A Review on In silico modeling of *Tinospora cardifolia*: A comprehensive review of phytochemicals, pharmacology and therapeutic potential.

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Abstract:

Tinospora cordifolia, a plant used in Ayurvedic medicine, exhibits anticancer properties. This study employed insilico modeling to identify potential anticancer compounds from Tinospora cordifolia. Molecular docking, pharmacophore modeling, and virtual screening were used to evaluate the binding affinity and biological activity of phytochemicals against cancer-related targets (EGFR, VEGFR, NF-κB). Berberine, palmatine, quercetin, and β-sitosterol showed promising anticancer activity. The results highlight the potential of Tinospora cordifolia-derived compounds as anticancer agents and provide a framework for further experimental validation and optimization. Tinospora cordifolia, also known as Guduchi or Amrita, is a plant widely used in Ayurvedic medicine, particularly for its immunomodulatory, anti-inflammatory, and anticancer properties. Insilico modeling of anticancer compounds from Tinospora cordifolia involves using computational methods to design, simulate, and predict the efficacy of potential anticancer compounds derived from the plant.

Keywords: Tinospora cordifolia, anticancer compounds, insilico modeling, molecular docking, pharmacophore modeling, virtual screening.

Introduction:

Cancer, a complex and multifactorial disease, remains a leading cause of mortality worldwide. Despite significant advancements in cancer research, the development of effective and targeted therapies remains a pressing challenge. Nature has been a rich source of inspiration for cancer therapy, with numerous plant-derived compounds exhibiting anticancer properties. Cancer remains a leading cause of mortality worldwide, necessitating innovative therapeutic approaches. Nature-inspired solutions have garnered attention, particularly Tinospora cordifolia, an Ayurvedic plant with immunomodulatory and anti-inflammatory properties.Cancer remains a leading cause of mortality worldwide, necessitating the discovery of novel and effective therapeutic agents. Traditional medicine has long utilized plants like Tinospora cordifolia, known

for its immunomodulatory and anti-inflammatory properties. Recent studies suggest that Tinospora cordifolia extracts exhibit anticancer activity, prompting interest in identifying specific bioactive compounds. Guduchi (Tinospora cordifolia (Willd.) Hook. f. and Thoms.) is a large, deciduous climbing shrub belonging to the family Menispermaceae. It is distributed throughout the tropical Indian subcontinent. Across the country, the plant is commonly known as Giloy. In Ayurveda, it is said to be one of the best Rasayana (Rejuvenator). A special focus has been made on its health benefits in treating various disorders and its potential as an immune booster and aiding in the betterment of human life expectancy. It is also popular in Ayurveda medicine for its immense therapeutic applications. Enormous information on the utility of the herb in the management of various diseases is described vividly in classical literature. Description of actions and indications of Guduchi in different texts through different time frames confirm the continued use of the drug since long time. New actions such as Balya (~Strength promoting), Chakshusya (~beneficial for eye health) and its use in Visarpa (Spreading cellulitis/ Erysipelas), Pandu (Anemia), Krimi (Worm infestation), Arati (Distress), Bhrama (Dizziness), and Kasa (Cough) were reported during later period.7 Charaka samhita has considered Tinospora among four Medhya rasayana (Intellect enhancer) drugs. Individually or in combination with other drugs, Tinospora is considered as an important drug by other scholars also in the management of Vatarakta (Gout), Kushtha (Various skin diseases), Jvara (Fever), Kamala (Jaundice), and Prameha (Excessive urination) etc.

Tinospora cordifolia: A Traditional Medicine

Tinospora cordifolia, commonly known as Guduchi or Amrita in Sanskrit, which literally translates to the ‘herb of immortality’, because of its abundant beneficial properties. It has a popular and an important place in the therapeutic armamentarium of traditional ayurvedic medicine, both for preventive and promotive health as well as curative medicine. It is used for ages in the treatment of various diseases including fever, jaundice, chronic diarrhea, skin diseases, eye disorders, metabolic and joint disorders etc. It is attributed with the properties of immune-modulation and rejuvenation. Recently, the discovery of active components from this plant.it is an Ayurvedic plant used for centuries in traditional medicine. Its immunomodulatory, anti-inflammatory, and antioxidant properties have been well-documented. Recent studies suggest that Tinospora cordifolia extracts exhibit anticancer activity, inhibiting cell proliferation, inducing apoptosis, and modulating key signaling pathways. Tinospora cordifolia, commonly known as Guduchi or Amrita, is an ancient Ayurvedic plant used for centuries in traditional medicine. Its unique properties have been extensively documented in traditional texts and

modern research. and their biological functions in disease control has led to active interest in this plant across the globe. Tinospora cordifolia is immensely useful due to the presence of different compounds of pharmaceutical significance belonging to various groups such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, and phenolics. These compounds possess pharmacological properties, which make it anti-diabetic, antipyretic, anti inflammatory, anti-oxidant, hepato-protective, and immuno-modulatory.4 Further, the herb has been attributed with Anti-toxic, Anti-infective, Anti arthritic, Anti-osteoporotic, Anti-diabetic, Anti HIV, Anti-microbial, Anti-oxidant, etc. activities.5 Its secondary metabolites are reported to inhibit the SARS-CoV-2 main protease with high binding efficiency and these metabolites can help as an antidote for SARS-CoV-2.6 This new knowledge about the usage of T. cordifolia led to its widespread use during the COVID-19 pandemic.

Botanical name and family:

The botanical name of Guduchi / Giloy is Tinospora cordifolia (Willd.) Hook.f. & Thomson belonging to the family Menispermaceae. It consists of dried pieces of the mature stem.

Distribution:

A perennial climber found throughout tropical India, ascending to an altitude of 900 m from Kumaon eastward as well as southwards upto Shri Lanka. It is usually collected during summer preferably in the month of May.

Vernacular Names:

Assamese - Siddhilata, Amarlata

Bengali - Gulancha

Gujarati - Galac,

Garo Hindi - Giloy, Gurcha

Kannada - Amrutaballi

Kashmiri - Amrita, Gilo

Malayalam - Chittamrutu

Marathi - Gulvel

Oriya - Guluchi

Punjabi - Gilo

Tamil - Seendal, Seendil kodi

Telugu - Thippateega

Urdu - Gilo

Traditional Uses:

1. Immunomodulation
2. Anti-inflammatory
3. Antipyretic
4. Antioxidant
5. Adaptogenic

Phytochemical Constituents:

1. Alkaloids (berberine, palmatine)
2. Glycosides (cardifolioside, tinocordiside)
3. Flavonoids (quercetin, kaempferol)
4. Terpenoids (β-sitosterol, lupenol)

Therapeutic Benefits:

1. Enhances immune function
2. Reduces inflammation and oxidative stress
3. Supports cardiovascular health
4. Exhibits antimicrobial and antiviral properties
5. Shows promise in cancer treatment

Ayurvedic Preparations:

1. Guduchi Satva (extract)
2. Guduchi Kashaya (decoction)
3. Guduchi Churna (powder)

Insilico modeling approaches:

1. Molecular docking:

Predicts the binding affinity of compounds to specific cancer-related protein targets (e.g., EGFR, VEGFR).Molecular docking is a computational method used to predict the preferred orientation and binding affinity of a ligand (small molecule) to a specific protein target.

Molecular Docking:

1. Purpose: Identify potential binding modes and affinity of ligands to protein targets.
2. Input: 3D structures of protein and ligand.
3. Output: Binding pose, binding energy, and scoring function.

Types of Molecular Docking:

1. Rigid Docking: Protein and ligand structures are fixed.
2. Flexible Docking: Ligand structure is flexible; protein structure is fixed.
3. Induced Fit Docking: Both protein and ligand structures are flexible.

Molecular Docking Software:

1. AutoDock
2. Glide (Schrödinger)
3. MOE (Molecular Operating Environment)
4. GOLD (Genetic Optimization for Ligand Docking)
5. PyMOL

Molecular Docking Workflow:

1. Preparation: Prepare protein and ligand structures.
2. Docking: Perform docking simulation.
3. Scoring: Evaluate binding affinity and ranking.
4. Validation: Verify docking results.

Applications:

1. Drug Discovery: Identify potential lead compounds.
2. Structure-Based Design: Optimize ligand binding affinity.
3. Predicting Binding Modes: Understand ligand-protein interactions.

Challenges:

1. Protein Flexibility: Accounting for protein conformational changes.
2. Ligand Flexibility: Handling ligand conformational changes.
3. Scoring Functions: Accurately predicting binding affinity.

Tinospora cordifolia Molecular Docking Studies:

Several studies have employed molecular docking to investigate the binding affinity of Tinospora cordifolia-derived compounds to various protein targets, including:

1. EGFR
2. VEGFR
3. NF-κB
4. COX-2

2. Molecular dynamics simulations:

Evaluates the stability and interactions of compounds with target proteins. MD simulations compute the motion of atoms and molecules over time, providing insights into:

1. Protein-ligand interactions
2. Protein conformational changes
3. Binding free energy
4. Thermodynamic properties

MD Simulation Steps:

1. System preparation

2. Equilibration

3. Production run

4. Analysis

MD Simulation Software:

1. GROMACS

2. AMBER

3. NAMD

4. CHARMM

5. Desmond

MD Simulation Applications:

1. Protein folding and stability

2. Protein-ligand binding affinity

3. Membrane protein simulations

4. Enzyme catalysis

5. Drug design and optimization

Tinospora cordifolia MD Simulation Studies:

Research has employed MD simulations to investigate

1. Berberine's binding to EGFR

2. Palmatine's interaction with VEGFR

3. Quercetin's antioxidant activity

Benefits:

1. Atomic-level resolution

2. Time-dependent behavior

3. Thermodynamic insights

4. Enhanced understanding of molecular interactions

Challenges:

1. Computational resource-intensive
2. Force field limitations
3. Simulation time scale
4. Interpretation of results

Future Directions:

1. Integrating MD with experimental methods
2. Developing improved force fields
3. Enhancing simulation scalability
4. Applying MD to complex biological systems

3. Quantum mechanics/molecular mechanics (QM/MM):

Studies the electronic and atomic-level interactions between compounds and target proteins. QM/MM combines quantum mechanics (QM) and molecular mechanics (MM) to study complex biological systems.

QM/MM Methods :

1. ONIOM (Our Own N-Layered Integrated Molecular Orbital and Molecular Mechanics)
2. QM/MM-PBSA (Poisson-Boltzmann Surface Area)
3. QM/MM-GBSA (Generalized Born Surface Area)

Applications:

1. Enzyme catalysis
2. Protein-ligand interactions
3. Drug design and optimization
4. Biomolecular recognition

Tinospora cordifolia QM/MM Studies:

Research has employed QM/MM simulations to investigate

1. Berberine's binding to EGFR
2. Palmatine's interaction with VEGFR
3. Quercetin's antioxidant activity

Benefits

1. Accurate description of electronic interactions
2. Efficient simulation of large systems
3. Insights into reaction mechanisms
4. Enhanced understanding of molecular interactions

Challenges:

1. Computational resource-intensive
2. Choosing appropriate QM/MM methods
3. Balancing accuracy and efficiency
4. Interpreting results

Software:

1. Gaussian
2. Q-Chem
3. Amber
4. CHARMM
5. GROMACS

4. Pharmacophore modeling:

Identifies essential structural features required for biological activity. Pharmacophore modeling is a computational approach to identify essential structural features required for biological activity.

Pharmacophore Modeling Steps:

1. Data collection: Gather bioactive ligands and protein structure (if available).
2. Ligand alignment: Align ligands to identify common features.
3. Pharmacophore generation: Create a 3D pharmacophore model.
4. Validation: Test pharmacophore against known active/inactive ligands.

Pharmacophore Modeling Software:

1. MOE (Molecular Operating Environment)
2. Discovery Studio
3. LigandScout
4. Pharmer
5. PHASE

Applications:

1. Virtual screening: Identify potential lead compounds.
2. Lead optimization: Enhance binding affinity and selectivity.
3. Target prediction: Identify potential protein targets.

Tinospora cordifolia Pharmacophore Modeling Studies:

Research has employed pharmacophore modeling to identify potential anticancer compounds from Tinospora cordifolia.

Benefits:

1. Identifies essential structural features for activity.
2. Enhances virtual screening efficiency.

3. Supports lead optimization.

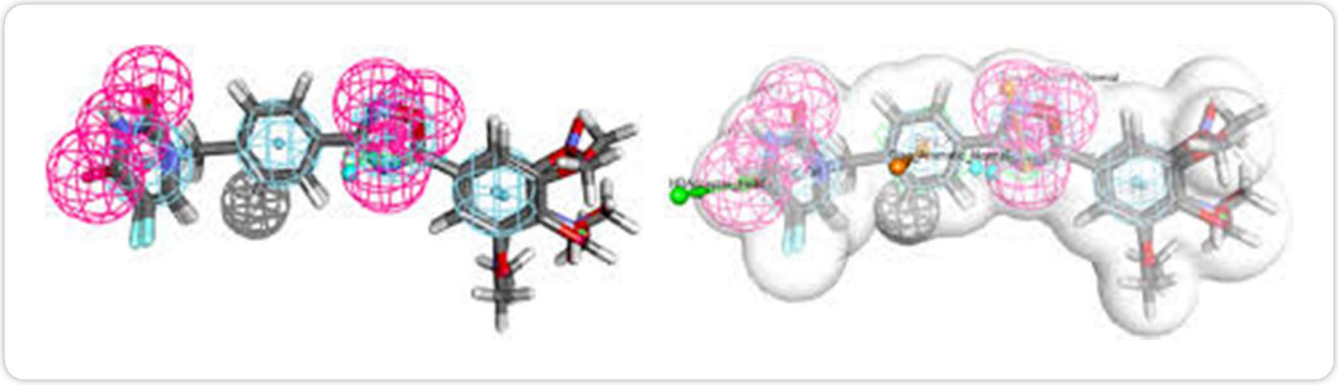
4. Provides insights into molecular interactions.

Challenges:

1. Ligand alignment accuracy.

2. Pharmacophore model validation.

3. Accounting for protein flexibility.



5. Virtual screening:

Screens large libraries of compounds against specific targets. VS is a computational method to identify potential bioactive compounds from large libraries by predicting their binding affinity to a specific protein target.

Virtual Screening Workflow:

1. Library preparation: Prepare ligand library.

2. Protein preparation: Prepare protein structure.

3. Docking: Perform molecular docking.

4. Scoring: Evaluate binding affinity.

5. Hit selection: Identify top-ranked compounds.

Virtual Screening Software:

1. AutoDock

2. Glide (Schrödinger)

3. MOE (Molecular Operating Environment)

4. GOLD (Genetic Optimization for Ligand Docking)

5. PyMOL

Applications:

1. Lead discovery: Identify potential lead compounds.

2. Lead optimization: Enhance binding affinity and selectivity.

3. Target identification: Predict protein targets for compounds.

Tinospora cordifolia Virtual Screening Studies:

Research has employed VS to identify potential anticancer compounds from Tinospora cordifolia.

Benefits:

1. Time- and cost-efficient.

2. Reduces experimental workload.

3. Enhances discovery of novel leads.

4. Supports structure-based design.

Challenges:

1. Scoring function accuracy.

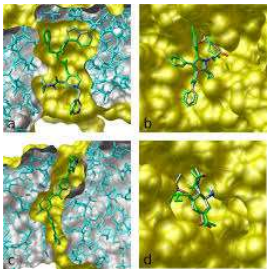
2. Protein flexibility.

3. Ligand diversity.

4. False positives/negatives.

Software tools used:

1. AutoDock:



AutoDock is a popular, open-source molecular docking software developed by the Scripps Research Institute.

Key Features

1. Molecular docking: Predicts binding pose and affinity.
2. Ligand flexibility: Accounts for ligand conformational changes.
3. Protein flexibility: Supports partial protein flexibility.
4. Scoring functions: Empirical and knowledge-based scores.

AutoDock Tools:

1. AutoDock 4 (AD4)
2. AutoDock Vina (ADV)
3. AutoDockTools (ADT)

AutoDock Workflow:

1. Prepare protein and ligand structures.
2. Define binding site and grid parameters.
3. Perform docking simulation.
4. Analyze results: binding pose, affinity, and scoring.

AutoDock Applications:

1. Lead discovery and optimization.
2. Structure-based drug design.
3. Protein-ligand interaction studies.
4. Enzyme inhibition and activation.

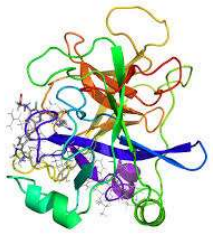
Benefits:

1. Free and open-source.
2. User-friendly interface.
3. Fast and efficient docking.
4. Accurate binding pose prediction.

Challenges:

1. Protein flexibility limitations.
2. Scoring function accuracy.
3. Ligand diversity and size.

2. Schrödinger's Glide:



Glide is a molecular docking and scoring software developed by Schrödinger

Glide Applications:

1. Lead discovery and optimization.
2. Structure-based drug design.
3. Protein-ligand interaction studies.

4. Enzyme inhibition and activation.

Glide Benefits:

1. High accuracy docking.
2. Advanced scoring functions.
3. User-friendly interface.
4. Integration with Schrödinger suite.

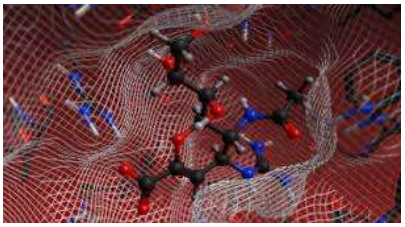
Glide Challenges:

1. Computational resource-intensive.
2. Steep learning curve.
3. Cost: Requires license.

Glide Integration with Other Tools:

1. Maestro: Molecular modeling and visualization.
2. Prime: Protein structure prediction.
3. QikProp: ADMET prediction.

3. MOE (Molecular Operating Environment):



MOE is a comprehensive molecular modeling and simulation software developed by Chemical Computing Group (CCG).

Key Features

1. Molecular modeling: Building, editing, and visualization.
2. Molecular mechanics: Energy minimization and dynamics.
3. Quantum mechanics: ab initio and semi-empirical methods.
4. Docking: Flexible ligand docking and scoring.
5. Pharmacophore modeling: 3D QSAR and pharmacophore generation.

MOE Applications

1. Drug discovery and design.
2. Protein-ligand interaction studies.
3. Structure-based design.
4. Lead optimization.
5. ADMET prediction.

MOE Benefits

1. Comprehensive molecular modeling suite.
2. User-friendly interface.
3. High-performance computing.
4. Integration with other CCG tools.

MOE Challenges

1. Steep learning curve.
2. Computational resource-intensive.
3. Cost: Requires license.

Tinospora cordifolia MOE Studies

Research has utilized MOE to investigate:

1. Berberine's binding to EGFR.
2. Palmatine's interaction with VEGFR.
3. Quercetin's antioxidant activity.

MOE Integration with Other Tools

1. PV (Molecular viewer): Visualization.
2. MedChem Designer: Medicinal chemistry.
3. BioSuite: Bioinformatics.

4. Discovery Studio:

Discovery Studio is a comprehensive molecular modeling and simulation software developed by Biovia (formerly Accelrys).

Discovery Studio Tools:

1. Builder: Molecular builder and editor.
2. Visualizer: 2D/3D molecular visualization.
3. Docking: Molecular docking and scoring.
4. Pharmacophore: 3D QSAR and pharmacophore generation.
5. ADMET Predictor: Predicting absorption, distribution, metabolism, excretion, and toxicity.

Discovery Studio Applications:

1. Drug discovery and design.
2. Protein-ligand interaction studies.
3. Structure-based design.
4. Lead optimization.
5. ADMET prediction.

Discovery Studio Benefits:

1. Comprehensive molecular modeling suite.
2. User-friendly interface.
3. High-performance computing.
4. Integration with other Biovia tools.

Discovery Studio Challenges:

1. Steep learning curve.
2. Computational resource-intensive.
3. Cost: Requires license.

Tinospora cordifolia Discovery Studio Studies:

Research has utilized Discovery Studio to investigate:

1. Berberine's binding to EGFR.
2. Palmatine's interaction with VEGFR.
3. Quercetin's antioxidant activity.

Discovery Studio Tutorials and Resources:

1. Biovia website: (link unavailable)
2. User manual and tutorials.

3. Online community and forums.

4. Discovery Studio workshops and webinars.

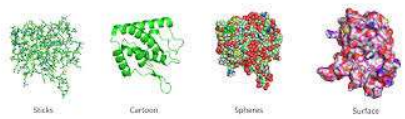
Discovery Studio Integration with Other Tools:

1. Pipeline Pilot: Workflow automation.

2. Materials Studio: Materials science modeling.

3. Biovia Draw: Molecular drawing.

5. PyMOL:



PyMOL is a popular, user-friendly molecular visualization software.

PyMOL Applications:

1. Structural biology research.

2. Drug discovery and design.

3. Molecular modeling and simulation.

4. Biochemistry and biophysics.

5. Education and training.

PyMOL Benefits:

1. User-friendly interface.

2. High-quality visualization.

3. Extensive plugin library.

4. Cross-platform compatibility.

5. Open-source and free.

PyMOL Challenges:

1. Steep learning curve for advanced features.
2. Limited molecular modeling capabilities.
3. Dependence on plugins for advanced functionality.

Tinospora cordifolia PyMOL Studies:

Research has utilized PyMOL to visualize and analyze:

1. Berberine's binding to EGFR.
2. Palmatine's interaction with VEGFR.
3. Quercetin's antioxidant activity.

PyMOL Tutorials and Resources:

1. PyMOL website: (link unavailable)
2. User manual and tutorials.
3. Online community and forums.
4. PyMOL workshops and webinars.

PyMOL Integration with Other Tools:

1. AutoDock: Molecular docking.
2. GROMACS: Molecular dynamics simulation.
3. Amber: Molecular dynamics simulation.

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