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Precision Medicine for Neurofibromatosis Type 1: Progress and Prospects in Drug Discovery

Sheilina Choudhary*

Abstract

Objective: *The development of neurofibromas, café-au-lait spots, and other neurological problems are the hallmarks of neurofibromatosis type 1 (NF1), a hereditary disorder. The dearth of efficacious pharmaceutical therapies underscores the need for novel therapeutic approaches, even in the face of clinical variability. Through very accurate prediction of the binding affinity of possible therapeutic drugs with the target protein, the computational technique known as "molecular docking" has become a potent tool in the drug development process. In the context of NF1 drug discovery, this research work intends to investigate the use of molecular docking. Using molecular docking techniques, the main goal of this work was to find tiny molecules or compounds that could control important proteins implicated in NF1 pathogenesis. Through a comprehensive literature review, relevant protein targets associated with NF1, such as neurofilament and its interacting partners, will be identified and selected for molecular docking studies. Virtual screening of complex libraries will be performed using state-of-the-art docking algorithms to predict binding affinities and modes of interaction between potential drugs and target proteins. Furthermore, this study aimed to confirm the effectiveness of lead compounds identified through SWISS ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis to assess their drug similarity and safety profile. The results of this research effort have the potential to accelerate the discovery and development of new treatments for NF1, bringing new hope to patients with this debilitating genetic disease.* ***Methods:*** *In this study, target proteins were downloaded from PDB and docked into BIOVIA. The binding affinity of standard and drug ligands to each target protein was compared and evaluated. Additionally, only four substances were selected for the final SWISS-ADME results.* ***Results:*** *When two molecules are coupled together to create a stable complex, the docking result predicts the preferred orientation of one molecule (the ligand) to the other (the target protein).* ***Conclusion:*** *These ligands could potentially be used for the treatment of neurofibromatosis type 1 in future approaches to study the necessary ligands in vitro and analyze them in vivo for the generation of new neurofibromatosis inhibitors.*

Keywords: Neurofibromatosis, NF1 gene, neurofibromin, tumor suppressor gene, NF1 gene mutation, Café-au-lait spots, neurofibromatosis tumors, attention-deficit hyperactivity disorder, and kinase inhibitors, malignant peripheral nerve sheath tumors, molecular docking

***Author for Correspondence**
Sheilina Choudhary
E-mail: sheilina2003@gmail.com

Student, Department of Bioengineering and Food Technology, Shoolini University, Solan, Himachal Pradesh, India

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INTRODUCTION

Neurofibromatosis is a common hereditary disorder that affects the nervous system, causing tumors to form on the nerve tissue. These disorders are classified into three main types: neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis, each of which is associated with distinct genetic mutations and clinical manifestations. Underlying genetic abnormalities involving tumor suppressor genes, especially NF1 and NF2, lead to dysregulation of cell signaling pathways and tumor development.

The NF1 gene on chromosome 17 encodes a neurofilament protein that controls the Ras signaling pathway. Neurofibromin acts as a negative regulator of Ras, a GTPase involved in cell development and multiplication [1]. Mutations in NF1 reduce nerve fiber function, leading to overactive Ras signaling and uncontrolled cell growth. This dysregulation contributes to the development of various tumors, including neurofibromas and gliomas [2].

NF1 is a genetic disorder that presents with a wide range of clinical manifestations that primarily affect the nervous system and skin. This relatively common condition is caused by changes in the NF1 gene on chromosome 17q11.2, resulting in the generation of an unusual neurofibromin protein that serves as a tumor silencer and plays a role in cell signaling pathways. The expression of NF1 can vary significantly among affected individuals, even within the same family, leading to diverse signs and symptoms [3].

NF1 features an assortment of clinical features, can be created at any age, and influences numerous organ frameworks. The best-known include NF1 is the development of neurofibromas, which are benign tumors that emerge from the peripheral nerves.

These neurofibromas vary in size and number from small nodules to large disfiguring masses. CNs typically appear in adolescence and continue to develop throughout adulthood, whereas plexiform neurofibromas, which are deeper and involve multiple nerve bundles, often develop in early childhood. The ability to compress structural structures can lead to significant morbidity [4].

In expansion to neurofibromas, NF1 patients frequently have café-au-lait plaques. Café-au-lait spots are level-pigmented skin lesions that appear as light brown spots. These spots are, as a rule, displayed at birth or created during the first few years of life and may increase in estimate and number with age. Other dermatological findings associated with NF1 include armpit or groin freckles, and optic tract gliomas. OTGs are low-grade tumors that affect the optic tract and can cause visual impairment or loss.

In addition to dermatological manifestations, NF1 is characterized by various systemic complications. Skeletal abnormalities, such as scoliosis and skeletal dysplasia, are relatively common, as are cognitive and behavioral problems, including learning disabilities, ADHD, and the autism spectrum. Additionally, individuals with NF1 have an increased tendency to develop certain tumors, including optic gliomas, MPNSTs, and GIST, emphasizing the importance of lifelong monitoring and care [5].

NF1 is caused by transformations within the NF1 gene, which encodes neurofibromin, a large protein that controls cell multiplication and separation. Neurofibromin acts as a negative regulator of the Ras signaling pathway and plays a fundamental role in cell development, separation, and survival. Loss of neurofibromin leads to dysregulation of Ras signaling, driving unusual cell expansion and tumor arrangement.

NF1 is highly penetrant, meaning that individuals with a mutation in one copy of NF1 are highly likely to develop clinical manifestations of the disease. However, the clinical presentation of NF1 can vary widely even in individuals with the same underlying genetic mutation. This variation is thought to be due to factors such as genetic modifiers, environmental influences, and stochastic events during development, highlighting the complex interactions between genetic factors and the environment in the pathogenesis of NF1 [6].

Phytocompounds

Phytochemicals are cancer prevention agents that maintain mitochondrial function and homeostasis, anticipate natural apoptosis and neuroinflammation, and activate cellular flag pathways to actuate anti-apoptotic and pro-survival properties.

The main proteins associated with neurofibromatosis include two: Neurofibromin, and SPRED1.

- The protein that has been observed to be affected in NF1 patients is neurofibromin, which is crucial to the RAS signaling cascade. NF1 is located on chromosome 17 and encodes nerve fibers. Mutations in NF1 can lead to reduced nerve fiber function, contributing to uncontrolled cell growth and tumor formation, as in NF1 [6].
- The SPRED1 protein, an important regulator of the Ras/MAPK pathway, is encoded by the SPRED1 gene, and its loss-of-function mutations are strongly associated with the development of Legius syndrome, a disorder with a clinical overlap with NF1. Understanding the complex interactions between SPRED1 and NF1 provides insights into the molecular mechanisms underlying these related conditions, providing potential avenues for targeted therapeutic interventions [7].

Some of the phytocompounds that can be used in NF1 treatment include the following:

1. Resveratrol
2. Curcumin
3. Sirolimus
4. Quercetin
5. Lovastatin
6. Fumagillin
7. Temsirolimus
8. Torin 1

METHODS

1. *Protein extraction and purification:* The protein alpha-synuclein 3D structure was determined using X-ray diffraction with a resolution factor of 2.16 Å. The structures were downloaded from the RCSB PDB (https://www.rcsb.org/) in PDB format. The missing residues were replaced with BIOVIA, which purifies the protein by removing water molecules atm and adding polar hydrogen to the retained Chain A remaining chains were removed. This pure protein was then saved in the pdb file format, which was used to generate the 2-dimensional structure and Ramachandran plot with PDBsum (https://www.rcsb.org/), and the hydrophobicity plot using the BIOVIA Discovery Studio program.
2. *Receptor recovery and absolution:* IMPAAT (https://cb.imsc.res.in/imppat/) yielded eight phytocompounds with potential anti-neurofibromatosis type 1 activity, including antioxidant, anti-mutagenic, anti-hepatotoxic, anti-inflammatory, anti-aging, and chemopreventive properties. Canonical SMILES, PubChem CID, and two-dimensional (2D) models of 2, Sirolimus, Resveratrol, and Lovastatin were obtained in SDF format from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and all structures were converted to PDB format using Open Babel software (http://openbabel.org).

Molecular Docking

Following protein and ligand retrieval, PyRx was used for molecular docking analysis. PyRx is a virtual molecular screening program that docks small-molecule libraries to macromolecules to identify lead compounds with the required biological properties. Eight phytocompounds and two conventional medicines were used as ligands, and the two purified proteins were uploaded as macromolecules. The additional ligands were energy-minimized and converted to the pdbqt format. All ligands were docked with the target proteins in distinct steps and evaluated based on their binding affinities. Binding affinity refers to the strength at which proteins bind to ligands. Negative values for the binding affinity (or binding free energy) imply that the ligand is expected to bind to a specific macromolecule.

The lower the numerical values for binding affinity, the better the projected interaction between a ligand and a macromolecule. The ligand with the lowest binding affinity and zero RMSD value was chosen for each protein and visualized using the BIOVIA Discovery Studio program. The RMSD value

was used to assess the docked conformation in relation to the other docked conformations or the reference conformation. The inhibitory activities of the ligands and conventional medicines were compared according to binding affinity. Eight phytocompounds and two conventional medicines were uploaded as ligands together with two target proteins, 1NF1 and 1TJ6. The loaded ligands had the lowest energy and were converted to.pdbqt format, after which the grid for the targeted protein was constructed as described below.

The values acquired for the grid dimensions are X=15Å, Y=15 Å, and Z=15Å. The center grid is shown in the table. This was comparable for all three points.

Visualization

PyRx was used to store each ligand's best model in the PDB file format after selecting the top ligands with the lowest binding affinity for each protein. BIOVIA Discovery Studio software was used to observe the three-dimensional (3D) structure and non-bond interactions. A 3D model was obtained in PNG file format.

Physiochemical Studies (ADMET Analysis)

Pharmacokinetics were assessed in ADMET (https://admetmesh.scbdd.com/) using Lipinski's rule of five (RO5) in physiochemical studies. Predictive factors for pharmacodynamic features include physiochemical characteristics, absorption, distribution, metabolism, medicinal chemistry, toxicity, and excretion. Using ADMETlab 2.0 (https://admetmesh.scbdd.com/), the top four docked ligands with the lowest binding affinity for each protein were evaluated.

RESULTS

Eight phytocompounds were selected; however, only three were chosen based on the docking results. Figure 1 depicts the two-dimensional chemical structures of the following compounds: To evaluate the inhibitory effectiveness of these compounds against the target proteins, three common medications were procured: resveratrol, lovastatin, and sirolimus, as depicted in Figure 1. Furthermore, it was discovered that the three phytocompounds with the greatest binding affinities with all the chosen receptors were sirolimus, lovastatin, and resveratrol.

Protein Extraction and Purification

After obtaining the necessary information, the PDB was able to obtain the three-dimensional (3D) crystal structure of the two target proteins. Proteins 1NF1 and 1TJ6 were purified using the BIOVIA Discovery program, and their respective structures are illustrated in Figures 2 and 3. The Ramachandran plot, hydropathy plot, and secondary structure were examined using structural analysis.

Molecular Docking

For this docking investigation, eight ligands were placed against 1NF1 and 1TJ6 in the PyRx program. The ideal docking orientation was determined by docking with the conformation that had the lowest binding affinity and the lowest root mean square deviation (RMSD). Following docking completion, binding affinity and RMSD were determined. Along with these eight phytocompounds, standard pharmaceuticals were docked with each target protein and their binding affinity was recorded. Of all the phytocompounds, the common phytocompounds for both target proteins with binding affinities lower than seven and above were selected.

Figure 4a Protein-ligand docking and Figure 4b Revealing Docking scores

- *Docking score:* -5.1
- *Binding pocket volume:* 437 Å^3
- *Center of binding pocket:* (28, -8, 29)
- *Potential:* Based on the docking score and the size of the binding pocket, resveratrol appears to be a potential ligand for 1NF1, as shown in Figure 4.

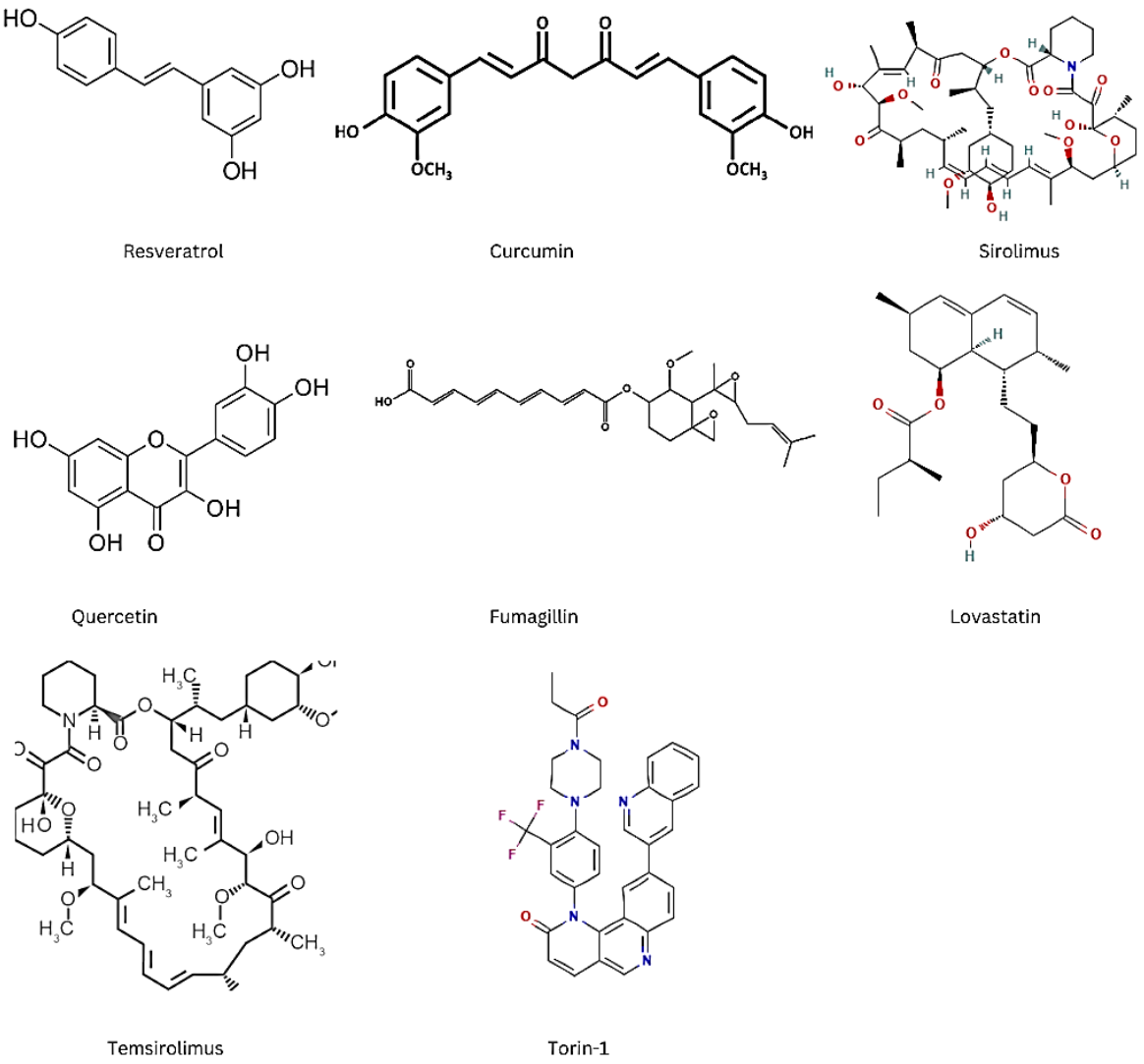
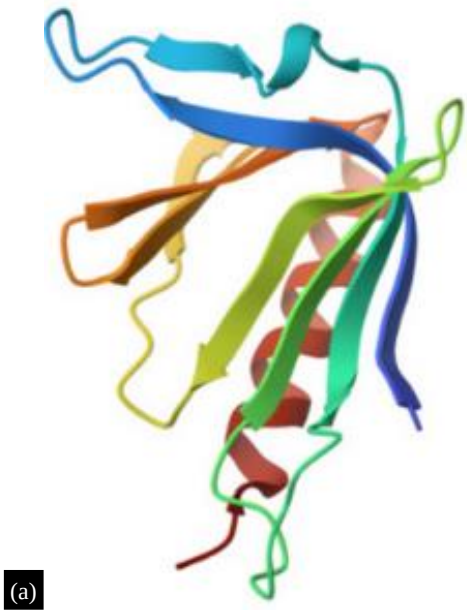
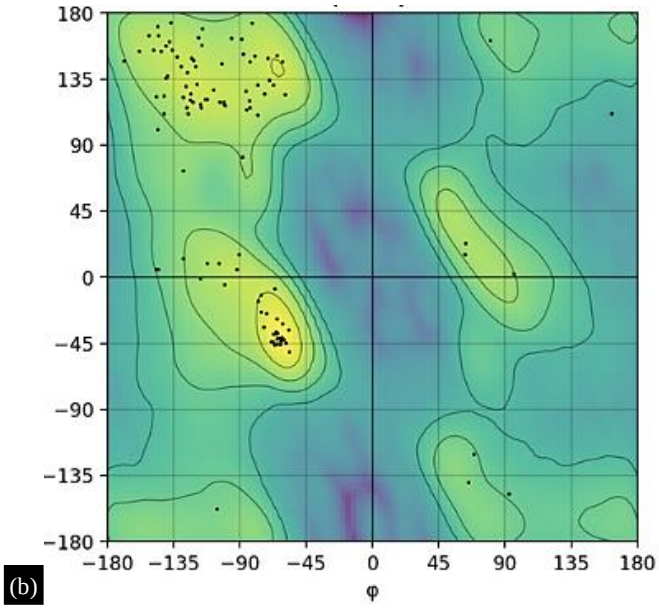
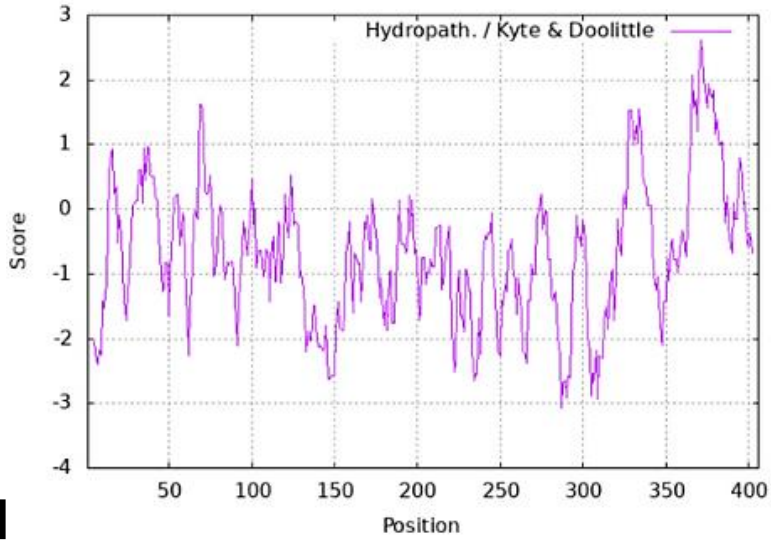


Figure 1. Chemical structure of top phytocompounds and standard drugs.



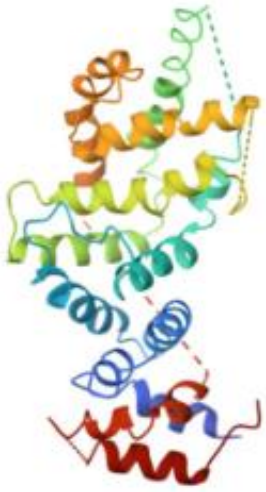


(b)

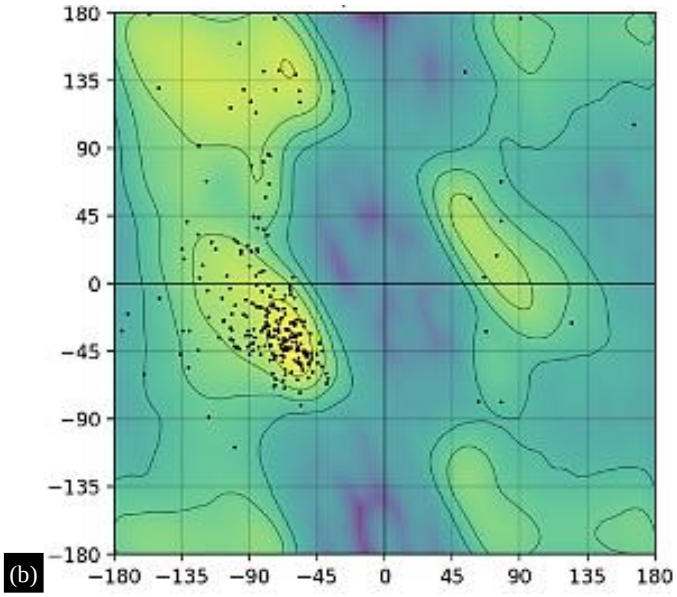


(c)

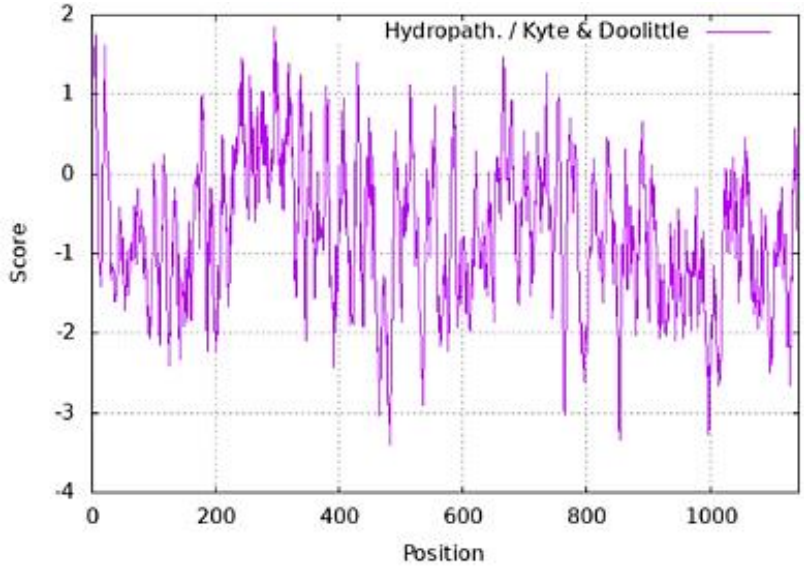
Figure 2. Structural analyses of 1TJ6: (a) structure, (b) Ramachandran plot, (c) hydropathy plot.



(a)

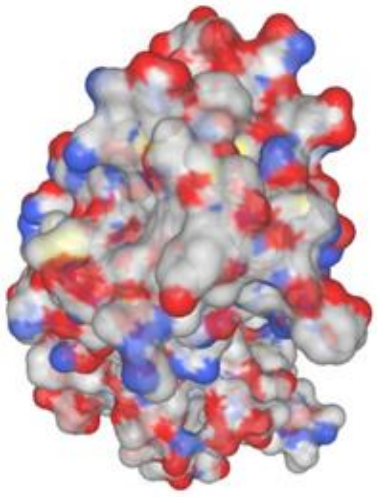


(b)



(c)

Figure 3. Structural analyses of 1NF1: (a) structure, (b) Ramachandran plot, (c) hydropathy plot.



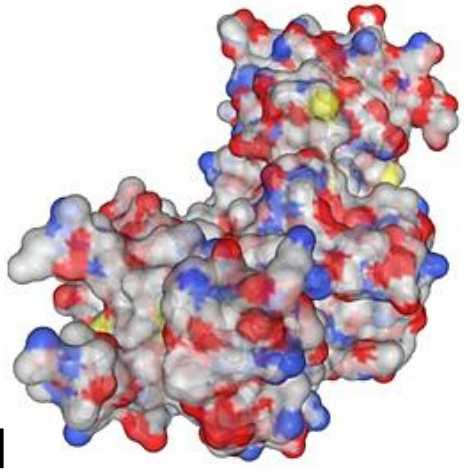
(a)

(b)

CurPocket ID	Vina score	Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
C2	-6.8	407	30, -28, -2	21, 21, 21
C5	-6.4	144	42, -15, 33	21, 21, 21
C4	-5.3	150	54, -9, 36	21, 21, 21
C1	-5.1	437	28, -8, 29	21, 21, 21
C3	-5.0	326	23, -23, 14	21, 21, 21

Figure 4. Molecular docking results of 1NF1 with resveratrol.

(a)



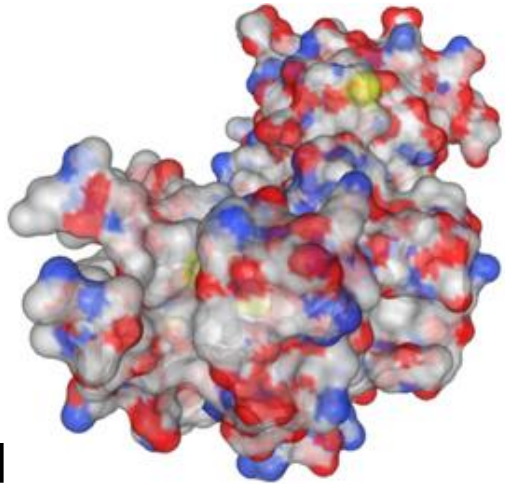
(b)

CurPocket ID	Vina score	Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
C5	-8.2	144	42, -15, 33	28, 28, 28
C4	-6.7	150	54, -9, 36	28, 28, 28
C1	-6.5	437	28, -8, 29	28, 28, 28
C3	-6.5	326	23, -23, 14	28, 28, 28
C2	-6.3	407	30, -28, -2	28, 28, 28

Figure 5. Molecular docking results of 1NF1 with sirolimus.

Figure 5a Protein-ligand docking and Figure 5b Revealing Docking scores

- *Docking score:* -5.8
- *Binding pocket volume:* 407 Å^3
- *Center of binding pocket:* (30, -28, 2)
- *Potential:* Sirolimus has a slightly higher docking score than resveratrol, indicating a potentially stronger binding affinity for 1NF1, as shown in Figure 5.



(a)

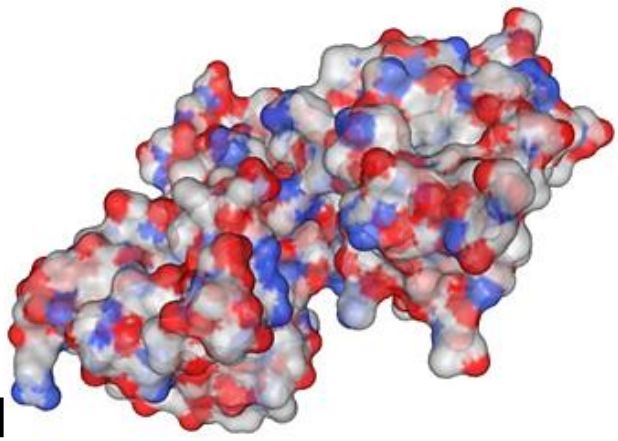
CurPocket ID	Vina score	Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
C5	-6.9	144	42, -15, 33	22, 22, 22
C3	-5.9	326	23, -23, 14	22, 22, 22
C1	-5.7	437	28, -8, 29	22, 22, 22
C4	-5.5	150	54, -9, 36	22, 22, 22
C2	-5.0	407	30, -28, -2	22, 22, 22

(b)

Figure 6. Molecular docking results of 1NF1 with lovastatin.

Figure 6a Protein-ligand docking and Figure 6b Revealing Docking scores

- *Docking score:* -6.4
- *Binding pocket volume:* 144 Å^3
- *Center of binding pocket:* (42, -15, 33)
- *Potential:* Lovastatin had the highest docking score among the three ligands, suggesting that it has the strongest potential binding affinity to 1NF1. However, its binding pocket volume was significantly smaller than those of the others, as shown in Figure 6.



(a)

(b)

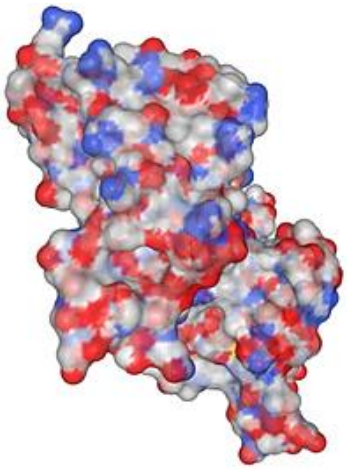
CurPocket ID	Vina score	Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
C1	-5.9	828	18, 8, 17	21, 21, 27
C3	-5.3	84	20, 5, 2	21, 21, 21
C2	-5.1	262	10, 9, 14	21, 21, 21
C4	-5.1	55	14, -4, 35	21, 21, 21
C5	-5.1	51	20, -4, 27	21, 21, 21

Figure 7. Molecular docking results of 1TJ6 with resveratrol.

Figure 7a Protein-ligand docking and Figure 7b Revealing Docking scores

- *Docking score:* -5.1
- *Binding pocket volume:* 55 Å^3
- *Center of binding pocket:* (14, -4, 35)
- *Potential:* The results of these docking experiments suggest that there is a moderate binding affinity between protein 1TJ6 and the ligand resveratrol, as shown in Figure 7.

(a)



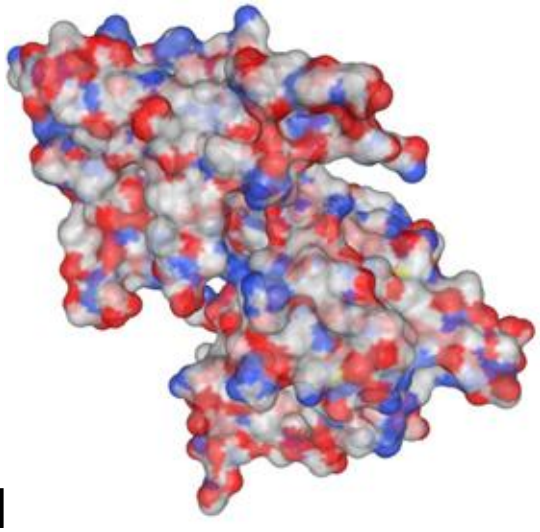
(b)

CurPocket ID	Vina score	Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
C2	-7.7	262	10, 9, 14	28, 28, 28
C4	-7.1	55	14, -4, 35	28, 28, 28
C5	-6.8	51	20, -4, 27	28, 28, 28
C1	-6.5	828	18, 8, 17	28, 28, 28
C3	-5.9	84	20, 5, 2	28, 28, 28

Figure 8. Molecular docking results of 1TJ6 with sirolimus.

Figure 8a Showing protein-ligand docking and Figure 8b Revealing docking scores

- *Docking score:* -7.7
- *Binding pocket volume:* 262 Å^3
- *Center of binding pocket:* (10, 9, 14)
- *Potential:* These scores suggest that sirolimus has a good affinity for 1TJ6, as shown in Figure 8.



(a)

CurPocket ID	Vina ↑F score	Cavity ↑F volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
○C1	-6.5	828	18, 8, 17	22, 22, 22
○C2	-6.4	262	10, 9, 14	22, 22, 22
○C4	-6.3	55	14, -4, 35	22, 22, 22
○C3	-5.3	84	20, 5, 2	22, 22, 22
○C5	-5.2	51	20, -4, 27	22, 22, 22

(b)

Figure 9. Molecular docking results of 1TJ6 with lovastatin:

Figure 9a Protein-ligand docking and Figure 9b Revealing Docking scores

- *Docking score:* -6.5
- *Binding pocket volume:* 828Å^3
- *Center of binding pocket:* (18, 8, 17)
- *Potential:* The results of these docking experiments suggest that there is a moderate binding affinity between protein 1TJ6 and the ligand lovastatin, as shown in Figure 9.

ADMET Analysis

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) of small organic compounds were predicted and computed using the web-based program SwissADME. It is frequently used in drug discovery and development, with a primary focus on compounds resembling drugs [8]. SwissADME offers numerous ADMET-related features and forecasts:

Lipophilicity

The lipophilicity of a chemical is determined by computing its octanol/water partition coefficient, which indicates its hydrophobicity and its capacity to cross biological membranes.

Pharmacology

By studying the biological effects of the medications, parameters such as chemical absorption, distribution, metabolism, and excretion were predicted.

Drug-likeness

Lipinski's rule of five is a widely used criterion for assessing drug-like properties based on molecular weight, lipophilicity, hydrogen bonding, and polar surface area. SwissADME evaluates the compliance of a compound with this rule.

Predictions of Toxicity

To ascertain potential toxicity, it makes many predictions about traits such as mutagenicity, tumorigenicity, irritability, and effects on reproduction were assessed.

Bioavailability

SwissADME anticipates oral bioavailability, a crucial factor in drug development.

Table 1 provides information on human intestinal absorption (HIA), Log S(ESOL), and ligand solubility. HIA may be the degree of the fraction of an orally administered dose of a compound that reaches the systemic circulation. All recorded ligands had high HIA values, demonstrating their potential for oral retention.

Log S(ESOL) is a measure of the aqueous solubility of a compound, with more negative values indicating a lower solubility. Resveratrol, curcumin, sirolimus, quercetin, lovastatin, fumagillin, and temsirolimus all had negative Log S(ESOL) values, indicating low solubility. Among the listed ligands, quercetin had the highest solubility at 0.211 mg/mL, whereas Torin-1 had the lowest solubility at 0.0000202 mg/mL. These data are valuable for understanding the pharmacokinetic properties of these ligands.

Table 2 provides information on the Lipinski rule of five and pain alerts for ligand selection. Using a series of criteria based on physicochemical features, the Lipinski rule of five determines whether a substance is drug-like. This rule states that substances that violate many criteria have a lower likelihood of becoming orally bioavailable [9]. Among the listed ligands, resveratrol, curcumin, sirolimus, lovastatin, and fumagillin are accepted by the Lipinski rule of five, indicating their potential oral bioavailability. Quercetin and temsirolimus are also accepted, but quercetin has one violation, whereas temsirolimus has none. Torin-1, however, is not accepted by the Lipinski rule of five because of its molecular weight, and it has one pain alert. Pain alerts are warnings of potential adverse effects associated with a compound, such as pain or irritation. This data are useful for evaluating the drug-likeness and safety of these ligands.

Table 3 presents the molecular weights, number of hydrogen acceptors, and number of hydrogen donors for the selection of compounds acting as ligands. Resveratrol has a molecular weight of 228.24 g/mol, three hydrogen acceptors, and three hydrogen donors. Curcumin and sirolimus have a molecular weight of 368.38 g/mol, with six hydrogen acceptors and two hydrogen donors. Quercetin, which has a molecular weight of 302.24 g/mol, possesses seven hydrogen acceptors and five hydrogen donors. Lovastatin, fumagillin, and temsirolimus share a molecular weight of 458.54 g/mol, with five or seven hydrogen acceptors and one hydrogen donor. Torin-1, with a molecular weight of 602.64 g/mol, has seven hydrogen acceptors and no hydrogen donors. These data are essential to understand the physicochemical properties of these ligands.

Table 1. Absorption of phytocompounds.

Ligand	HIA	Log S(ESOL)	Solubility
Resveratrol	High	-3.62	5.51e-02mg/ml
Curcumin	High	-3.94	4.22e-02mg/ml
Sirolimus	High	-3.94	4.22e-02mg/ml
Quercetin	High	-3.16	2.11e-01mg/ml
Lovastatin	High	-4.57	1.09e-02mg/ml
Fumagillin	High	-4.45	1.62e-02mg/ml
Temsirolimus	High	-4.45	1.62e-02mg/ml
Torin-1	Low	-7.48	2.02e-05mg/ml

Table 2. Medicinal chemistry of phytochemicals.

Ligands	Lipinski	Pain Alerts
Resveratrol	Accepted	0
Curcumin	Accepted	0
Sirolimus	Accepted	0
Quercetin	Accepted	1
Lovastatin	Accepted	0
Fumagillin	Accepted	0
Temsirolimus	Accepted	0
Torin-1	Not Accepted	1

Table 3. Physiochemical properties of phytochemicals.

Ligands	Molecular weight	No. of hydrogen acceptors	No. of hydrogen donors
Resveratrol	228.24gms	3	3
Curcumin	368.38gms	6	2
Sirolimus	368.38gms	6	2
Quercetin	302.24gms	7	5
Lovastatin	404.54gms	5	1
Fumagillin	458.54gms	7	1
Temsirolimus	458.54gms	7	1
Torin-1	602.64gms	7	0

Table 4. Distribution of phytochemicals.

Ligands	Blood-Brain-Barrier	Skin Permeation
Resveratrol	Yes	-5.47 cm/s
Curcumin	No	-6.28 cm/s
Sirolimus	No	-6.28 cm/s
Quercetin	No	-7.05 cm/s
Lovastatin	Yes	-5.74 cm/s
Fumagillin	No	-6.29 cm/s
Temsirolimus	No	-6.29 cm/s
Torin-1	No	-5.75 cm/s

Table 4 provides information on the permeability of various compounds across the blood-brain barrier and skin. The permeability values are given in centimeters per second. Among the listed compounds, resveratrol and lovastatin are identified as ligands, with permeability values of -5.47 cm/s and -5.74 cm/s, respectively. The remaining compounds, including curcumin, sirolimus, quercetin, fumagillin,

temsirolimus, and Torin-1 exhibit permeability values ranging from -5.75 cm/s to -7.05 cm/s. These data are valuable for understanding the potential of these compounds to cross the blood-brain barrier and permeate the skin, which has implications for their pharmacological and therapeutic applications.

As shown in Table 5, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 are specific CYP450 chemicals. These proteins are found at a very basic level inside the liver, even though they can also be found in other tissues such as the inner parts and lungs [10]. A few points of interest regarding cytochromes are presented in Table 5.

- CYP1A2: Metabolizes caffeine, nicotine, and other environmental toxins.
- CYP2C19: Metabolizes proton pump inhibitors, antidepressants, and antiplatelets.
- CYP2C9: Metabolizes Warfarin, NSAIDs, and some antiviral drugs.
- CYP2D6: Metabolizes codeine, opioids, and antidepressants.
- CYP3A4: Metabolizes a wide range of drugs, including statins, antibiotics, and anticancer drugs.

DISCUSSION

Emerging data show a glimmer of hope for people with NF1, a complex neurological disorder characterized by tumor growth along the nerves.

This discussion explores the potential of three compounds, resveratrol, sirolimus, and lovastatin, as promising therapeutic candidates based on their attractive properties.

1. *Multifaceted approach:* Each compound has unique mechanisms that may counteract different aspects of NF1. Resveratrol, a natural polyphenol, targets inflammation and oxidative stress, which are the key factors in the development of NF1. Sirolimus, an immunosuppressant, may hinder tumor growth by regulating cell proliferation. Lovastatin, a cholesterol-lowering drug, demonstrated surprising antitumor effects in an NF1 model. This diversity provides a multipronged attack on the disease.
2. *Blood-brain barrier permeability:* Unlike many drugs, resveratrol and lovastatin easily cross the BBB, allowing them to directly target the nervous system where tumors arise from NF1. Effective treatment of this disease is very important. Although sirolimus has limited BBB permeability, its systemic effects may still be beneficial.
3. *Encouraging preclinical data:* Studies on cell cultures and animal models of NF1 have shown promising results. Resveratrol has been shown to inhibit tumor growth and improve neurological function. Sirolimus exhibits antitumor activity and reduces the size of neurofibromas. Lovastatin exhibits similar tumor-inhibiting effects.

These results warrant further investigation in human trials.

- *Safety considerations:* All three compounds have established safety profiles and have been used in various clinical settings for other conditions.
- Previous experience bodes well for their potential application in the treatment of NF1, potentially accelerating the approval process and reducing risks to patients.

Table 5. Excretion and toxicity of phytochemicals.

Ligands	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Resveratrol	No	No	Yes	No	Yes
Curcumin	No	No	Yes	No	Yes
Sirolimus	Yes	No	Yes	Yes	Yes
Quercetin	No	No	No	No	Yes
Lovastatin	No	No	Yes	No	Yes
Fumagillin	No	No	Yes	No	Yes
Temsirolimus	No	No	Yes	No	Yes
Torin-1	No	Yes	Yes	No	Yes

CONCLUSION

Research on potential treatments for neurofibromatosis type 1 (NF1) has identified resveratrol, sirolimus, and lovastatin as promising candidates for targeting nervous system tumors associated with NF1. These compounds have demonstrated different pharmacological properties, which may contribute to their potential effectiveness in treating NF1. Resveratrol and sirolimus have been shown to inhibit the mTOR pathway, which has been implicated in the development of NF1-related tumors. Lovastatin, a statin, has been shown to exert an antiproliferative effect on NF1-related tumor cells. The results of this study highlight the potential of repurposing existing drugs and the importance of continued research into new treatment strategies against NF1.

Nomenclature

NF1: Neurofibromatosis type 1

ADHD: Attention-deficit hyperactivity disorder

MPNSTs: Malignant peripheral nerve sheath tumors

GISTs: Gastrointestinal stromal tumors

OTGs: Optic tract gliomas

CNs: Cutaneous neurofibromas

REFERENCES

1. McClatchey AI. Neurofibromatosis. Annu. Rev. Pathol. Mech. Dis. 2007 Feb 28;2(1):191–216.
2. Rubenstein J, Rakic P. Neurodevelopmental Disorders: Comprehensive Developmental Neuroscience. New York: Academic Press; 2020.
3. Martins GJ. Neurobiology of autism spectrum disorders. Autism spectrum disorders in adults. 2017:29–93.
4. Kunder N, de la Peña JB, Lou TF, Chase R, Suresh P, Lawson J, Shukla T, Black B, Campbell ZT. The RNA-binding protein HuR is integral to the function of nociceptors in mice and humans. Journal of Neuroscience. 2022 Dec 7;42(49):9129–41.
5. Carcao MD, Chang L, Poon A, Olivieri NF, Waye JS, Eng B, Patterson M, Chui DH. Compound heterozygosity for Hb S and Hb G-Copenhagen. Hemoglobin. 1999 Jan 1;23(4):379–81.
6. Simó S, Cooper JA. Rbx2 regulates neuronal migration through different cullin 5-RING ligase adaptors. Developmental cell. 2013 Nov 25;27(4):399-411.
7. Gotovac Jercic K, Zigman T, Delin S, Krakar G, Duranovic V, Borovecki F. A novel disease-causing NF1 variant in a Croatian family with neurofibromatosis type 1. Molecular and experimental biology in medicine. 2019 Oct 5;2(2):21–7.
8. Venkatesh S, Lipper RA. Role of the development scientist in compound lead selection and optimization. Journal of pharmaceutical sciences. 2000 Feb 1;89(2):145–54.
9. Bradbury S, Kamenska V, Schmieder P, Ankley G, Mekenyan O. A computationally based identification algorithm for estrogen receptor ligands: part 1. Predicting hERα binding affinity. Toxicological Sciences. 2000 Dec 1;58(2):253–69.
10. Roberts AG, Stevens JC, Szklarz GD, Scott EE, Kumar S, Shah MB, Halpert JR. Four decades of Cytochrome P450 2B research: from protein adducts to protein structures and beyond. Drug Metabolism and Disposition. 2023 Jan 1;51(1):111–22.

