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Screening Phytocompounds of *Tinospora cordifolia* to Find Potential Drug Targets for Cystic Fibrosis

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Abstract

This study aimed to evaluate the therapeutic potential of phytocompounds derived from Tinospora cordifolia in treating cystic fibrosis (CF), a genetic disorder caused by mutations in the CFTR gene that lead to severe respiratory and digestive complications. Phytocompounds were retrieved from the IMPPAT database and subjected to molecular docking simulations using PyRx to assess their binding affinity to the CFTR protein. The top-scoring compounds – sterol, magnoflorine, tembetarine, kaempferol, and tinosporinone – were identified based on their strong interaction with the target protein. To evaluate their suitability as drug candidates, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis was performed. Results revealed that all five compounds demonstrated favorable pharmacokinetic and pharmacodynamic properties, including high gastrointestinal absorption, good bioavailability, and low predicted toxicity. Additionally, the compounds satisfied essential drug-likeness criteria, highlighting their potential for therapeutic application. These findings underscore the promise of Tinospora cordifolia phytocompounds as a natural source for CF drug development. However, while the In silico approach provides a strong basis, further validation through in vitro and in vivo studies is necessary to confirm their biological activity and clinical relevance. This study highlights the role of bioinformatics in discovering plant-based treatments for genetic disorders like CF.

Keywords: *Tinospora cordifolia*, cystic fibrosis, CFTR, molecular docking, ADMET analysis, phytocompounds, drug-likeness

INTRODUCTION

Tinospora cordifolia, commonly known as giloy, guduchi, amrita, gurbel, or heart-leaved moonseed, belongs to the Menispermaceae family. This smooth, climbing shrub is widespread across India, typically thriving in deciduous and dry forests. It is also abundant in regions of Myanmar, Sri Lanka, and China [1–4].

T. cordifolia exhibits a range of biological activities, including immunomodulatory, antioxidant, anti-inflammatory, antihypertensive, antidiabetic, and anticancer effects. Various parts of the plant – such as the stem, leaves, root, and their extracts – have demonstrated numerous beneficial properties, including antioxidant, antimicrobial, antiviral, antiparasitic, antidiabetic, anticancer, anti-inflammatory, analgesic, antipyretic, hepatoprotective, and cardioprotective effects [5–9].

Its leaves, stem and roots extract contain phytocompounds which are used in reducing the effect of lung related disorders, such as asthma,

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allergies, chronic bronchitis, and cancer. There are many studies which back the claim of the therapeutic properties of the plant. Numerous studies back up the claim that *Tinospora cordifolia* is used for treating asthma, allergies, chronic bronchitis, and cancer [2, 5].

The medicinal plant contains a diverse range of compounds that exhibit various biological activities. Terpenoids, found in the stem, are effective against respiratory tract infections and skin diseases and have anti-hyperglycemic properties. Alkaloids present in the stem and root possess anti-cancer and antioxidant activities. Lignans from the plant's root display anti-neoplastic and antioxidant effects. Steroids located in the aerial parts of the stem help alleviate stress. The entire plant is known for its use as an antidote to snakebites and scorpion stings and is beneficial in treating conditions, such as pain, neurological disorders, diabetes, rheumatoid arthritis, gout, cancer, high cholesterol, fever, leprosy, and radiation damage [6–10].

Cystic fibrosis (CF) is a genetic disorder that leads to mucus buildup, causing organ damage, especially in the lungs and pancreas. This unusually thick mucus obstructs airways and promotes bacterial growth (e.g., *Pseudomonas*, *Streptococcus*), leading to recurring lung infections. Over time, chronic infection and inflammation progressively damage the lungs, resulting in fibrosis (scarring) and cyst formation, which further reduce lung function. Symptoms may include salty-tasting skin, persistent coughing, frequent lung infections, wheezing or shortness of breath, poor growth, weight loss, greasy and bulky stools, difficulty with bowel movements, and, in males, infertility [9–11].

Cystic fibrosis is caused by genetic changes in the CFTR gene and inheritance is autosomal recessive. Cystic fibrosis is caused by mutations in the CFTR gene, which encodes a protein responsible for creating a channel that transports chloride ions – negatively charged particles – in and out of cells. Chloride, a key component of sodium chloride (salt), plays crucial roles in cells, including regulating the flow of water in tissues, which is essential for producing thin, easily flowing mucus. The disease is chronic and typically progressive, with symptoms often appearing in early childhood or, in some cases, at birth [6, 12–14].

The severity of the condition may be influenced by other genetic and environmental factors. For instance, mutations in genes beyond CFTR could explain why the disease affects some individuals more severely than others, though many of these genetic factors remain unidentified.

Despite significant advancements in cystic fibrosis (CF) treatment, a definitive cure remains elusive. Outcomes for individuals with CF continue to improve, with ongoing research and therapeutic developments expected to drive further progress in the coming years. Advances in patient care, including new drug combinations and therapies, along with pharmacological studies, have significantly enhanced survival rates. However, many patients still face the need for organ transplants as part of long-term treatment for severely affected organs. This study focuses on screening the phytocompounds of *Tinospora cordifolia* as potential drug targets for cystic fibrosis through silico pharmacology, encompassing ADMET analysis, molecular docking, interaction visualization in Biovia Discovery Studio, and protein structure validation using Ramachandran plots.

MATERIALS AND METHODS

Retrieval of Phytocompound

In this study, we explored the medicinal compounds of the plant *Tinospora cordifolia* as potential drug targets for cystic fibrosis. The phytocompounds were obtained from the IMPPAT database (https://cb.imsc.res. in/imppat/), which serves as a repository of Indian medicinal plants based on their phytochemical composition, therapeutic uses, and traditional medicinal formulations. These compounds' 2d structure was downloaded from PubChem database which serves as the largest chemical compound database.

Retrieval of the Proteins

The crystal structures of CFTR (PDB ID: 2BBO), were retrieved from the RCSB PDB repository (https://www.rcsb.org/), with a resolution of 2.55 Å. The structure was resolved through X-ray diffraction methodologies. The protein structure was subjected to purification in DS Biovia Discovery Studio. The non-structural components including water molecules, hetero atoms and ligands were removed from the crystal structure of the protein. To reduce the structural complexity only the A chains were retained in the protein and the additional chains were removed. The protein structure was prepared by adding polar hydrogen atoms and the purified structure was saved in .pdb format.

ADMET Predictions

The retrieved phytocompounds were screened using the SwissADME tool (http://www.swissadme.ch/), which provides various parameters and predictive models to assess physicochemical properties and estimate pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules. The screening was based on pharmacokinetic properties and drug-likeness, evaluated against the following criteria: Lipinski's rule violation (0), high gastrointestinal absorption (GI), Silicos-IT solubility class (soluble or very soluble), bioavailability score (≤0.55), PAINS (0), and synthetic accessibility (≤5). The screened compounds were subjected to toxicity prediction using the ProTox tool (https://tox.charite.de/). ProTox 3.0 utilizes molecular similarity, fragment propensities, frequent features, and machine learning (with fragment similarity-based cluster cross-validation), incorporating a total of 61 models to predict toxicity endpoints. These endpoints include acute toxicity, organ toxicity, toxicological markers, molecular initiating events, metabolism, adverse outcome pathways (Tox21), and toxicity targets. The toxicity prediction was based on toxicity class (Classes 4, 5, and 6), LD50, and specific toxicities, such as hepatotoxicity, nephrotoxicity, carcino toxicity, neurotoxicity, and respiratory toxicity [15, 16].

Molecular Docking and Visualization

Molecular docking is a key technique in computational drug discovery, providing insights into the interactions between small molecules and their protein targets. In this study, PyRx was utilized to perform docking of various antiviral drugs with multiple protein targets. A blind docking approach was employed, which does not assume prior knowledge of the ligand's binding site. The docking area was defined by grid dimensions that encompassed the entire protein structure. During the simulations, the protein was treated as rigid, while the ligands were allowed to remain flexible. An exhaustiveness parameter of 8 was set to ensure a comprehensive search, and the results were primarily assessed based on binding affinities calculated at zero RMSD (Root Mean Square Deviation).

Structural Validation

The protein structure validation was done through errat and procheck tools (https://saves.mbi.ucla.edu/). Procheck tool analyzes the overall model geometry and evaluates the stereochemical quality of the predicted model. Additionally, it generates a Ramachandran plot, highlighting favored, allowed, and disallowed regions. This analysis helps assess structural stability, enabling validation of the model based on these criteria. The Errat server generates a graph plotting the nine-residue sliding window positions against the error function. The result is presented as an overall quality score for the input structure. A quality score above 91% is regarded as good, with a resolution range of 2–3 Å. Scores below 85% are considered poor and are not acceptable.

RESULTS

Ligand Preparation

A total of 66 compounds retrieved from IMPPAT database. The 2D structural file in SDF format of these compounds obtained from PubChem database. The structure was visualized with DS Biovia Discovery Studio Visualizer. A total of five compounds obtained after molecular docking. The ligand was prepared by adding the universal force filed (UFF) and the ligand structural files were converted to PDBQT format using PyRx for docking simulations (Figure 1).

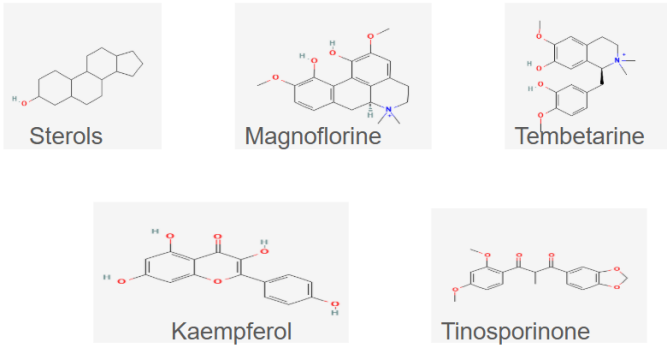

Figure 1. Structures of ligands.

Retrieval of Protein

The ΔF508 mutation in nucleotide-binding domain 1 (NBD1) of the cystic fibrosis transmembrane conductance regulator (CFTR) is the main cause of cystic fibrosis. This study uses the human NBD1 protein with Phe508, represented by 2BBO (Figure 2).

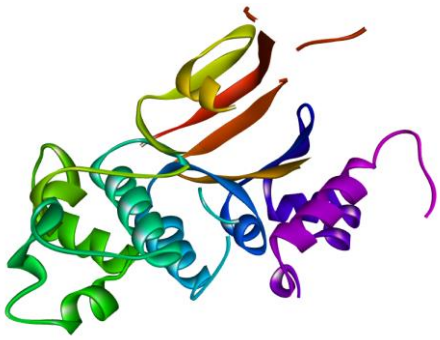

Figure 2. Illustration of the protein structure of 2BBO from RCSB PDB.

PHARMACOLOGICAL STUDIES

The table summarizes key physicochemical and pharmacokinetic properties of five compounds: Tinosporinone, Kaempferol, Tembetarine, Magnoflorine, and Sterol, providing insights into their drug-likeness and bioavailability. Molecular weights range from 248.4 g/mol (Sterol) to 344.42 g/mol (Tembetarine), reflecting structural diversity. Hydrogen acceptor (HA) and donor (HD) counts vary, with Sterol being the simplest (HA = 1, HD = 1) and Kaempferol the most complex (HA=6, HD=4). All compounds exhibit high gastrointestinal (GI) absorption, indicating favorable oral bioavailability. They fully comply with Lipinski's Rule of Five, suggesting strong drug-likeness, and have no PAINS (Pan-Assay Interference Compounds) or Brenk structural alerts, minimizing risks of assay interference or toxic reactive groups. Synthetic accessibility scores (SA) are consistent at 0.55, highlighting ease of synthesis, while lipophilicity (logP) ranges from 3.14 (Kaempferol) to 3.78 (Magnoflorine). Toxicity scores (TOX) are similar across the compounds, with Tinosporinone slightly higher (5) compared to others (4–5). Overall, these properties suggest that the compounds have strong potential for pharmaceutical applications (Table 1).

Table 1. Pharmacological properties of screened phytocompounds.

Compound Name	PubChem ID	MW	HA	HD	GI Absorption	LIPINSKI	PAINS	BS	SA	TOX
Tinosporinoe	42607646	342.34	6	0	High	0	0	0.55	3.36	5
Kaempferol	5280863	286.24	6	4	High	0	0	0.55	3.14	5
Tembetarine	167718	344.42	4	2	High	0	0	0.55	3.21	4
Magnoflorine	73337	342.41	4	2	High	0	0	0.55	3.78	4
Sterol	1107	248.4	1	1	High	0	0	0.55	3.76	4

Molecular Docking and Visualization

The docking study evaluated the binding affinities between various ligands, including sterols, magnoflorine, tembetarine, kaempferol, and tinosporinone, with the protein target 2bbo. This analysis provided essential insights for potential drug discovery. Binding affinities were expressed in kilocalories per mole (kcal/mol), where the highest negative value indicated stronger and more energetically favorable interactions between the ligand and protein (Table 2).

Table 2. Molecular docking of screened ligands against 2BBO.

S.N.	Ligand	Binding Affinity
A	1107	–6.6
B	73337	–6.8
C	167718	–6.5
D	5280863	–6.3
E	42607646	–6.4

Visualization

Magnoflorine (73337) exhibits the highest binding affinity (–6.8 kcal/mol) to the protein 2bbo compared to the other ligands. This strong binding affinity is driven by multiple stabilizing interactions, including a Pi-Anion interaction with Glu A:528, a conventional hydrogen bond with Asp A:529, and a Pi-Alkyl interaction with Leu A:581. These interactions enhance the compound's electrostatic, polar, and hydrophobic stabilization within the binding pocket, making Magnoflorine the most favorable ligand for binding to 2bbo among the tested compounds (Figure 3).

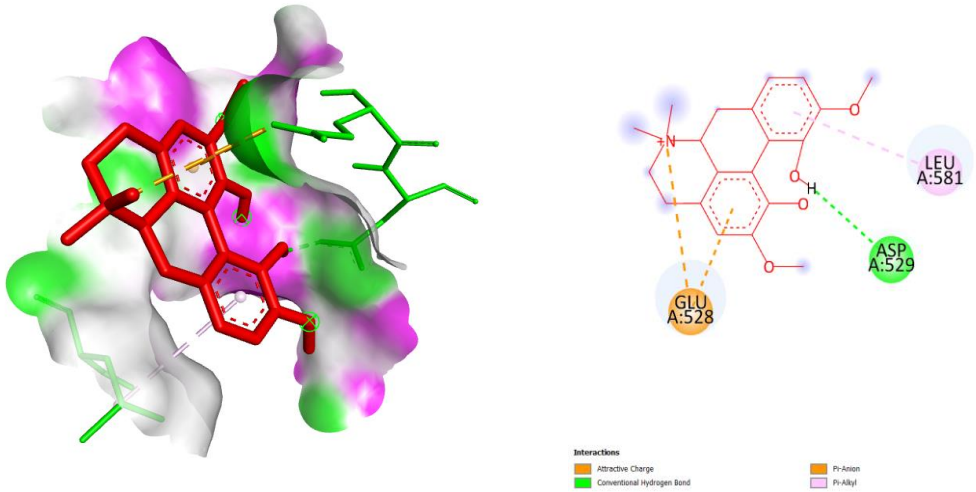

Figure 3. Interactions of top ligand (73337) interacting with 2BBO protein.

Ramachandran Plot Analysis

The Ramachandran plot (Figure 4) analysis generated by procheck indicates that 91.7% of the residues are in the most favored regions, which aligns with the criteria for a high-quality protein model, typically defined by having over 90% of residues in these regions. Additionally, 7.3% of the residues are in the additional allowed regions, while 1.0% are in generously allowed regions, reflecting minor deviations from ideal conformations. Importantly, there are no residues (0%) in the disallowed regions, suggesting that the model does not exhibit any severe structural anomalies. Overall, the high percentage of residues in the favored regions, coupled with the absence of residues in disallowed regions, supports the model's stereochemical integrity and reliability for further structural analysis. Based on Errat analysis, the overall quality factor is 100%. The result reflects minimal structural errors, demonstrating the model's robustness and suitability for further applications or analyses (Table 3).

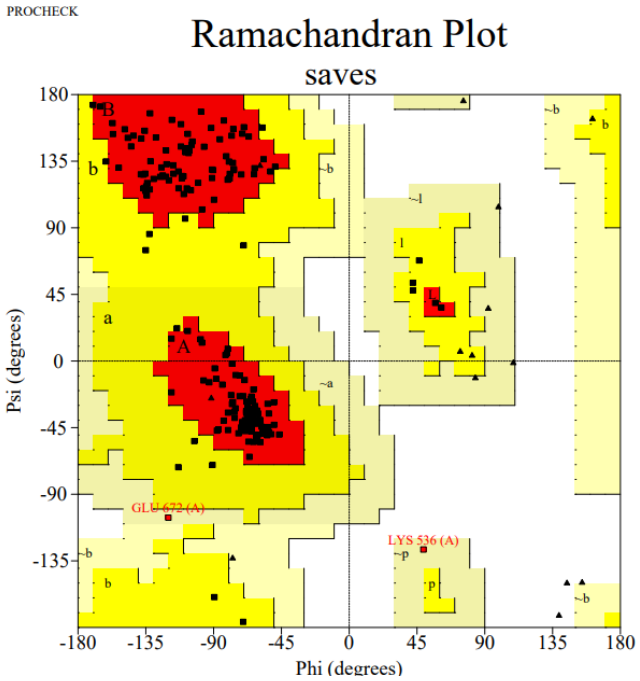

Figure 4. Ramachandran Plot.

Table 3. Ramachandran plot statistics.

S.N.	Ramachandran Plot Statistics	Total Residue	Percentage
1	Residues in most favoured regions	188	91. 7%
2	Residues in additional allowed region (yellow)	15	7. 3%
3	Residues in generously allowed region (cream)	2	1. 0%
4	Residues in disallowed region (white)	0	0. 0%
5	No. of non-glycine and non-proline residues	205	100%
6	Number of end residues (excl. Gly and Pro)	14	
7	Number of glycine residues (shown in triangle)	17	
8	Number of proline residues	6	
9	*Total number of residues*	*242*	

DISCUSSION

Cystic fibrosis (CF) remains an incurable disease due to the multifaceted nature of its pathophysiology and the complexity of the underlying CFTR gene mutations. Despite advancements in treatment, including CFTR modulators, like Trikafta, these therapies only target specific mutations and fail to address the broader genetic and environmental contributors influencing disease severity. Moreover, the progressive nature of CF, characterized by chronic inflammation, persistent lung infections, and eventual fibrosis, exacerbates the difficulty of developing a definitive cure. Limited therapeutic options to completely reverse the structural and functional damage caused by CF highlight significant research gaps. These include the need for novel drug targets, improved understanding of modifier genes, and therapeutic approaches that address the root causes beyond CFTR dysfunction [17–20].

The current therapeutic landscape for CF is heavily reliant on symptomatic management and mutation-specific drugs. However, over 10% of CF patients, including those with rare mutations, do not benefit from these modulators, necessitating alternative approaches. Additionally, the limited efficacy of current drugs in preventing long-term complications, such as fibrosis and multi-organ failure underscores the urgency for innovative solutions. Other challenges include the high cost of CF treatments, potential drug resistance, and limited accessibility in resource-poor settings. This calls for

research into cost-effective, broad-spectrum, and mutation-agnostic therapies that can alleviate disease burden globally [21–25].

Tinospora cordifolia, a traditional medicinal plant known for its broad-spectrum pharmacological activities, has shown promise in addressing key aspects of CF pathophysiology. Its phytochemicals, including alkaloids, terpenoids, and lignans, possess potent antioxidant, anti-inflammatory, and immunomodulatory properties that could mitigate chronic inflammation and oxidative stress, pivotal in CF progression. Notably, the anti-bacterial and anti-neoplastic activities of these compounds may help combat persistent infections and reduce the risk of secondary complications, such as pulmonary cancer. Additionally, *T. cordifolia*'s bioactive constituents, like magnoflorine and tinosporinone, exhibit favorable pharmacokinetic profiles, including high GI absorption, Lipinski compliance, and minimal toxicity, making them attractive candidates for drug development [26].

The molecular docking results of T.cordifolia-derived compounds provide critical insights into their therapeutic potential. Among the screened compounds, magnoflorine demonstrated the highest binding affinity (–6.8 kcal/mol) to the NBD1 domain of the CFTR protein (2BBO). Stabilizing interactions, including hydrogen bonds and hydrophobic interactions, suggest that magnoflorine may effectively modulate CFTR function or influence associated pathways. Other compounds, such as tinosporinone and kaempferol, also displayed promising binding affinities and favorable pharmacological properties, reinforcing their potential as drug candidates. These findings underscore the need for further in vitro and in vivo studies to validate the therapeutic efficacy of these compounds in CF models [27–29].

The versatility of *T. cordifolia* in modulating multiple pathways relevant to CF pathogenesis positions it as a promising source for novel therapies. While synthetic drugs focus on singular targets, the multifaceted nature of *T. cordifolia* compounds could provide a holistic approach to managing CF. The integration of bioinformatics-driven drug discovery with traditional knowledge accelerates the identification of lead compounds, as evidenced by the current study. Future research should focus on optimizing these compounds for enhanced bioavailability and specificity, alongside exploring their synergistic effects with existing CF therapies.

The incurable nature of CF highlights the critical need for innovative and integrative therapeutic strategies. Tinospora cordifolia, with its rich phytochemical profile and diverse pharmacological activities, offers a promising avenue for addressing the complex challenges of CF treatment. The in-silico findings provide a strong foundation for further research into the development of phytocompound-based therapies, potentially revolutionizing the management of this debilitating condition.

CONCLUSIONS

The present study aimed to identify potential drug candidates for the treatment of cystic fibrosis using in silico virtual screening techniques, focusing on compounds derived from the Indian medicinal plant *Tinospora cordifolia*. Through a comprehensive virtual screening process, five promising ligands were identified: sterol, magnoflorine, tembetarine, kaempferol, and tinosporinone. According to the results of this study, the ligand magnoflorine exhibited the best binding affinity with the target protein 2BBO associated with cystic fibrosis, showing a binding energy of –6.8 kcal/mol. Among the other ligands, sterol displayed a binding affinity of –6.6 kcal/mol, tembetarine showed –6.5 kcal/mol, kaempferol demonstrated –6. 4 kcal/mol, and tinosporinone exhibited the lowest binding affinity of –6.3 kcal/mol. These findings highlight magnoflorine as the most promising candidate for further investigation. In vitro and in vivo studies could provide deeper insights into the therapeutic potential of these compounds.

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