Multi-Target Drug Design Using Cheminformatics Approaches

Sudeep Roy, Ph.D.

Assistant Professor-Cheminformatics(SysBio)

Department of Biomedical Engineering

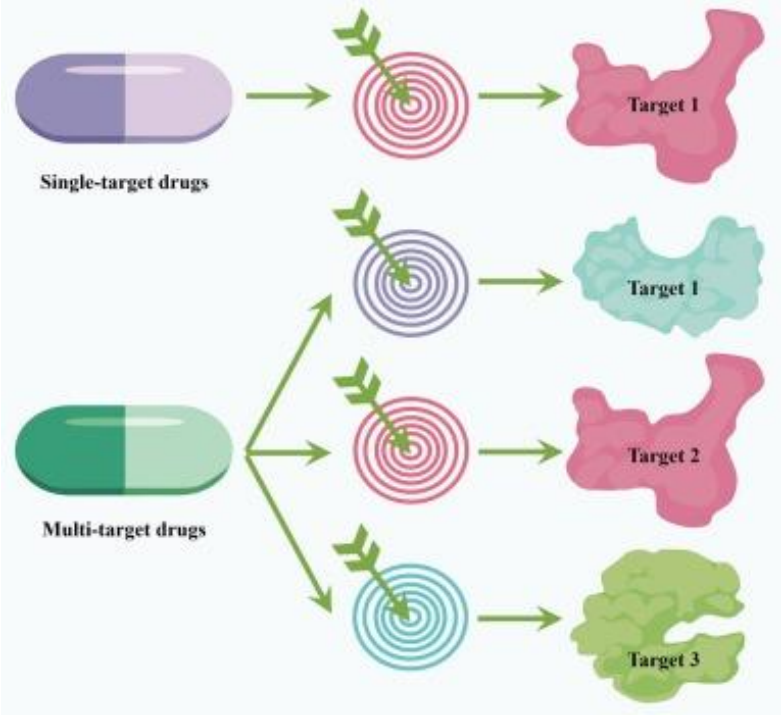
Brno University of Technology-Brno

Introduction

Definition: Multi-target Drug Design (MTDD) aims to develop single molecules acting on multiple biological targets.

Importance: Suitable for multifactorial diseases like cancer, neurodegeneration.

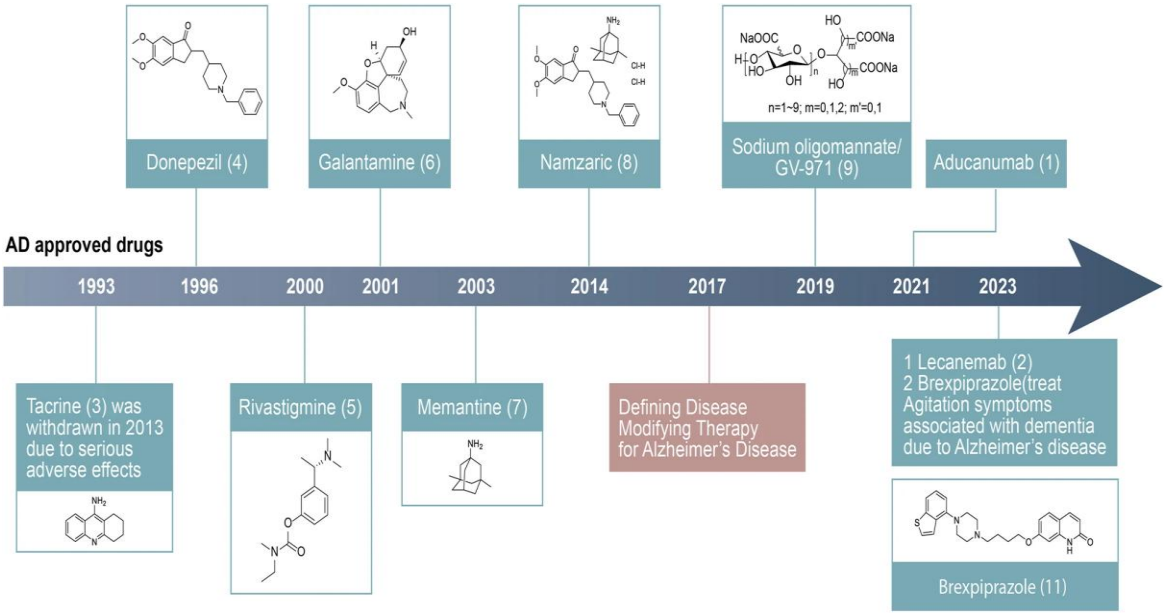
Cheminformatics role: Integrates chemical, biological, and pharmacological data.



Source: https://doi.org/10.1016/j.pharmthera.2023.108550

Limitations of Single-Target Drugs and Recent Therapies

- Paradigm Shift Needed(Cost and develop.)
- Lack of Efficacy (AD, Diabetes and CD)
- Variable Patient Response (Genetic)
- Research Challenges (Off-Targets)
- Cannot Halt Progression (AD)
- Significant Side Effects.



Source: https://www.nature.com/articles/s41392-024-01911-3

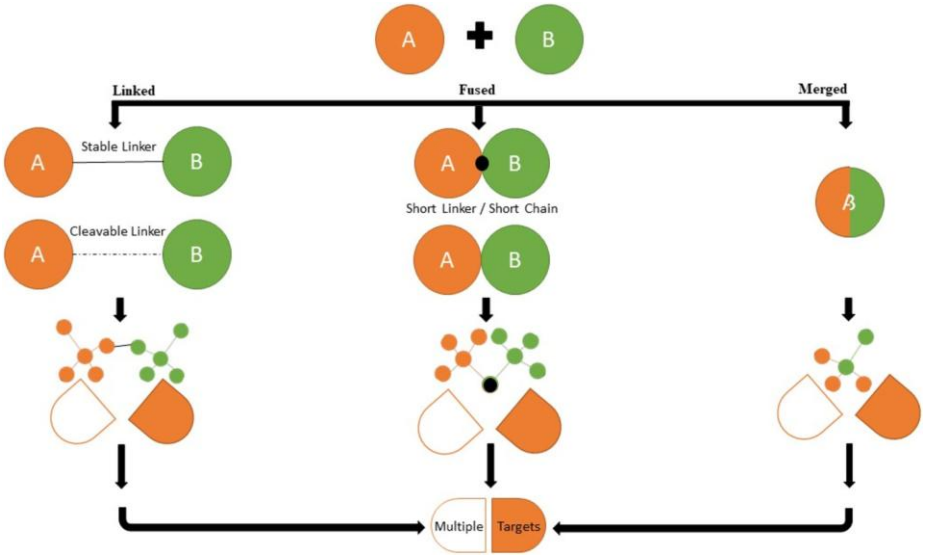
Advantages of MTDD

Synergistic effects-(Lower Doses)

Lower likelihood of resistance-single point mutation (Cancer and Infectious Diseases)

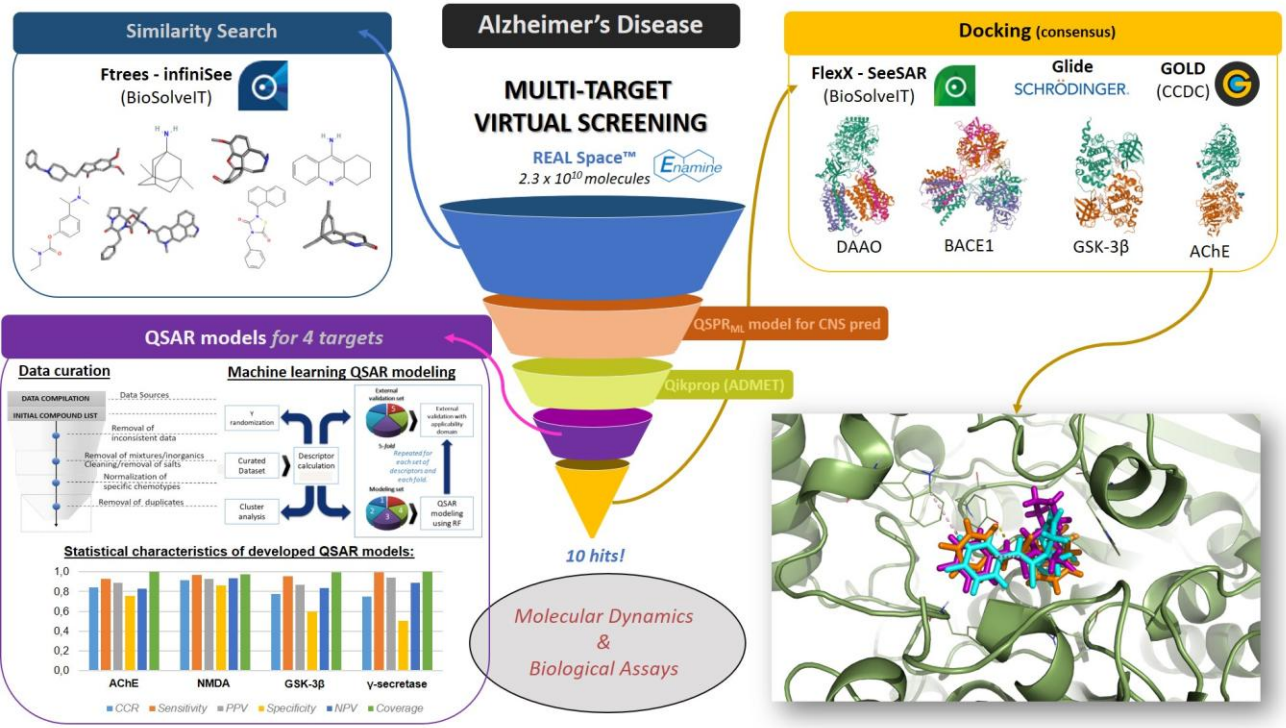
Reduced pill burden (Drug-Drug Interaction)

Better efficacy in complex diseases (Heterogenous Diseases or Diverse patient population)



Source: https://doi.org/10.1002/prp2.70131

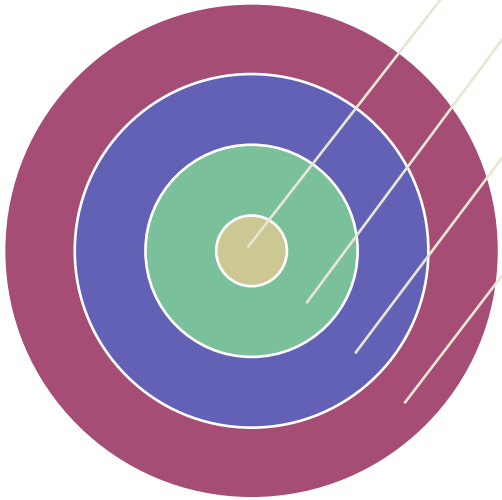
MTDD Workflow



Source: https://www.biosolveit.de/scientific-challenge/project/?projectId=16376243929290

1. Target Identification (System Biology, Network Pharmacology, Disease mapping).
2. Ligand Design / Selection (SBDD, Scaffold Hopping, Fragment based Methods)
3. Virtual Screening (SBVS, LBVS, Optimal Pharmacological Profiles)
4. ADMET Prediction (Exclude Unfavourable pharmacokinetics or high toxicity risk compounds)
5. Molecular Dynamics Simulation (Assess Binding stability and potential off-target effects)
6. In vitro / In vivo Validation (Synthesis, Animal Models)

Target Selection Strategies

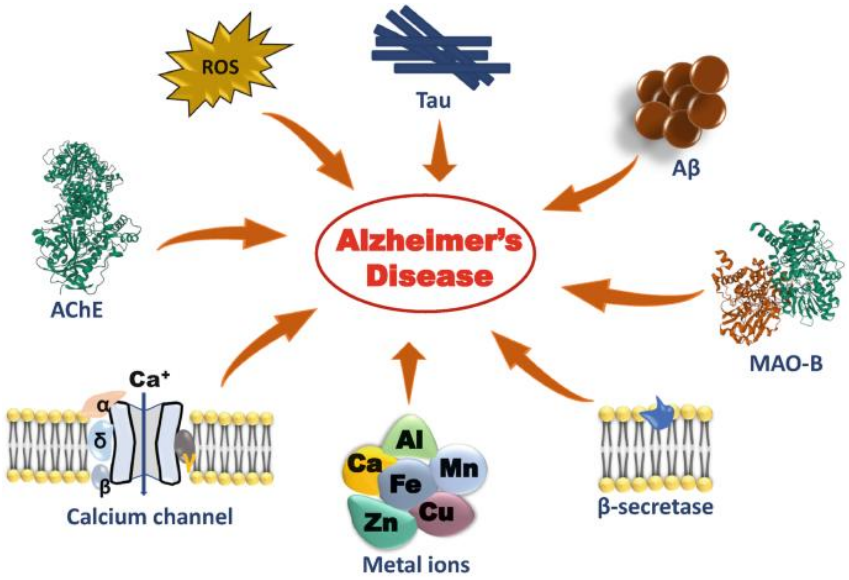


Pathway analysis

Network pharmacology mapping

Disease gene/protein interaction networks

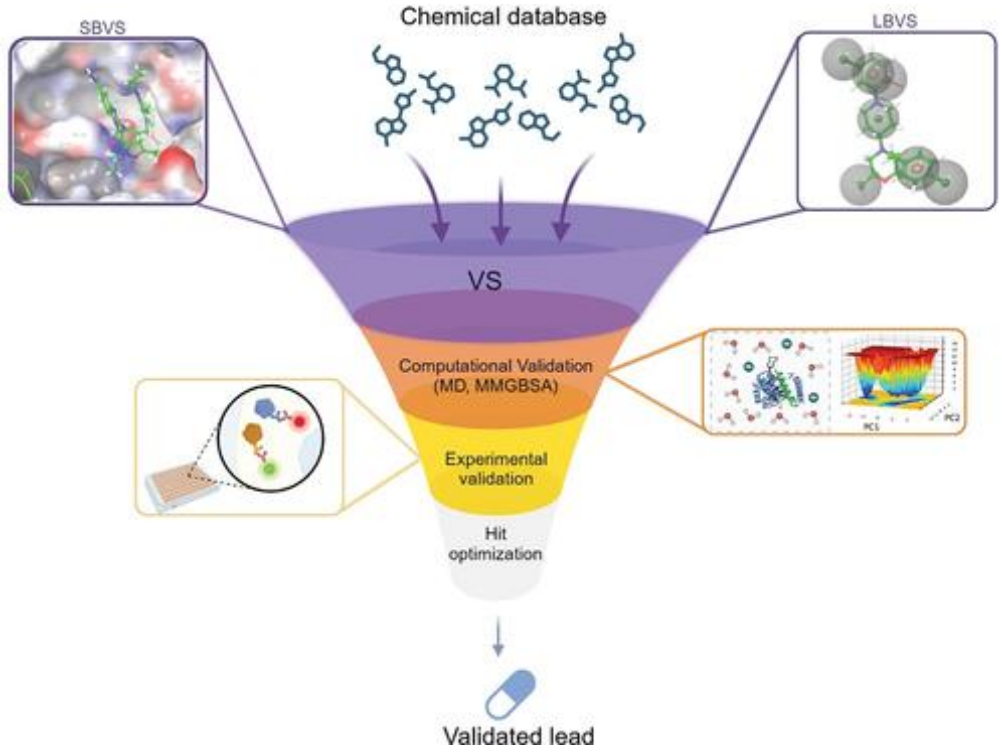
Example: Amyloid-β aggregation + Tau hyperphosphorylation in Alzheimer's



Source: https://link.springer.com/chapter/10.1007/978-981-99-6038-5_13

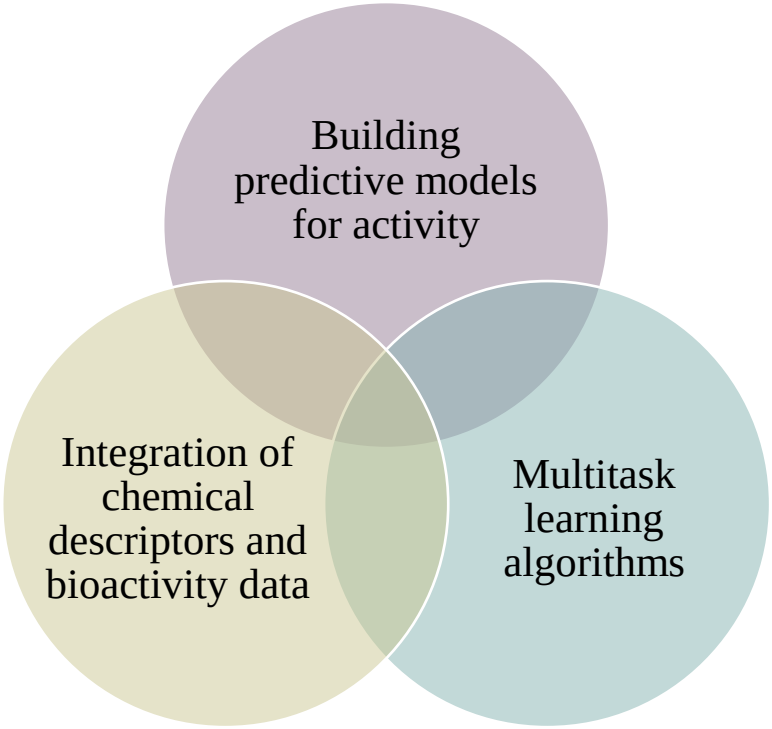
Virtual Screening in MTDD

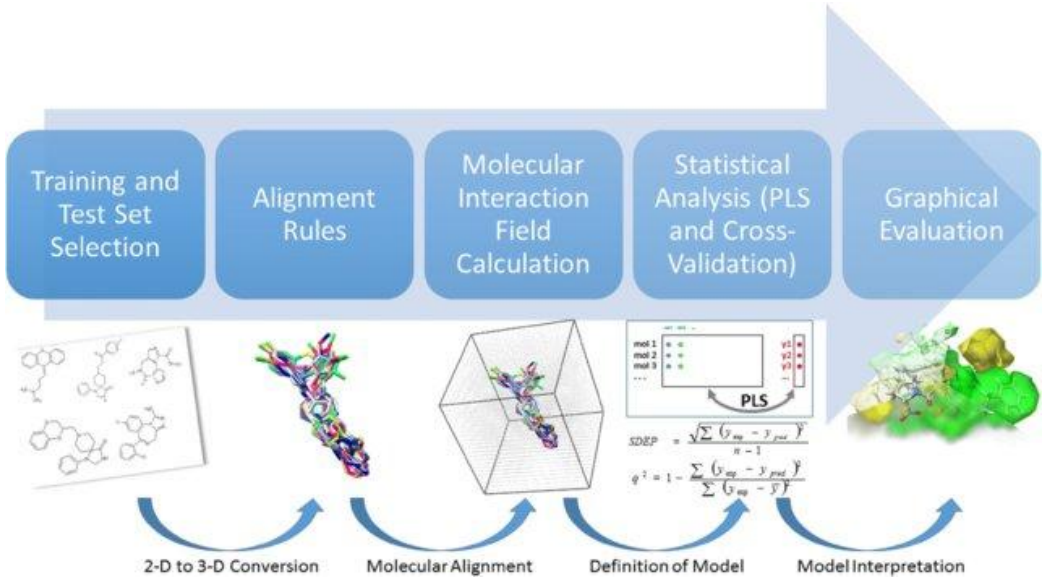
- Ligand-based screening
- Structure-based screening
- Multi-target docking workflows
- Filtering ligands with affinity for multiple targets



Source:
https://www.tandfonline.com/doi/full/10.1080/17460441.2025.2458666?scroll=top&needAccess=true

QSAR & Machine Learning

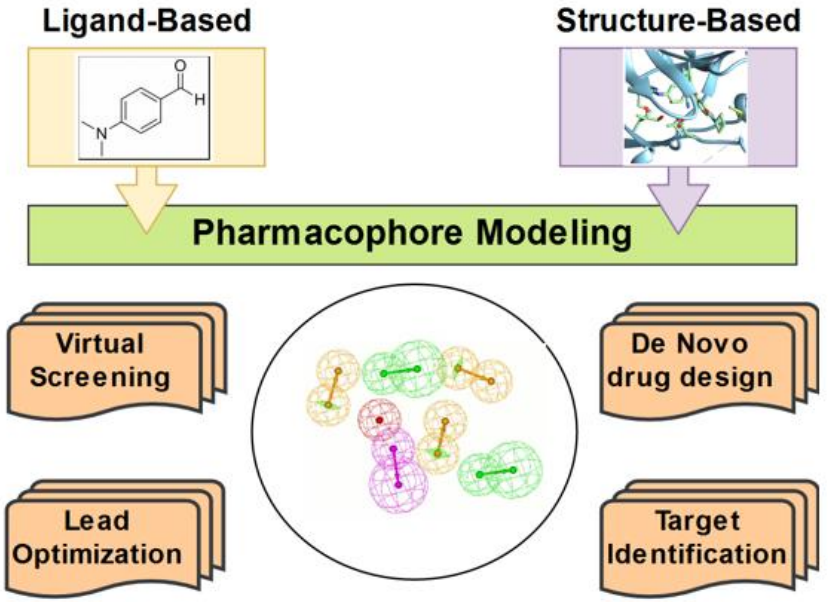




Source: https://link.springer.com/article/10.1007/s10822-019-00231-x

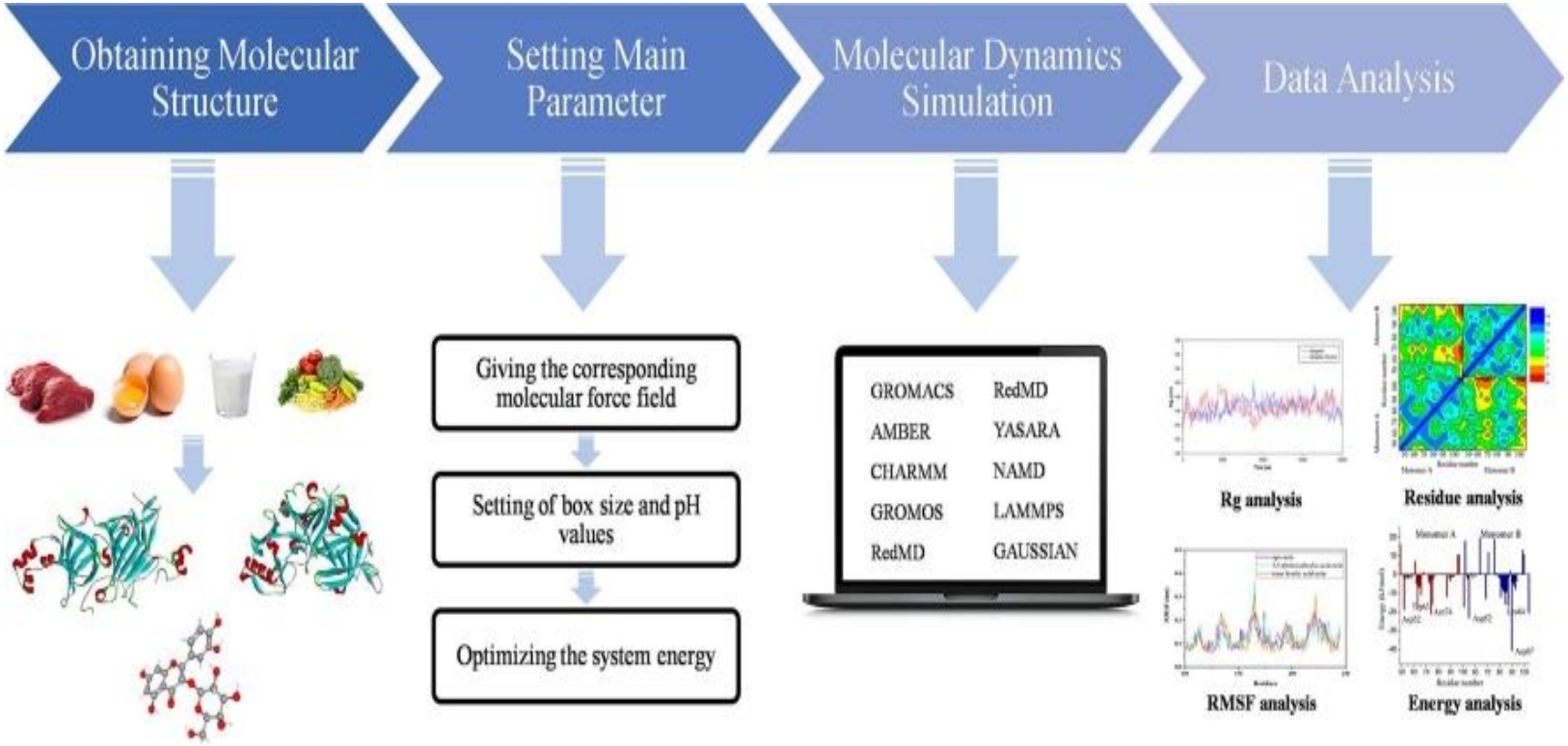
Pharmacophore Modeling

- Collect a set of experimental compounds for a target
- Select a threshold for the activity values and mark compounds as Actives and Inactives.
- Generate conformers and create pharmacophore model
- Identify the points essential for the activity of the molecules
- Perform statistical analysis on your model for model refinement to get virtual hits



Source: https://www.profacgen.com/pharmacophore-modeling.htm

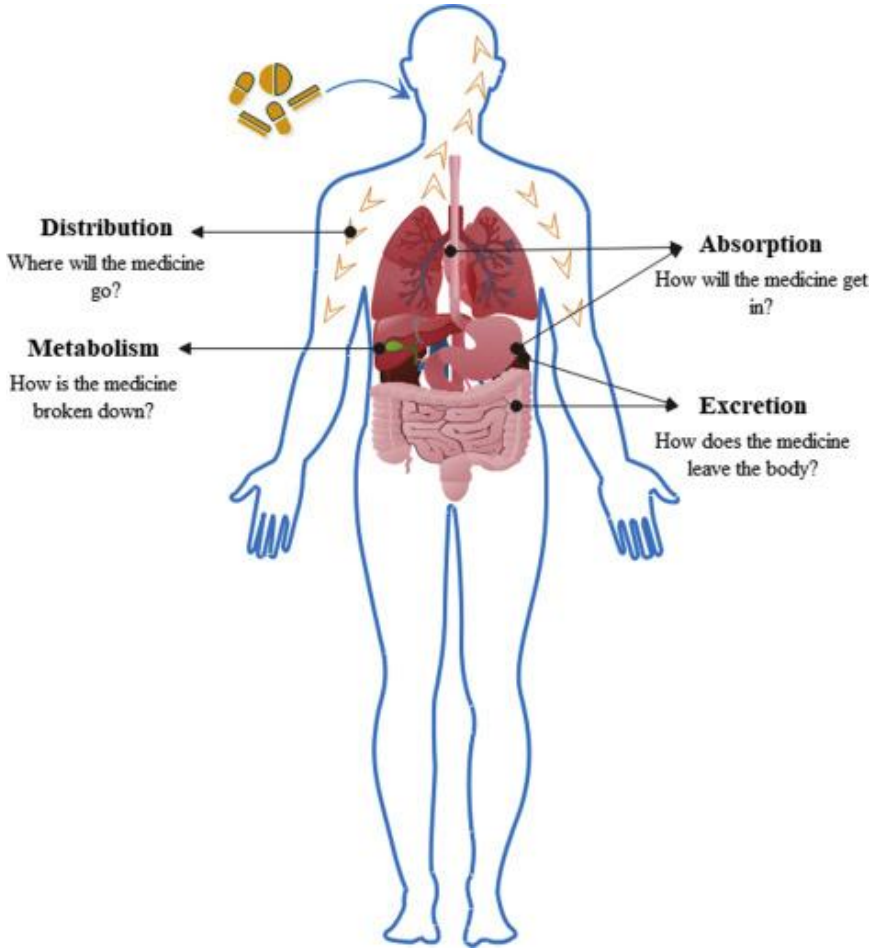
Molecular Dynamics in MTDD



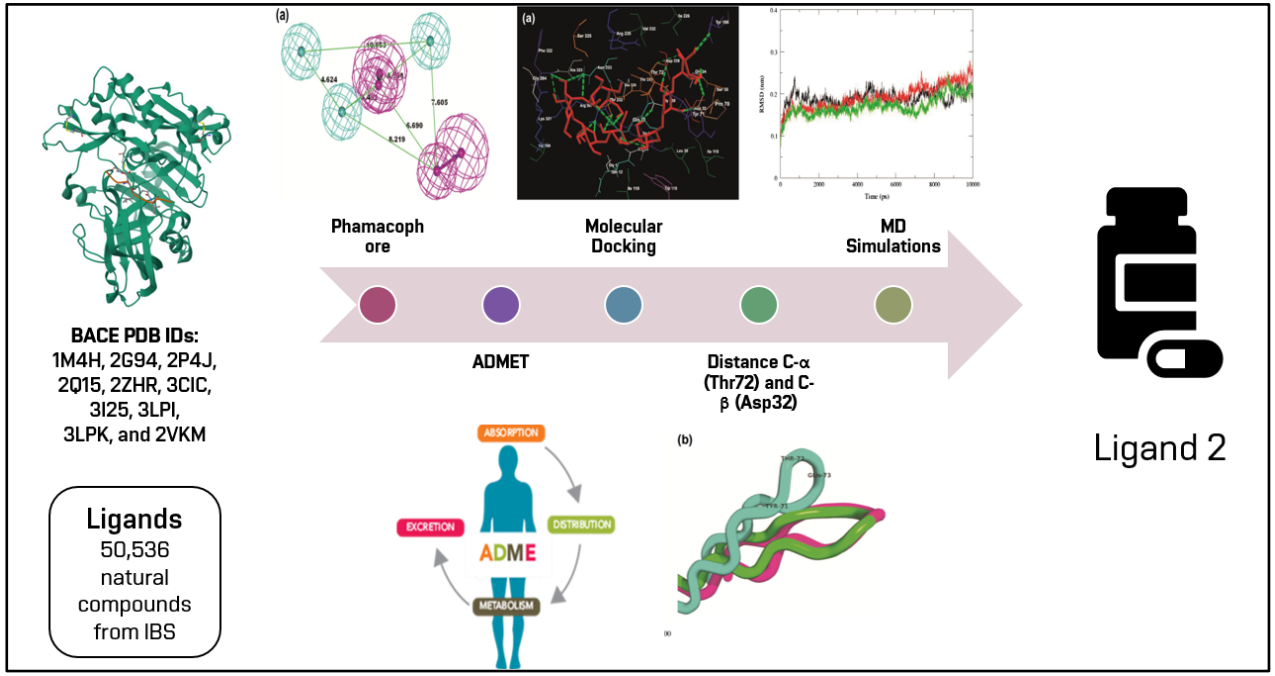
Source: https://www.creative-biostructure.com/molecular-dynamics-simulations.html?srsltid=AfmBOopF4wPKdEYd8c0oh_KQmUK2x2-PABlXthn7ZDTEbpcMD0PNd6wU

ADMET & Toxicity Prediction

- In silico evaluation of:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
  - Toxicity
- Filtering out problematic compounds early



Source:
https://www.sciencedirect.com/science/article/abs/pii/B978012814421300021X



Purpose

- Identify natural compounds as potential BACE1 inhibitors using *in-silico* approaches.

Target Proteins / Pathways

- BACE1 (β-secretase 1)
- Amyloid-β formation pathway in AD.

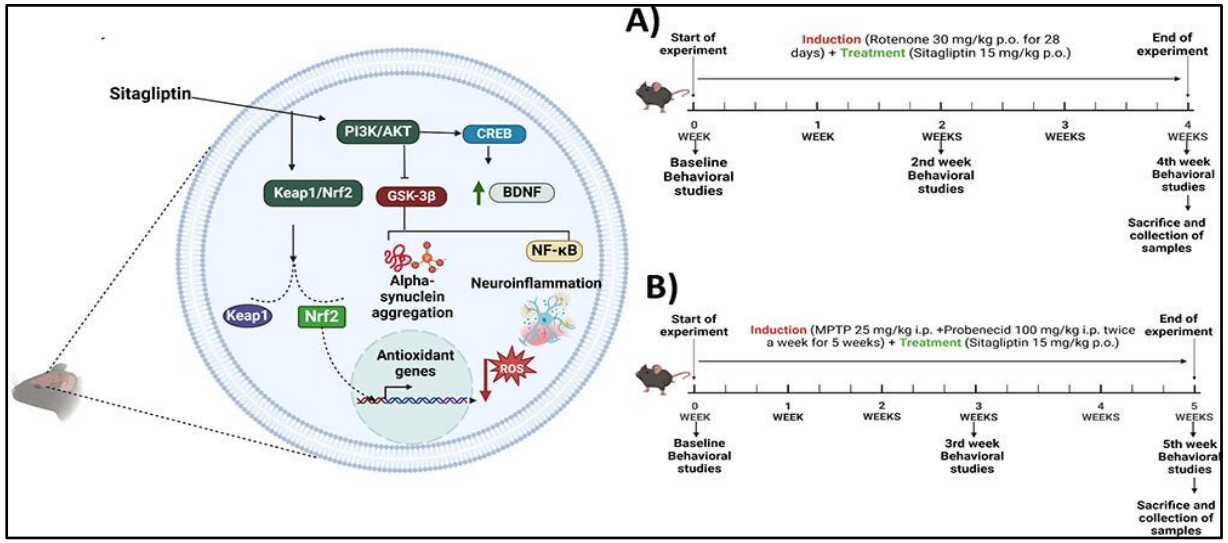
Goals Achieved

- Virtual screening of natural compounds
- 3D–QSAR pharmacophore model developed
- Molecular dynamics confirmed stability
- Promising BACE1 inhibitor leads identified

Case Study 1: Molecular docking based virtual screening of natural compounds as potential BACE1 inhibitors: 3D – QSAR pharmacophore mapping and molecular dynamics analysis

Source: https://www.tandfonline.com/doi/full/10.1080/07391102.2015.1022603

- Large flexible binding sites like BACE1.
- Catalytic ASPDyad (D32 and D228) and Flexible Flap(V67-E77). Imp Residue: T72.
- 10ns Run.
- BBB, Hepatotoxicity, PPB, solubility and mutagenicity. Scaffolds safe for CNS delievery.
- 3 Oligosaccharides Hits.
- Reduction of amyloid levels in AD



Purpose

- Investigate the neuroprotective role of sitagliptin in PD mouse models.

Target Proteins / Pathways

- PI3K/AKT → neuronal survival
- Nrf2 → antioxidant defense
- DPP-4 inhibition → upstream trigger

Goals Achieved

- Upregulated PI3K/AKT & Nrf2
- Reduced oxidative stress & neuronal degeneration
- Neuroprotection demonstrated
- Supports repurposing for PD therapy

Case Study 2: Upregulation of the PI3K/AKT and Nrf2 Pathways by the DPP-4 Inhibitor Sitagliptin Renders Neuroprotection in Chemically Induced Parkinson's Disease Mouse Models

Source: https://pubs.acs.org/doi/10.1021/acschemneuro.5c00112

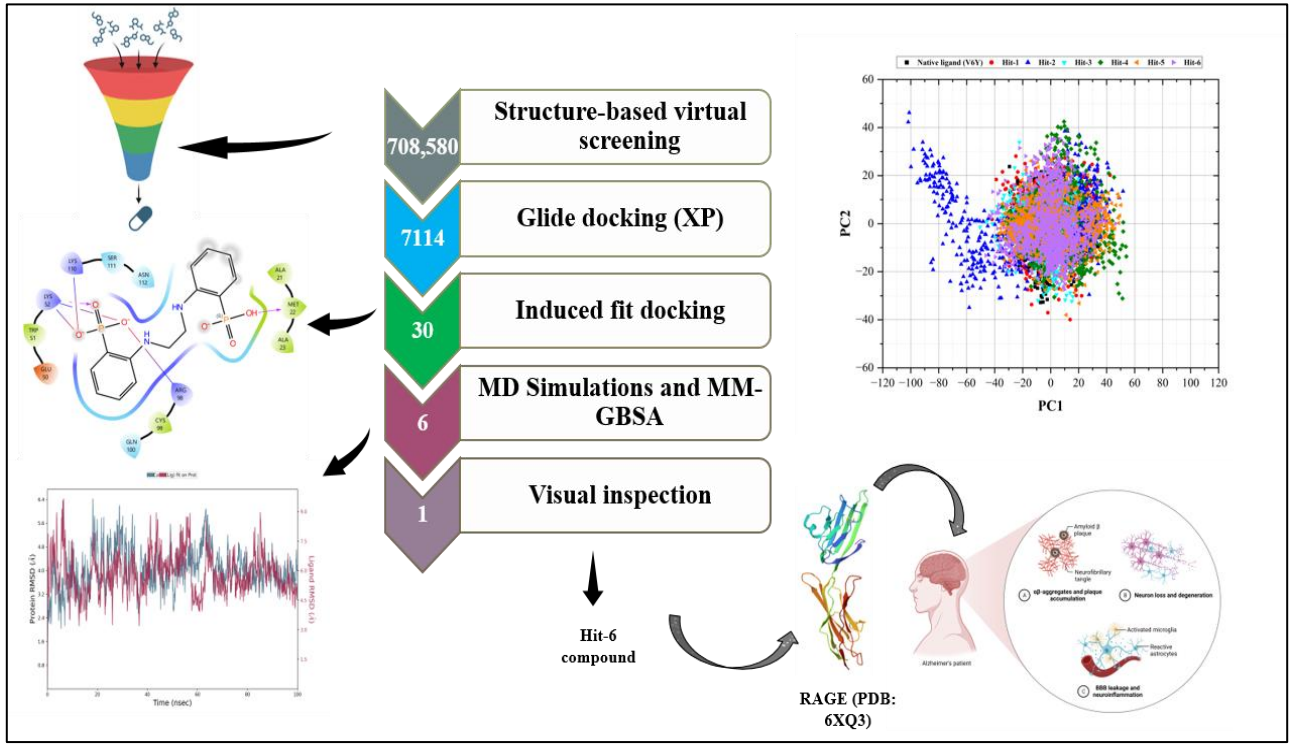
Sita, Lina, Alo, Vilda, saxa- DPP4 Inhibitors

Sita alleviated motor and cognitive deficits.

Upregulated: PI3K, AKT, Nrf2(promotes cellular survival, growth and anti-oxidant), CREB and BDNF(neuronal survival factors).

Downregulated: GSK-3ß (Neuro and Ototoxicity-ENT), NF-Kb(Cancer, Diabetes, atherosclerosis and auto-immune disorders) and alpha-synuclein (PD).

Restored neuronal density and integrity



Purpose

- Identify RAGE inhibitors via in-silico approaches to combat Alzheimer's disease.

Target Protein/ Pathway

- RAGE—block receptor to inhibit amyloid-β and inflammatory signaling.

Goals Achieved

- Screened over 700,000 compounds.
- Identified Hit-6 as a potential inhibitor of RAGE

Case Study 3: Identifying RAGE inhibitors as potential therapeutics for Alzheimer's disease via integrated *in-silico* approaches

Source: https://www.nature.com/articles/s41598-025-01271-0

RAGE: Receptor for advanced glycation end products.

RAGE: Cancer, Diabetes, Kidney Failure, Cardiovascular disease, COPD, Rheumatoid Arthritis, Systemic Lupus, IBS, Asthma and neurological disorders(PD, AD…).

Enamine, TTD, FDA library, ChemDiv, InterBioScreen, Zinc.

Lys39, Lys52, Arg98, Asn112 and Lys110 (HotSpots).

Contact

BioSys_BUT

Email:

roy@vut.cz