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"QUANTIFYING POLY PHARMACOLOGY: SCORING FUNCTIONS AND COMPOSITE INDICES FOR AD MTDLS"

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Abstract:
Alzheimer's disease (AD) is a complex, multifactorial neurodegenerative disorder characterized by amyloid-β aggregation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, and neuroinflammation. The failure of single-target therapies has shifted attention toward multi-target directed ligands (MTDLs), which aim to modulate multiple pathological pathways simultaneously. A critical challenge in developing and evaluating MTDLs lies in quantifying their degree of polypharmacology—how effectively a compound engages multiple targets with therapeutic relevance. Scoring functions and composite indices have emerged as promising approaches to measure and compare polypharmacological profiles. These methods integrate binding affinity data, pharmacokinetic parameters, and network-based interactions into numerical descriptors that capture both the breadth and balance of target modulation. Computational scoring functions, such as docking-based affinity predictions and machine learning models, allow rapid in silico assessment of polypharmacological potential. Meanwhile, composite indices combine multiple criteria—efficacy, selectivity, drug-likeness, and safety—to provide holistic evaluations of candidate molecules. In the context of AD, such metrics can guide the rational design and prioritization of MTDLs targeting cholinesterases, NMDA receptors, monoamine oxidases, and amyloidogenic proteins. Furthermore, polypharmacology scoring can help predict off-target liabilities and optimize therapeutic windows. This review highlights the methodological advances in quantifying polypharmacology, discusses their application in AD drug discovery, and proposes future perspectives on integrating systems biology, network pharmacology, and artificial intelligence for more precise evaluation of MTDLs. By refining these scoring strategies, researchers can accelerate the identification of safe and effective multi-target therapeutics, offering renewed hope in the battle against Alzheimer's disease.

Keywords: Alzheimer's disease, multi-target directed ligands (MTDLs), Polypharmacology, Scoring functions, Composite indices, Network pharmacology, Drug discovery, Computational modeling, Neurodegeneration, Artificial intelligence

Introduction:

1. Alzheimer's Disease as a multifactorial neurodegenerative disorder:

1.1 Definition & overview:

Alzheimer's disease is the most common cause of dementia, accounting for 60%-80% of cases.
It is progressive and irreversible, leading to cognitive decline, memory loss, and behavioral changes.
AD is considered multifactorial because it arises from a combination of genetics, environmental, and lifestyle factors, rather than a single case. (1)

1.2 Key Pathological Features:

- **Amyloid-beta plaques:**

Origin: these plaques form when a protein called amyloid precursor protein (APP) is abnormally cleaved by enzymes called beta-secretase and gemma-secretase.
Aggregation: these peptides are sticky and tend to clump together outside neurons, forming insoluble plaques in the brain.
Location: plaques typically start accumulating in the neocortex and eventually spread to deeper brain regions like the hippocampus. (2)

- **Neurofibrillary tangles:**

Composition: NFTs are twisted made up of a protein called tau, which normally helps stabilize microtubes inside neurons.
Pathology: In Alzheimer's tau becomes hyperphosphorylated - meaning chemically altered in a way that causes it to detach from microtubes and clamp together into insoluble filaments.
Location: These tangles from inside neurons, especially in areas critical for memory and cognition like the hippocampus and cerebral cortex. (3,4)

- **Chronic neuroinflammation:**

Amyloid-beta plaques and tau tangles act as irritants, activating the brain's immune cells.
Microglia (the brain's resident immune cell) becomes overactive and releases pro-inflammatory cytokines.
Astrocytes also contribute by amplifying the inflammatory signals.
Peripheral immune cells (like T cells and monocytes) may infiltrate the brain due to leaky blood-brain barriers, worsening the inflammation. (5,6)

- **Synaptic dysfunction:**

Synapses are the junctions were neurons exchanges information via neurotransmitters.
In AD, these synapses lose their structural integrity and functional efficiency, leading to impairment to impaired signal transmission.
This dysfunction precedes neuronal death, making it a critical early target for understanding and treating Alzheimer's. (7)

1.3 Multifactorial Etiology:

- **Genetic factors:**

APOE e4 allele: strongest known genetic risk factor.
Other genes involved in proteostasis, lipid metabolism, and immune response also play roles.

- **Molecular & cellular mechanisms:**

Oxidative stress**,** mitochondrial dysfunction, and impaired autophagy contribute to neuronal damage.(7)
Imbalance in neurotransmitters like acetylcholine and glutamate affects cognition.

- **Environmental & Lifestyle Factors:**

Diet, physical activity, education level, and social engagement influence risk.
Exposure to toxins, head trauma, and vascular issues also contribute. (8,9)

2. Limitations of single-target drug design in AD treatment:

Single-target drug design in Alzheimer's disease (AD) treatment has faced significant limitations, largely because AD is a multifactorial disorder—not driven by a single cause, but by a complex interplay of genetic, molecular, and environmental factors.(10)

- Limitations of single-target drug design in AD: [11,12]

A. Oversimplification of Disease Mechanisms

AD involves **multiple pathological processes**: amyloid-β accumulation, tau hyperphosphorylation, neuroinflammation, oxidative stress, synaptic dysfunction, and vascular issues.

Targeting just one pathway (e.g., amyloid-β) ignores the **interconnected nature** of these mechanisms.

B. **Limited Clinical Efficacy**

Drugs like **Aducanumab** and **Lecanemab**, which target amyloid-β, have shown **modest cognitive benefits** at best.

Many single-target drugs fail in **late-stage clinical trials**, despite promising early results.

C. Disease Heterogeneity

AD patients differ in **genetic background**, **biomarker profiles**, and **disease progression**.

A drug that works for one subgroup may be **ineffective or harmful** for others.

D. Timing Sensitivity

Single-target drugs often work best in **early stages**, but AD is usually diagnosed **after significant damage** has occurred.

Once tau tangles and neuroinflammation are established, targeting amyloid alone may be **too late**.

E. Compensatory Mechanisms

The brain can **adapt or compensate** when one pathway is blocked.

This can lead to **drug resistance** or activation of alternative harmful pathways.

F. Side Effects and Safety Concerns

High specificity can lead to **off-target effects** or **immune reactions**, especially with monoclonal antibodies.

Example: Amyloid-targeting drugs have been associated with **ARIA** (amyloid-related imaging abnormalities), including brain swelling and bleeding.

- **Real-World Evidence[13]**

Drug Name	Target	Outcome	Limitation
Aducanumab	Amyloid-β	Approved with limited benefit	ARIA risk, modest cognitive impact
Semagacestat	γ-secretase	Failed in Phase III	Worsened cognition
Tau inhibitors	Tau protein	Still in early trials	Limited efficacy so far

3. Multi-Target-Directed Ligands (MTDLs)[14,15]

MTDLs are single chemical entities designed to simultaneously interact with multiple biological targets involved in a disease. Unlike traditional drugs that hit one target, MTDLs aim to tackle several pathological pathways at once-a perfect match for complex diseases like AD.

- **Examples of MTDL Strategies in AD**

MTDL Type	Targets	Potential Benefits
Dual inhibitors	Acetylcholinesterase + β-secretase	Boost cognition + reduce amyloid load
Hybrid molecules	Antioxidant + metal chelator	Protect neurons + regulate metal ions
Multi-receptor modulators	NMDA + serotonin receptors	Improve mood + reduce excitotoxicity

- **Principles of MTDLs:**

Pharmacophore fusion: Combining active sites of two drugs into one molecule.

Linker-based hybrids: Connecting two pharmacophores with a flexible linker.

Fragment-based design: Assembling small bioactive fragments targeting different sites.

Poly pharmacology and its relevance in AD

Poly pharmacology refers to the design or use of single therapeutic agents that act on multiple biological targets simultaneously. In contrast to traditional "one drug–one target" approaches, Poly

pharmacology embraces the complexity of diseases—especially multifactorial ones like Alzheimer's—by aiming to modulate several pathways with a single molecule.

❖ **Major molecular targets in AD[16,17]**

1. Aβ aggregation

Aβ peptides are short fragments derived from the cleavage of amyloid precursor protein (APP) by enzymes β-secretase and γ-secretase.

Among these, Aβ42 is especially prone to misfolding and aggregation due to its hydrophobic nature. These peptides aggregate into oligomers, then fibrils**,** and finally form extracellular amyloid plaques in the brain.

2. Tau phosphorylation

Tau is a microtubule-associated protein that helps stabilize the internal skeleton of neurons.

Phosphorylation is the addition of phosphate groups to tau by enzymes called kinases (e.g., GSK-3β, CDK5).

In healthy neurons, tau is normally phosphorylated to regulate its function.

In AD, tau becomes hyperphosphorylated meaning it has too many phosphate groups, which causes it to detach from microtubules and misfold.

3. Acetylcholinesterase (AChE)

Function: AChE breaks down acetylcholine (ACh**)**, a neurotransmitter essential for learning, memory, and attention.

Location: Found in synaptic clefts of cholinergic neurons, especially in the hippocampus and cerebral cortex**.**

Mechanism: It hydrolyzes acetylcholine into choline and acetate, terminating the signal between neurons.

4. NMDA receptor

Type: Ionotropic glutamate receptor.

Function: Mediates excitatory neurotransmission by allowing calcium (Ca^{2+}), sodium (Na^{+}), and potassium (K^{+}) ions to flow across the neuronal membrane.

Activation: Requires both glutamate and glycine (or D-serine) as co-agonists, and membrane depolarization to remove a magnesium block.

5. Oxidative stress pathways

Amyloid-β aggregation: Promotes ROS production and mitochondrial dysfunction.

Tau hyperphosphorylation: Disrupts microtubule stability and contributes to oxidative damage.

Mitochondrial dysfunction: Impaired energy production increases ROS leakage.

Neuroinflammation: Activated microglia release ROS and pro-inflammatory cytokines.

6. Inflammatory pathways (e.g., TNF-α)

Inflammatory pathways are cell signaling networks that regulate the body's response to injury, infection, or stress.

Microglia: The brain's resident immune cells.

Astrocytes: Support cells that also modulate inflammation.

Cytokines: Small proteins like TNF-α, IL-1β, and IL-6 that mediate immune responses.

4. Scoring Functions in Poly pharmacology[18,19]

Scoring functions estimate the binding affinity between a ligand and its target by evaluating:

Strength of interactions (e.g., hydrogen bonds, van der Waals forces)

Shape complementarity

Electrostatic compatibility

Desolvation and entropy effects

- **Types of scoring functions:**

Type	Description	Pros	Cons
Force-field based	Uses physics-based equations to model atomic interactions	Accurate for detailed energy calculations	Computationally intensive
Empirical	Combines weighted terms from experimental data (e.g., hydrogen bonds, hydrophobicity)	Fast and interpretable	May oversimplify complex interactions
Knowledge-based	Derived from statistical analysis of known protein-ligand complexes	Captures real-world binding trends	Depends on quality of structural database
Machine learning-based	Uses AI to learn patterns from large datasets	Can model nonlinear relationships	Requires extensive training data and validation

- **Role of molecular docking:**

Ligands are **positioned** in the binding site of the target protein.
Each pose is **scored** using a scoring function.
The best-scoring poses are **ranked** to identify top candidates for experimental validation.

5. Composite Indices for Poly pharmacological Profiling[20]

Composite indices are numerical or weighted scoring systems that integrate multiple individual parameters into a single, unified metric. They are widely used in fields like computational drug design, economics, public health, and machine learning to simplify complex, multidimensional data into a form that's easier to interpret, compare, and rank.

➢ Key Features of Composite Indices:

Multi-parameter integration: Combine diverse metrics (e.g., binding affinities, toxicity scores, ADME properties) into one score.
Weighting: Assign relative importance to each parameter based on context or desired outcomes.
Normalization: Standardize inputs (e.g., Z-scores, min-max scaling) to ensure comparability.
Aggregation: Use mathematical formulas (e.g., weighted sums, geometric means) to compute the final index.

➢ Application in Drug Design (e.g., MTDLs for Alzheimer's):

Rank compounds based on overall performance across multiple targets.
Balance efficacy and safety by integrating binding scores with toxicity and off-target risks.
Guide optimization by highlighting trade-offs (e.g., strong AChE inhibition vs. hERG liability).

➢ Examples of composite indices:

1. Poly pharmacology Index (PPI)

Purpose: Quantifies how evenly and effectively a compound engages multiple therapeutic targets.

$$\mathrm{PPI} = \frac{1}{n}\sum_{i=1}^{n} Z_i$$

where Zi is the normalized binding score for target ii, and n is the number of targets.
Interpretation: Higher PPI suggests broader and balanced multi-target activity.
Use case: Prioritizing MTDLs that avoid dominance by a single target.

2. Multi-Target Activity Score (MTAS)

Purpose: Aggregates binding affinities across selected targets into a weighted score.

$$\text{MTAS} = \sum_{i=1}^{n} w_i \cdot S_i$$

where SiS_i is the binding score (e.g., docking score or predicted pKdpK_d) and wiw_i is the weight for target ii.

Interpretation: Reflects both potency and therapeutic priority.

Use case: Ranking compounds based on strategic target engagement (e.g., BACE1 > AChE > GSK-3β).

3. Weighted Binding Affinity Score

Purpose: Integrates binding strengths with safety and pharmacokinetic filters.

$$\text{WBAS} = \sum_{i=1}^{n} w_i \cdot \left(-\Delta G_{\text{bind},i} \right) - \sum_{j=1}^{m} p_j \cdot R_j$$

where ΔGbind,i is the binding free energy for target i, and Rj are risk scores (e.g., hERG, CYP inhibition).

Interpretation: Balances efficacy with safety.

Use case: Filtering high-affinity compounds that also meet toxicity thresholds**.**

4. Selectivity Index

Purpose: Measures how much more a compound binds to desired targets vs. off-targets.

$$\text{Selectivity Index} = \frac{\text{Avg on-target score}}{\text{Avg off-target score}}$$

Interpretation: Higher values indicate better specificity.

Use case: Avoiding promiscuous compounds that may cause side effects.

6. Integration of In Silico and Experimental Data[21,22,23]

Integration of in silico and experimental data refers to the strategic combination of computational predictions with laboratory-based validation to enhance drug discovery, development, and biomedical research. This approach leverages the strengths of both domains to create a more efficient, accurate, and cost-effective workflow.

Role of molecular docking:

Simulates how a ligand fits into the binding site of a target protein.

Predicts binding orientation (pose) and binding strength (affinity) using scoring functions.

Role of molecular dynamics:

Simulates atomic-level motion of molecules over time.

Reveals conformational changes, binding stability, and interaction dynamics.

Role of QSAR model:

Uses statistical or machine learning models to correlate chemical structure with biological activity.

Predicts potency, selectivity, or ADME properties based on molecular descriptors.

7. Challenges and Limitations[24]

Quantifying Poly pharmacology—especially for multi-target-directed ligands (MTDLs) in Alzheimer's disease (AD)—is a powerful but complex endeavor. While scoring functions and composite indices offer structured ways to evaluate multi-target engagement, they come with significant challenges and limitations that must be carefully managed.

1. Target Diversity and Mechanistic Complexity

AD involves diverse targets: AChE, BACE1, GSK-3β, NMDA receptors, tau, Aβ, MAO-B, and inflammatory mediators.

Each target has **distinct binding sites**, structural dynamics, and pharmacological roles.

Scoring functions may not be equally accurate across all targets.

2. Scoring Function Bias

Many scoring functions are **optimized for single-target binding**.

They may **overestimate affinity** for rigid pockets (e.g., AChE) and **underperform** for flexible or allosteric sites (e.g., NMDA receptor).

Lack of standardization across scoring platforms leads to **inconsistent rankings**.

3. **Composite Index Construction**

Choosing appropriate **weights** for each target is subjective and context dependent.

Normalization across targets with different scoring scales can distort results.

Composite scores may **mask critical trade-offs**, such as strong binding to one target but poor selectivity.

4. Protein Flexibility and Dynamics

Most docking tools assume **rigid receptors**, ignoring conformational changes.

MD simulations help but are **computationally expensive** and hard to scale across multiple targets.

5. Off-Target and Safety Profiling

Poly pharmacology increases the risk of **off-target effects** (e.g., hERG inhibition, CYP interactions).

Composite indices often **lack integrated safety penalties**, leading to false positives.

6. Data Quality and Validation

QSAR models and scoring functions rely on **high-quality experimental data**.

Sparse or noisy datasets can lead to **overfitting** and poor generalization.

Experimental validation of multi-target predictions is **resource intensive**.

8. Future Prospective [25]

The future of quantifying Poly pharmacology in Alzheimer's disease (AD) multi-target-directed ligands (MTDLs) is likely to be shaped by advances in computational modeling, artificial intelligence (AI), and systems biology. Emerging deep learning and multi-task learning frameworks are expected to improve the accuracy of scoring functions by simultaneously predicting binding affinities across multiple AD-relevant targets, surpassing the limitations of conventional docking-based approaches. Likewise, network pharmacology and systems biology will enable the incorporation of pathway-level and target connectivity metrics, allowing for a more holistic evaluation of drug action within the complex AD interactome. Composite indices may also evolve from static affinity-based models to dynamic frameworks that integrate molecular dynamics simulations and free energy calculations, capturing allosteric modulation and protein flexibility. In parallel, the integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, will pave the way for patient-specific Poly pharmacology profiling, supporting the design of precision MTDLs tailored to individual molecular signatures. Another critical direction will be the coupling of Poly pharmacology scoring with ADMET assessments to ensure that compounds demonstrate not only multi-target efficacy but also optimal pharmacokinetic and safety properties. Equally important is the establishment of standardized, reproducible composite scoring frameworks and benchmarking datasets, which will enhance the reliability of in silico predictions and enable cross-study comparisons. Finally, the future of this field will depend on the integration of computational indices with clinical and real-world trial data, where machine learning models can be continuously refined to bridge the gap between predictive scoring and therapeutic success. Collectively, these innovations hold promise for advancing MTDL development from a theoretical concept toward clinically viable, personalized therapeutic strategies for Alzheimer's disease.

9. Conclusion

Alzheimer's disease remains a highly complex and multifactorial disorder, where single-target approaches have largely failed to provide meaningful clinical benefits. Multi-target-directed ligands

(MTDLs) represent a promising paradigm by simultaneously modulating multiple pathological pathways, yet their rational design requires robust strategies to quantify Poly pharmacology. Scoring functions and composite indices provide valuable frameworks to evaluate multi-target interactions, rank ligand efficacy, and balance selectivity with safety. While conventional affinity-based scoring has laid the foundation, emerging composite indices offer more holistic insights by integrating binding potency, target relevance, and system-level interactions. However, challenges such as the lack of standardization, insufficient integration of ADMET properties, and limited validation against experimental and clinical outcomes continue to restrict progress. Future efforts should focus on AI-driven scoring, network pharmacology, and multi-omics integration to refine Poly pharmacology quantification and enable patient-specific drug profiling. Ultimately, the development of standardized, clinically validated indices will be essential to accelerate the discovery of effective, safe, and personalized MTDLs for Alzheimer's disease therapy.

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