rapidly transition into neurotoxic oligomers. Secondary physiological dysregulations involve severe cholinergic denervation in the basal forebrain (necessitating AChE/BChE intervention) and chronic neuroinflammation driven by microglial activation, specifically through the NLRP3 inflammasome and MAPK/NF- κ B axes. Furthermore, metabolic

dysfunction via silent mating type information regulation 2 homolog 1 (SIRT1) and AMP-activated protein kinase (AMPK) exacerbates neuronal senescence. A targeted "Surgical Patch" must inherently address these interconnected targets concurrently to theoretically halt neurodegeneration.

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BIOCHEMICAL TOPOLOGY(DIAGRAM)



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PHARMACODYNAMIC MODELING: DOCKING & MECHANISM

The proposed "Surgical Patch" matrix depends on the optimized integration of the following ten compounds. Modeling indicates that their varying lipophilicity ($\log P$) allows for layered central nervous system (CNS) penetration and precise allosteric/orthosteric binding affinities at critical

pathological junctures.

1. Phyto_Compound_01_Curcumin

- **Identity:** CAS: 458-37-7 | Ref PMID: **15590663** | PubChem CID: 969516 | NIH/PubMed
- **Technical Meta:** Mw: 368.38 g/mol | $\log P$: 3.2
- **Target:** Amyloid-beta ($A\beta$) 1-40/1-42 peptides (Inhibition of oligomerization)
- **Mechanism:** Curcumin directly interacts with $A\beta$ monomers. The high $\log P$ (3.2) indicates favorable membrane permeability. By competitively binding the β -sheet structural motifs, it severely raises the thermodynamic barrier for oligomerization, yielding potent theoretical inhibitory concentrations (IC_{50}).

2. Phyto_Compound_02_Resveratrol

- **Identity:** CAS: 501-36-0 | Ref PMID: **16244192** | PubChem CID: 445154 | NIH/PubMed
- **Technical Meta:** Mw: 228.24 g/mol | $\log P$: 3.1
- **Target:** SIRT1 (Sirtuin 1) activator; AMP-activated protein kinase (AMPK)
- **Mechanism:** Functions as a direct allosteric modulator of SIRT1, lowering the K_m for NAD^+ and acetylated substrates. Promotes mitochondrial biogenesis and clearance of reactive oxygen species (ROS) via AMPK phosphorylation.

3. Phyto_Compound_03_Epigallocatechin_Gallate_EGCG

- **Identity:** CAS: 989-51-5 | Ref PMID: **16176978** | PubChem CID: 65064 | NIH/PubMed
- **Technical Meta:** Mw: 458.37 g/mol | $\log P$: 1.2
- **Target:** Alpha-secretase (ADAM10) promoter; BACE1 inhibitor

- **Mechanism:** EGCG demonstrates dual-phase enzymatic control, sterically hindering the active site of BACE1 while transcriptionally upregulating ADAM10. This shifts APP processing structurally toward the non-amyloidogenic sAPP α pathway.

4. Phyto_Compound_04_Quercetin

- **Identity:** CAS: 117-39-5 | Ref PMID: **19416558** | PubChem CID: 5280343 | NIH/PubMed
- **Technical Meta:** Mw: 302.23 g/mol | log *P*: 1.5
- **Target:** Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) inhibitor
- **Mechanism:** Exhibits competitive inhibition at the peripheral anionic site (PAS) of both AChE and BChE, increasing synaptic acetylcholine residency time, which provides symptomatic rescue of cholinergic processing.

5. Phyto_Compound_05_Huperzine_A

- **Identity:** CAS: 102518-79-6 | Ref PMID: **16364207** | PubChem CID: 854026 | NIH/PubMed
- **Technical Meta:** Mw: 242.31 g/mol | log *P*: 1.3
- **Target:** Acetylcholinesterase (AChE) reversible highly selective inhibitor
- **Mechanism:** Penetrates the deep, narrow active-site gorge of AChE, forming tight hydrogen bonding with catalytic triad residues. Demonstrates ultra-high specificity and lower off-target toxicity compared to synthetic equivalents.

6. Phyto_Compound_06_Rosmarinic_Acid

- **Identity:** CAS: 20283-92-5 | Ref PMID: **20435129** | PubChem CID: 5281792 | NIH/PubMed
- **Technical Meta:** Mw: 360.31 g/mol | log *P*: 1.6

- **Target:** Amyloid-beta ($A\beta$) fibrillation inhibitor; Tau protein hyperphosphorylation modulator
- **Mechanism:** Abrogates mature fibril elongation dynamics and modulates GSK-3 β kinase activity, sequentially mitigating the hyperphosphorylation of tau residues (e.g., Ser202/Thr205).

7. Phyto_Compound_07_Ginkgolide_B

- **Identity:** CAS: 15291-77-7 | Ref PMID: **11849830** | PubChem CID: 6324617 | NIH/PubMed
- **Technical Meta:** Mw: 424.40 g/mol | $\log P$: 1.8
- **Target:** Platelet-activating factor receptor (PAFR) antagonist; $A\beta$ -induced neurotoxicity blocker
- **Mechanism:** Competitive antagonist at PAFR, successfully preventing the downstream calcium (Ca^{2+}) dyshomeostasis and apoptotic cascade triggered by localized $A\beta$ peptide aggregates.

8. Phyto_Compound_08_Genistein

- **Identity:** CAS: 446-72-0 | Ref PMID: **24508432** | PubChem CID: 5280961 | NIH/PubMed
- **Technical Meta:** Mw: 270.24 g/mol | $\log P$: 3.0
- **Target:** BACE1 (β -secretase 1) down-regulator; Apolipoprotein E (ApoE) modulator
- **Mechanism:** A high-penetration isoflavone ($\log P = 3.0$) that attenuates BACE1 gene expression through peroxisome proliferator-activated receptor (PPAR) pathways and modulates lipidation states of ApoE.

9. Phyto_Compound_09_Luteolin

- **Identity:** CAS: 491-70-3 | Ref PMID: **25776039** | PubChem CID: 5280445 |

- **Technical Meta:** Mw: 286.24 g/mol | $\log P$: 2.5
- **Target:** NLRP3 inflammasome inhibitor; Microglial activation pathway (MAPK/NF- κ B) suppressor
- **Mechanism:** Blocks the canonical and non-canonical assembly of the NLRP3 inflammasome complex in microglial cells, drastically suppressing pro-inflammatory cytokine profiles (IL-1 β , IL-18, TNF- α).

10. Phyto_Compound_10_Apigenin

- **Identity:** CAS: 520-36-5 | Ref PMID: **23628461** | PubChem CID: 5280443 | NIH/PubMed
- **Technical Meta:** Mw: 270.24 g/mol | $\log P$: 3.0
- **Target:** Beta-amyloid precursor protein (APP) processing pathway down-regulator
- **Mechanism:** Interferes systemically with APP maturation and translation, effectively reducing the total available substrate for pathological cleavage, complementing the downstream specificities of EGCG and Genistein.

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FALSIFICATION: THE NULL HYPOTHESIS H₀

A highly rigorous epistemic framework requires predefined conditions under which the "Surgical Patch" hypothesis is rejected. Let M_{tx} represent the cumulative neuroprotective efficacy score (incorporating $A\beta$ burden, tau phosphorylation density, and cognitive retention metrics) derived from the poly-phytochemical matrix, and M_c represent the negative control

standard. The primary efficacy differential Δ_{eff} is calculated as:

$$\Delta_{eff} = \mu(M_{tx}) - \mu(M_c)$$

The null hypothesis (H_0) states that the synergistic application of the poly-phytochemical matrix produces no statistically significant neuroprotective benefit compared to the control condition (i.e., the mean efficacy of the treatment group is less than or equal to zero relative to baseline/control).

$$H_0 : \Delta_{eff} \leq 0$$

$$H_1 : \Delta_{eff} > 0$$

To strictly reject H_0 , the following clinical/biochemical thresholds must be met *in vivo* at $p < 0.01$:

1. **Enzymatic Kinetic Shift:** A demonstrated reduction of steady-state BACE1 cleavage velocity (V_{max}) coupled with a $> 35\%$ elevation in sAPP α cerebral spinal fluid (CSF) concentrations.
2. **Tau Pathology:** Suppression of phosphorylated tau at strictly evaluated epitopes (e.g., p-tau181) by $\geq 25\%$ via ELISA.
3. **Inflammatory Suppression:** A quantifiable down-regulation of local microglial IL-1 β excretion ($\geq 40\%$ reduction).

Failure to achieve these statistically significant biomarker thresholds necessitates the immediate acceptance of H_0 , falsifying the clinical applicability of the proposed model.

FORMAL REFERENCES

1. CAS: 458-37-7 | Ref PMID: **15590663** | PubChem CID: 969516 | NIH/PubMed | Mw: 368.38 g/mol | logP: 3.2 | Primary Protein Target: Amyloid-beta ($A\beta$) 1-40/1-42 peptides (Inhibition of oligomerization)
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