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Author Affiliation:
School of Bioengineering and Food Technology, Shoolini University, Solan, India, Email: sheilina2003@gmail.com

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DISCOVERY SCIENTIFIC SOCIETY

Decoding facial paralysis: Investigating potential small molecules for Moebius syndrome therapy

Sheilina Choudhary

ABSTRACT

Objective: The goal of this study is to conduct a thorough assessment of current knowledge about Moebius syndrome, including clinical symptoms, etiology, and related disorders. The study intends to investigate existing knowledge on prospective medication treatments for the treatment of Moebius syndrome, focusing on efficacy, safety, and symptom relief. This study aims to provide insights into the current state of pharmacological research for Moebius syndrome and identify prospective avenues for future research by reviewing the available literature and synthesizing the findings. The ultimate goal is to contribute to developing viable pharmaceutical methods to improve the quality of life for people with Moebius syndrome. *Methods:* In this investigation, target proteins were downloaded from the PDB and docked in Biovia. The ligands' and standard medications' binding affinity with each target protein was compared and assessed. Also, only 4 substances were chosen for SWISS-ADME final results. *Results:* The docking result revealed that the ligands selected have the best binding affinity with all the four target proteins. *Conclusion:* The ligands could potentially be used to treat Moebius Syndrome in the future approaches for studying the urge ligands in vitro and in vivo analysis to create novel Moebius's inhibitors.

Keywords: Moebius syndrome, cranial nerves, facial paralysis, eye movement problems, speech and swallowing problems, limb deformities, prognosis.

1. INTRODUCTION

A sophisticated web of neurological diseases exists across the vast range of human health, which continues to perplex and fascinate the medical profession. Moebius Syndrome, a mysterious and rare syndrome that drastically alters an individual's capacity to govern facial movements and express emotions, is one of these captivating disorders. Its etiology, clinical manifestations, and ramifications on the lives of individuals affected have yet to be fully explored. Moebius Syndrome is an extremely rare neurological disorder that affects the muscles that control facial

expressions and eye movements. The illness is characterized by facial paralysis and the inability to move the eyes laterally. Because of their lack of facial expression and eye movement, people with Moebius Syndrome frequently have a distinct facial appearance. This syndrome can also cause various other issues, such as trouble articulating speech, feeding difficulties, and limb deformities (Ayva et al., 2022).

The sixth and seventh cranial nerves, which govern facial movements and expressions, are considered underdeveloped or absent in Moebius Syndrome. The specific source of this illness, however, is yet unknown. It is assumed to have a complex aetiology, with genetic and environmental factors playing a role. While the majority of cases occur sporadically and without a family history, there have been reports of Moebius Syndrome running in families, implying a hereditary component. Moebius Syndrome symptoms often appear at birth or shortly after that. Due to their inability to suck efficiently, newborns may have feeding issues, and as they grow, they may face delays in attaining developmental milestones involving facial and ocular movements. Moebius Syndrome is characterised by crossed or misaligned eyes (strabismus), a high or arched palate, and other dental abnormalities in children. Aside from physical issues, people with Moebius Syndrome may face social and emotional difficulties as a result of their lack of facial emotions, which can affect their communication and interactions with others.

In recent years, genetic variables have also emerged as a research focus. Potential genetic abnormalities and alterations in genes responsible for cranial nerve development and face muscle innervation have been found in studies. These genetic changes may affect cranial nerve development, resulting in the typical facial paralysis and other related characteristics found in Moebius Syndrome. However, the syndrome's genetic landscape is complex, and researchers continue to investigate the involvement of several genes and genetic interactions in its development. Environmental factors have also been proposed as possible causes of Moebius Syndrome. Certain teratogens have been hypothesized to play a role in the etiology of the illness. While these environmental factors may interact with genetic factors, more research is needed to determine their precise roles in the development of Moebius Syndrome. Moebius Syndrome's clinical presentations are diverse, with significant variation across affected people. The characteristic facial paralysis usually appears at birth or shortly thereafter, resulting in a mask-like appearance devoid of spontaneous facial expressions.

The inability to smile or show emotion through facial movements can have a significant influence on social relationships and emotional expression, posing specific obstacles for persons who suffer from the illness. Despite its rarity, Moebius syndrome can substantially impact those who suffer from it, impairing their ability to interact nonverbally and execute fundamental activities such as eating, drinking, and expressing emotions. However, it is crucial to emphasize that the severity of the illness varies greatly from person to person, and individuals with Moebius syndrome can lead satisfying and meaningful lives with sufficient support. Living with Moebius Syndrome necessitates exceptional perseverance and adaptation. Affected individuals adopt alternative modes of communication from a young age to compensate for the lack of facial expressions. They frequently use gestures, body language, and voice inflections to express their feelings, resulting in the development of unique and innovative forms of interpersonal connection.

Abbreviations

Moebius Syndrome	MS
Cranial Nerves	CN
Magnetic Resonance Imaging	MRI
Physical Therapy	PT
Autism Spectrum Disorder	ASD
Cytochrome P450	CYP

Phytocompounds

Phytochemicals are antioxidants, that maintain mitochondrial function and homeostasis, prevent intrinsic apoptosis and neuroinflammation, and activate cellular signal pathways to induce anti-apoptotic and pro-survival genes. Such as PLXND1 is the main protein associated with Moebius disease, a member of the plexin family of transmembrane proteins involved in various cellular processes like cell migration, adhesion, and signaling.

Table 1 Phytocompounds and its source

S. No.	Phytocompound	Plant from which it's obtained
1.	Quercetin	Sophora japonica
2.	Kaempferol	Gingko biloba leaves
3.	Anthocyanins	Aronia berries
4.	Isoflavones	Alfalfa
5.	Myricetin	Parsley
6.	Limonene	Cannabis sativa
7.	Caryophyllene	Cinnamomum verum
8.	Cannabichromene	Cannabis sativa
9.	Pinene	Pine, Cedar, Spruce
10.	Linalool	Lavandula angustifolia

2. METHODS

Protein Extraction and Purification

The three-dimensional (3D) structure of the protein alpha-synuclein was resolved using the X-ray diffraction method with a resolution factor of 2.16 Å. The structures were obtained from the PDB Research Collaboratory for Structural Bioinformatics (RCSB PDB) (https://www.rcsb.org/) in pdb format. The missing residues were replaced using BIOVIA, which purifies the protein by eliminating the water molecules hetatm and adding polar hydrogen to the retained Chain A, while the rest of the chains are eliminated. This purified protein is then stored in pdb file format, which was utilized to obtain the 2-dimensional structure and Ramachandran plot using PDBsum (https://www.rcsb.org/) and the Hydrophobicity plot from the BIOVIA Discovery Studio program.

Ligand Retrieval and Purification

A total of 10 phytocompounds of different plant specimens were selected from IMPAAT (https://cb.imsc.res.in/imppat/) which has potential anti-moebius activity based on their antioxidant, anti-mutagenic, anti-hepatotoxic, anti-inflammatory, anti-aging, and chemopreventive properties. The canonical SMILES, PubChem CID, and the two-dimensional (2D) models of 2 of Quercetin and Cannabichromene were retrieved in SDF format via the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and all the structures were converted to PDB format with the help of Open Babel software (http://openbabel.org/).

Molecular Docking

After the retrieval of protein and ligand, molecular docking was executed using PyRx. PyRx is mainly a virtual molecular screening application used to dock small-molecule libraries to a macromolecule to find lead compounds with desired biological functions. The 15 phytocompounds and two standard drugs were added as ligands, and the two purified proteins were uploaded as macromolecules. The added ligands were energy-minimized and were all converted into. pdbqt format. All the ligands were docked with target proteins discretely and were evaluated based on binding affinity. The strength of protein–ligand binding is known as binding affinity. The negative values for binding affinity (or binding free energy) indicate that the ligand is predicted to bind to a target macromolecule. The more negative the numerical values for the binding affinity, the better the predicted binding between a ligand and a macromolecule.

Therefore, the ligand with the least binding affinity along with zero RMSD value was selected for each protein and was visualized in BIOVIA Discovery Studio software. RMRMSD value is utilized to evaluate the docked conformation compared to other docked conformations or the reference conformation. Based on binding affinity the inhibitory activity of ligands and standard drugs will be compared. Here, 10 phytocompounds and two standard drugs were uploaded as ligands and two target proteins I.e., 5o8k and 3h6n. The ligands loaded were with minimum energy and were converted to .pdbqt format and the grid was generated for the targeted protein which is as follows. The grid for the center is shown in the table and the values obtained for grid dimensions are as follows: X=15 Å Y=15 Å and Z=15 Å. This was similar for all the three points.

Table 2 PDB ID of selected proteins and their specifications

PDB id of Protein	X	Y	Z
5o8k	28	14	20
3h6n	28	16	20

Visualization

The top three ligands with the lowest binding affinity for each protein were chosen, and the best model of each ligand was saved in PyRx in pdb file format. The three-dimensional (3D) structure and non-bond interaction were observed using BIOVIA Discovery Studio software, and the 3D model was retrieved in PNG file format.

Physiochemical Studies (ADMET analysis)

The pharmacokinetics were evaluated in ADMET (https://admetmesh.scbdd.com/) using Lipinski's rule of five (RO5). Pharmacodynamic properties were predicted by parameters such as physiochemical properties, absorption, distribution, metabolism, medical chemistry, toxicity, and excretion. The highest four docked ligands having the least binding affinity for each protein were evaluated ADMET analysis was performed using ADMETlab 2.0 (https://admetmesh.scbdd.com/).

Table 3 Drugs used in MS treatment and their specifications

Drug	Formula	No. Of H-bond acceptors	No. Of H-bond donors	Blood-Brain Barrier Permeant	Lipinski
Quercetin	C15H10O7	7	5	No	Yes
Kaempferol	C15H10O6	6	5	No	Yes
Anthocyanins	C15H11O+	5-21	1	Yes	Yes
Cannabichromene	C21H30O2	1	0	No	Yes

3. RESULTS

A total of 16 phytocompounds were chosen, out of which only 10 were selected based on docking results. The two-dimensional chemical structure of the following is shown in (Figure 1). To test these compounds' inhibitory efficacy against the target proteins, two standard medicines, Quercetin and Caryophyllene, were obtained, as shown in (Figure 1). Also, Quercetin and Caryophyllene are the two phytocompounds found to have the best binding affinity with all the proteins selected

Protein retrieval and purification

PDB retrieved the two target proteins' Three-Dimensional (3D) crystal structure, after getting its proper sources, as discussed in (Tables 1 and 2). After that, the proteins 5o8k and 3h6n were purified in the BIOVIA Discovery software which is subjected to its structure analysis which is seen in Figures 2 and 3 respectively. In structural analysis, the Ramachandran plot, Secondary Structure, and hydropathy plot are analyzed. Then, as shown in Table 3, several drugs that are used in Moebius treatment with their specifications are discussed.

Molecular Docking

Ten ligands were docked in the PyRx software against the proteins 5o8k and 3h6n for this docking study. The conformation with the lowest binding affinity and zero root mean square deviation (RMSD) was selected as the compound's optimal docking orientation upon the docking. Once the docking was completed the RMSD as well as binding affinity were recorded. Out of all the fifteen phytocompounds, the common phytocompounds for all the three target proteins that had lower binding affinity than 7 and above were selected along with these 10 phytocompounds the standard drugs were also docked with each protein and their binding affinity was recorded.

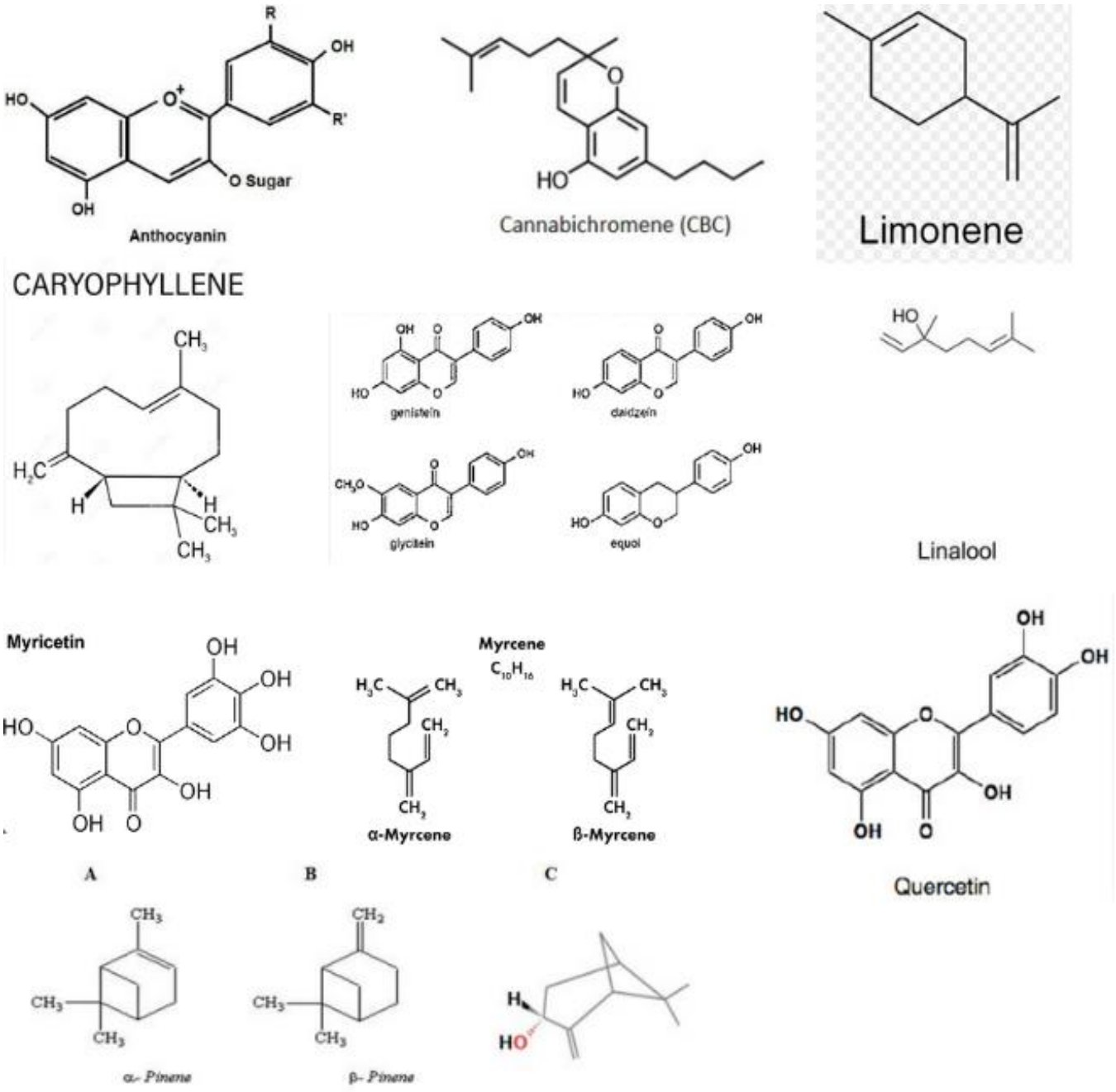
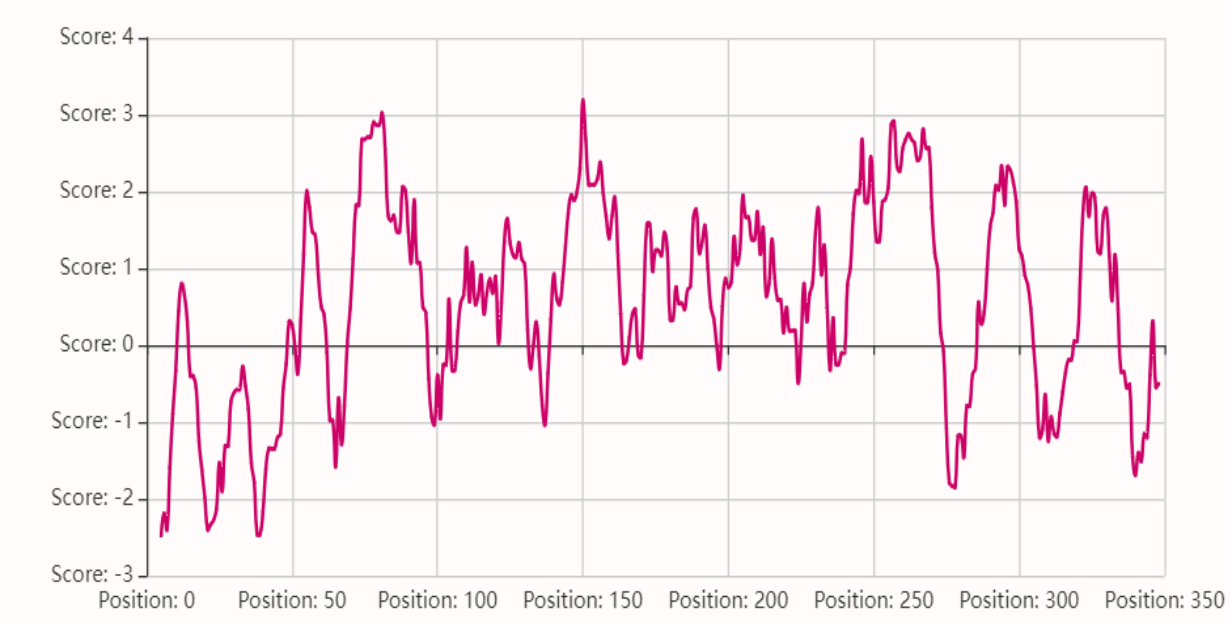


Figure 1 Chemical structure of top 10 phytocompounds and standard drugs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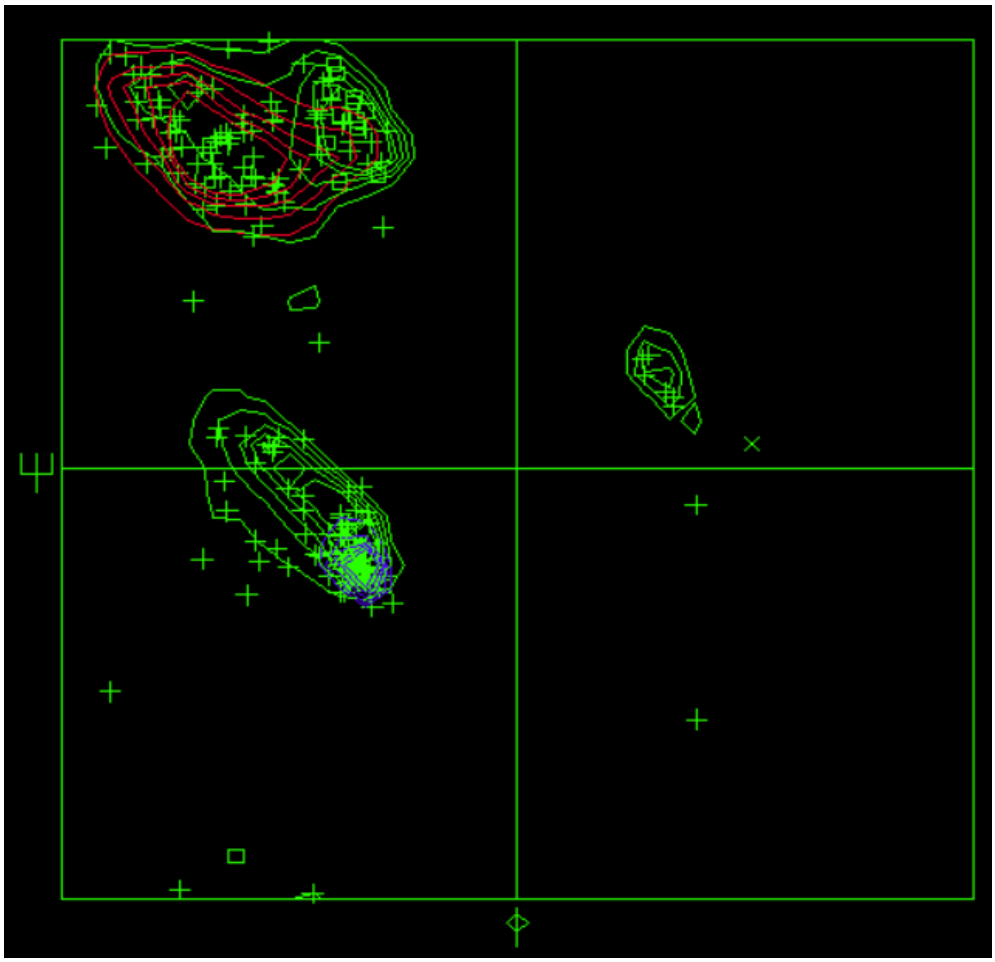
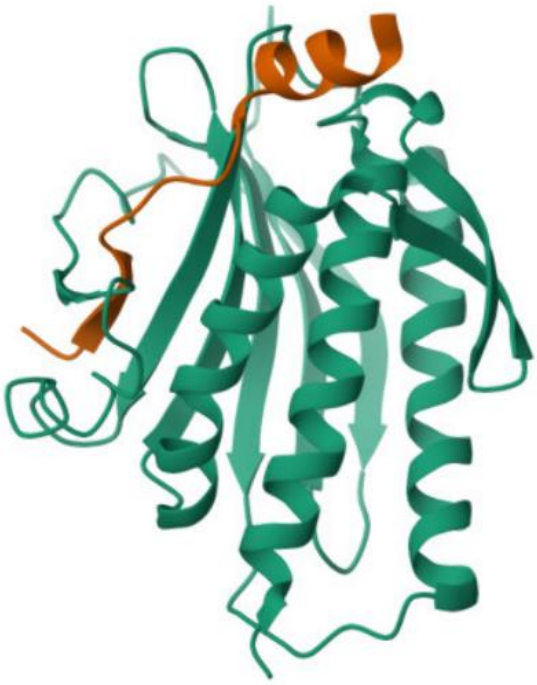
(a)

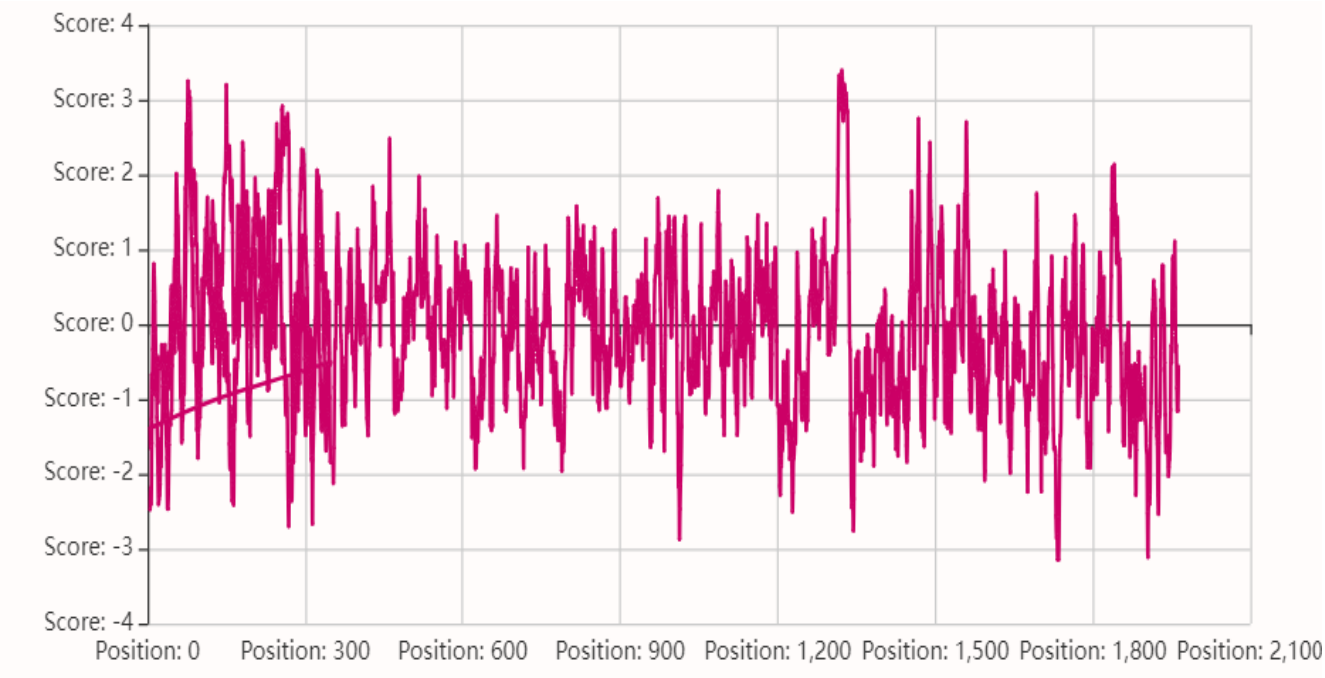


(b)

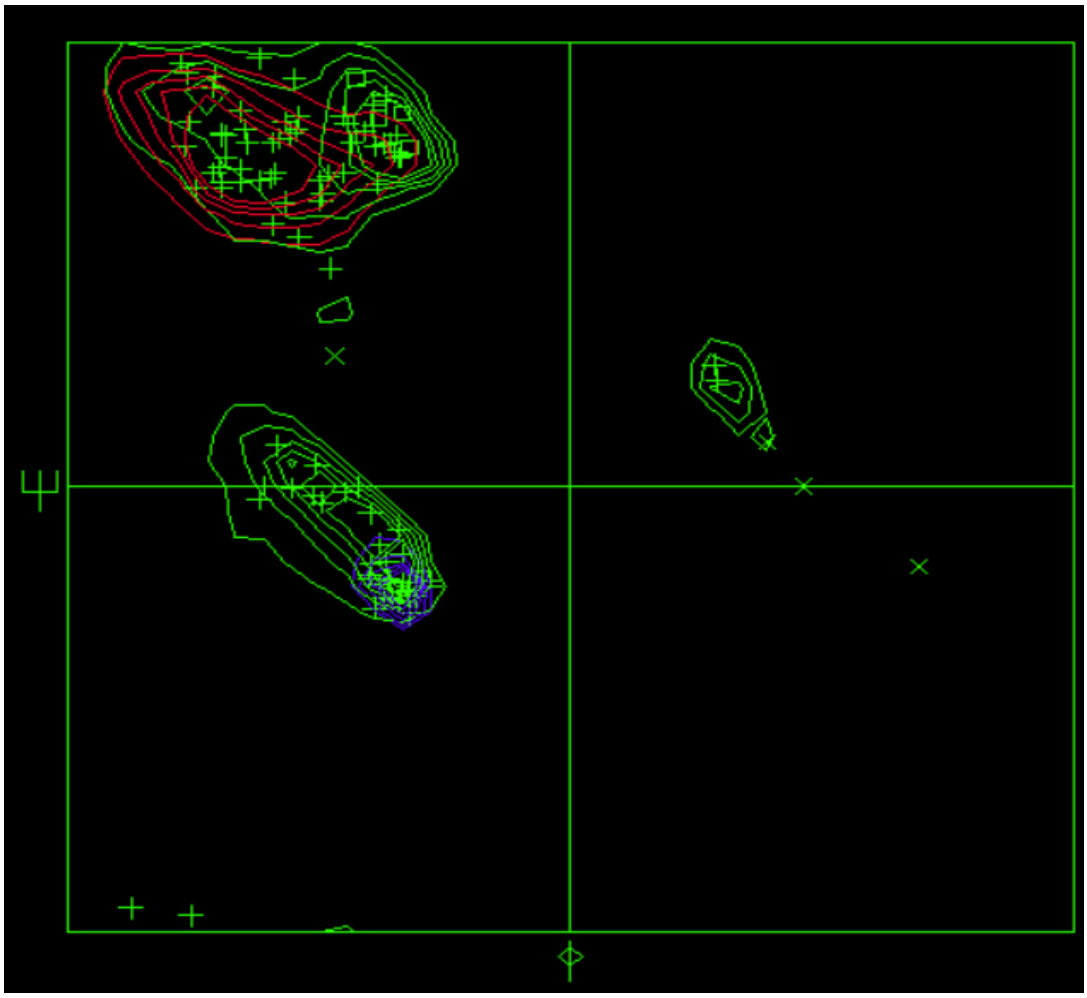


(c)

Figure 2 Structural analyses of 5o8k: (a)Hydropathy plot, (b) Ramachandran plot, (c) Structure



(a)



(b)

(c)

Figure 3 Structural analyses of 3h6n: (a)Hydropathy plot, (b) Ramachandran plot, (c) Structure

ADMET Analysis

SwissADME is a web-based program that predicts and calculates the properties of small organic compounds' absorption, distribution, metabolism, excretion, and toxicity (ADMET). It focuses mostly on drug-like molecules and is commonly utilized in drug discovery and development.

SwissADME provides a variety of ADMET-related features and predictions, including:

Lipophilicity: It computes the octanol/water partition coefficient, which shows the compound's hydrophobicity and ability to pass biological membranes.

Pharmacokinetics: It predicts parameters such as chemical absorption, distribution, metabolism, and excretion.

Drug-likeness: SwissADME assesses the compound's adherence to Lipinski's rule of five, a commonly used guideline for evaluating drug-like qualities based on molecular weight, lipophilicity, hydrogen bonding, and polar surface area.

Toxicity predictions: It predicts numerous qualities such as mutagenicity, tumorigenicity, irritability, and reproductive impacts to determine possible toxicity.

Bioavailability: SwissADME forecasts the compound's oral bioavailability, an important aspect of drug development.

The assimilation of phytocompounds such as quercetin, kaempferol, anthocyanins, isoflavones, myricetin, limonene, pinene, linalool, cannabichromene, and caryophyllene may be a basic angle impacting their bioavailability and consequent physiological impacts, as shown in (Table 4). Quercetin and kaempferol, both flavonoids, are retained within the little digestive tract through detached dissemination and dynamic transport components (Papakyriakopoulou et al., 2022; Barrington et al., 2009). Anthocyanins, water-soluble pigments mindful of the dynamic colors in natural products, are retained within the stomach and small digestive tract.

Isoflavones, found in soy items, are retained within the little digestive system, with their assimilation impacted by components such as intestine microbiota (Gómez-Zorita et al., 2020). Myricetin, a flavonol, is ingested within the small intestine and colon, contributing to its systemic dissemination (Pluta et al., 2021). Limonene, pinene, and linalool, terpenes copious in basic oils, are absorbed through detached dissemination within the gastrointestinal tract (Abd-Rashed et al., 2021). Cannabichromene, a cannabinoid in cannabis, is retained within the little digestive tract and experiences a digestion system within the liver (Shebaby et al., 2021). Caryophyllene, a terpene found in different plants, is retained through inactive dissemination and may connected with cannabinoid receptors within the gastrointestinal tract (Mödinger et al., 2022).

Table 4 Absorption of Phytocompounds

LIGAND	HIA	Log S (ESOL)	SOLUBILITY
Quercetin	52 %	-3.16	2.11e-01 mg/ml
Kaempferol	20-50%	-3.31	1.40e-01mg/ ml
Anthocyanins	3-4%	-4.01	2.02e-02 mg/ ml
Isoflavones	20-30%	-2.97	4.42e-01 mg/ ml
Myricetin	10-20 %	-3.01	3.14e-01 mg/ ml
Limonene	20-30%	-3.50	4.33-02 mg/ ml
Pinene	20-30%	-3.31	6.74-02 mg/ ml
Linalool	20-30%	-2.40	6.09-01 mg/ ml
Cannabichromene	13-20%	-3.87	2.78-02 mg/ ml
Caryophyllene	10-20%	-5.84	4.52-04 mg/ ml

The restorative chemistry of phytochemicals, such as quercetin, kaempferol, anthocyanins, isoflavones, myricetin, limonene, pinene, linalool, cannabichromene, and caryophyllene, envelops a range of bioactive properties that hold helpful potential as shown in (Table 5). Quercetin and kaempferol, as flavonoids, are known for their anti-inflammatory, antioxidant, and anticancer properties, making them subjects of intrigued in sedate improvement. Anthocyanins, with their antioxidant and anti-inflammatory impacts, have been

investigated for their potential cardiovascular benefits. Isoflavones, recognized for their estrogenic action, are beneath examination for their part in hormone-related conditions, including menopause.

Myricetin, a flavanol, shows antioxidant and anti-inflammatory properties, recommending its potential in different malady states. Limonene, pinene, and linalool, terpenes found in fundamental oils, have antimicrobial and anti-inflammatory exercises, contributing to their therapeutic importance. Cannabichromene, a cannabinoid in cannabis, is being considered for its potential anti-inflammatory and neuroprotective impacts. Caryophyllene, a terpene with particular actuation of cannabinoid receptors, holds a guarantee for its anti-inflammatory and pain-relieving properties. The therapeutic chemistry of these phytochemicals gives an establishment for investigating their restorative applications in different well-being settings.

Table 5 Medicinal Chemistry of Phytochemicals

LIGAND	LIPINSKI	PAIN ALERT
Quercetin	Accepted	1
Kaempferol	Accepted	0
Anthocyanins	Accepted	0
Isoflavones	Accepted	0
Myricetin	Accepted	1
Limonene	Accepted	0
Pinene	Accepted	0
Linalool	Accepted	0
Cannabichromene	Accepted	0
Caryophyllene	Accepted	0

The physicochemical properties of phytochemicals play a significant part in deciding their behavior inside natural frameworks as shown in (Table 6). Quercetin and kaempferol, as flavonoids, display antioxidant properties owing to their capacity to give electrons. Anthocyanins, capable of the dynamic colors in natural products and vegetables, have water-soluble characteristics, affecting their steadiness in fluid situations. Isoflavones, found in soy items, show estrogenic action due to their basic similitude to estrogen. Myricetin, a flavanol displayed in different plant nourishments, shows antioxidant and anti-inflammatory properties. Limonene, pinene, and linalool, terpenes inexhaustible in citrus natural products and herbs, contribute to the characteristic smell of plants and may display antimicrobial properties. Cannabichromene, a cannabinoid in cannabis, offers basic similitudes with other cannabinoids, impacting its interaction with the endocannabinoid framework. Caryophyllene, a terpene shown in different plants, including cannabis and dark pepper, shows anti-inflammatory impacts through the enactment of cannabinoid receptors.

Table 6 Physiochemical Properties of Phytochemicals

Ligand	Molecular weight	No. Of hydrogen acceptors	No. Of hydrogen donors
Quercetin	282.46	7	5
Kaempferol	384.47	6	4
Anthocyanins	444.74	1	0
Isoflavones	959.12	9	5
Myricetin	228.24	8	6
Limonene	150.22	0	0
Pinene	194.19	0	0
Linalool	368.38	1	1
Cannabichromene	302.24	0	0
Caryophyllene	470.60	2	1

The dissemination of phytochemicals, counting quercetin, kaempferol, anthocyanins, isoflavones, myricetin, limonene, pinene, linalool, cannabichromene, and caryophyllene, inside the human body could be an energetic prepare affected by their chemical properties and metabolic pathways as shown in (Table 7). Quercetin and kaempferol, being flavonoids, are regularly found in a wide run of natural products, vegetables, and grains, guaranteeing wide dissemination upon utilization. Anthocyanins, capable of the distinctive colors in berries and other natural products, are dispersed all through the body after ingestion.

Isoflavones, predominant in soy-based items, display systemic dispersion after retention. Myricetin, found in berries and certain vegetables, is disseminated in different tissues. Limonene, pinene, and linalool, common terpenes in citrus natural products and herbs, are dispersed through the circulatory system after assimilation. Cannabichromene, a cannabinoid in cannabis, and caryophyllene, a terpene found in cannabis and dark pepper, are disseminated all through the body upon ingestion, with their nearness affected by variables such as digestion system and tissue-specific take-up.

Table 7 Distribution of Phytochemicals

LIGAND	BLOOD BRAIN BARRIER	SKIN PERMEATION
Quercetin	No	-7.50 cm/s
Kaempferol	No	-6.70 cm/s
Anthocyanins	Yes	-5.70 cm/s
Isoflavones	No	-8.36 cm/s
Myricetin	No	-7.40 cm/s
Limonene	Yes	-3.89 cm/s
Pinene	Yes	-4.18 cm/s
Linalool	Yes	-5.13 cm/s
Cannabichromene	No	-4.44 cm/s
Caryophyllene	No	-3.35 cm/s

Phytochemicals, counting quercetin, kaempferol, anthocyanins, isoflavones, myricetin, limonene, pinene, linalool, cannabichromene, and caryophyllene, display different organic exercises, but their harmfulness and excretion pathways are pivotal contemplations as shown in (Table 8). Quercetin and kaempferol, both flavonoids commonly found in natural products and vegetables, are for the most part well-tolerated, with negligible harmfulness detailed at ordinary dietary levels. Anthocyanins, mindful of the dynamic colors in numerous natural products, have a moo poisonous quality profile. Isoflavones, copious in soy items, have been related to well-being benefits and are regularly secure. Myricetin, found in different berries and vegetables, has appeared to be harmful in exploratory considers. Limonene, pinene, and linalool, terpenes copious in citrus natural products and herbs, are for the most part considered secure.

Cannabichromene, a cannabinoid within the Cannabis plant, and caryophyllene, a terpene found in different plants, including cannabis and dark pepper, have restricted detailed harmfulness. Be that as it may, personal reactions may change, and control in utilization is fitting. The excretion pathways for these phytochemicals include a digestion system within the liver and consequent end through pee or feces, contributing to their general security in sensible dietary sums. As described in table 8, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, are all particular CYP450 chemicals. These are protein atoms found fundamentally within the liver, even though they can moreover be found in other tissues just like the insides and lungs. CYPs play a vital part in the sedate digestion system, breaking down and changing different remote substances. Some details of cytochromes described in Table 8 are as follows:

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 some anti-cancer drugs.

Table 8 Toxicity and Excretion of Phytochemicals

LIGAND	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Quercetin	Yes	No	No	Yes	Yes
Kaempferol	Yes	No	No	Yes	Yes
Anthocyanins	Yes	No	No	Yes	No
Isoflavones	No	No	No	No	No
Myricetin	Yes	No	No	No	Yes
Limonene	No	No	Yes	No	No
Pinene	No	No	Yes	No	No
Linalool	No	No	No	No	No
Cannabichromene	No	Yes	Yes	No	Yes
Caryophyllene	No	No	Yes	Yes	Yes

4. DISCUSSION

As discussed in the results section, quercetin, and caryophyllene are attractive prospective medications for the treatment of Moebius syndrome. Quercetin is a naturally occurring flavonoid molecule present in a variety of fruits and vegetables that has been demonstrated to have a high affinity for the target proteins linked with Moebius syndrome. Caryophyllene, on the other hand, is a sesquiterpene found in the essential oils of a wide range of plant species. These two phytocompounds have great therapeutic potential for people suffering from Moebius syndrome, providing a ray of hope for better management of this unusual ailment. Quercetin, which is found in many plant-based foods such as onions, apples, and citrus fruits, has significant potential in the treatment of Moebius's illness. Its antioxidant and anti-inflammatory qualities have been thoroughly researched and are proven to provide numerous health advantages. It has the potential to solve the specific issues posed by Moebius Syndrome (Papakyriakopoulou et al., 2022).

Caryophyllene, on the other hand, is a naturally occurring chemical found in a variety of plants, including black pepper, cloves, and some strains of cannabis. According to my findings, it has a high affinity for the target proteins involved in Moebius syndrome. While caryophyllene is best known for its role in the endocannabinoid system, which regulates a variety of physiological processes, its potential therapeutic applications extend far beyond this. Caryophyllene's anti-inflammatory and neuroprotective characteristics make it an appealing possibility for Moebius syndrome treatment. More research into its precise mechanisms of action and safety profiles is needed, but its potential as a medication for treating the neurological and facial symptoms of Moebius syndrome is a promising route for future research and development (Mödinger et al., 2022).

5. CONCLUSION

Moebius syndrome is a rare congenital neurological disorder characterized by facial and, occasionally, limb abnormalities. The sixth (abducens) and seventh (facial) cranial nerves, which govern eye movements and facial emotions, are most affected by this illness. Moebius syndrome patients generally lack facial emotions, are unable to smile or frown, and have trouble coordinating eye movements. They may experience other symptoms in addition to facial paralysis, such as trouble swallowing, difficulties speaking, and limb anomalies such as atypical legs or arms. Certain genetic alterations that can cause Moebius disease have been identified by researchers.

However, these are unusual except in rare circumstances where multiple family members have Moebius disease. Some gene variations, on the other hand, appear to enhance the chance of Moebius disease, but with a relatively low risk of Moebius disease for each of these genetic markers. Common top 10 ligands listed in the Table were run through ADMET analysis, in which all the ligands were examined for their physiochemical properties. The results obtained tell us that these ligands could potentially be used to treat Moebius disease in the future approaches for studying the urge ligands *in vitro* and *in vivo* analysis to create novel Moebius's inhibitors.

Informed consent

Not applicable.

Conflicts of interests

The authors declare that there are no conflicts of interests.

Ethical approval

Not applicable.

Funding

The study has not received any external funding.

Data and materials availability

All data associated with this study are present in the paper.

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