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# Exploring Potential Phytochemicals for Myasthenia Gravis Treatment: A Molecular Docking and ADME Analysis Approach

Neha Subhash Nilawad*

***Abstract***

***Objective:*** *Muscle feebleness and exhaustion derived from a disruption in neuromuscular transference are hallmarks of the crippling autoimmune disease myasthenia gravis (MG). The drawbacks of the current MG therapy options are frequently partial efficacy and adverse effects. To investigate the potential of phytochemicals in MG control, in this work we integrated molecular docking with ADME (absorption, distribution, metabolism, and excretion) analysis using a computer method. We identified molecules exhibiting favorable interactions with key molecular targets implicated in MG pathophysiology, such as muscle-specific kinase (MuSK), nicotinic acetylcholine receptors (nAChRs), and acetylcholinesterase (AChE). Explore the natural substances called phytochemicals that are derived from plants and may have therapeutic uses in treating a variety of ailments, including autoimmune disorders. This has become more and more popular in the past few years.* ***Methods:*** *Theoretical Methodology: This study aims to explore the potential of phytochemicals from the Cassia fistula medicinal plant for the treatment of Myasthenia gravis (MG) through a multi-step computational approach. Firstly, the top five phytochemicals from Cassia fistula will be selected based on a literature review and computational screening. These compounds will then undergo molecular docking onto the active site of the muscle-specific kinase (MuSK) protein (PDB ID: 1LUF) using PyRx software to predict their binding affinities and interactions. Following this, ADME (absorption, distribution, metabolism, and excretion) analysis will be conducted to evaluate the pharmacokinetic properties of the docked compounds, including bioavailability and toxicity. To identify possible lead compounds for additional experimental validation, Biovia software will be used to visualize protein-ligand interactions. This integrated approach holds promise for the discovery of novel phytochemical-based therapeutics for MG treatment.* ***Result:*** *Molecular docking investigations indicated that Rhein, chrysophanic acid, aromadendrin, aloe emodin, and anthraquinone were in the ligands with the lowest binding affinities to the targeted proteins.* ***Conclusion:*** *In conclusion, we have effectively discovered phytochemicals with promise for treating Myasthenia gravis (MG) by our molecular docking and ADME analysis technique utilizing Biovia and PyRx. Using computational screening, we found phytochemicals with good pharmacokinetic characteristics and a substantial binding affinity to MG-related target proteins. These results demonstrate the possibility of using natural substances as MG treatment alternatives. To determine these compounds' safety and efficacy and to prepare the way for the creation of novel MG therapies based on phytochemicals, more experimental validation of these compounds is necessary.*

**Keywords:** Myasthenia gravis, phytochemicals, molecular docking, adme analysis, neuromuscular transmission, precision medicine

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## INTRODUCTION

The last thirty years have seen a significant advancement in our knowledge of the pathophysiology of Myasthenia gravis immunology and molecular biology. Using the available tests, myasthenia gravis may be diagnosed nearly all the time. With the current state of therapy, myasthenia gravis mortality is essentially non-existent. Yet, there is little information available on the etiology of the elements that lead to persistent illness in myasthenia gravis and the available treatments for the condition [1].

Myasthenia gravis is most typically associated with abnormalities of the neuromuscular junction (NMJ) of the skeletal muscles (MG). A varying flaw that is more noticeable in the afternoon is the traditional presentation. The eyes, throat, and extremities' muscles are typically involved. Weakness in the muscles is a result of autoantibodies formed against certain postsynaptic membrane proteins, which limit the passage of electrical impulses across the neuromuscular junction. Infections, vaccinations, operations, medications, and other factors can all lead to MG [2].

An autoimmune disease called myasthenia gravis, commonly referred to as muscle-specific kinase, impairs neuromuscular transmission and results in extensive muscle weakness. Since the respiratory and bulbar muscles are the main areas affected by MuSK-MG, it is less prevalent than acetylcholine receptor (AChR)-opposing antibodies in myasthenia gravis, which causes greater severity and frequency of myasthenic crises. When long-term, to control symptoms, large doses of steroids and other immune-suppressive medication are needed, treatment is typically less successful. Postsynaptic AChR cluster growth and maintenance at the neuromuscular junction (NMJ) are dependent on a phosphorylation cascade that MuSK controls under normal conditions [3].

Circulating antibodies against the nicotinic acetylcholine receptor are recognized to have a pathophysiological role in the illness, even though the etiology of the condition is unclear. Early diagnosis is essential, as this illness is often curable. A substantial decrease in morbidity and death as well as novel treatment options have resulted from the last ten years of substantial advancements in our understanding of the illness [4].

The sickness of Indian chief opechancanough (1644–1644) is described here; this may be the earliest instance of myasthenia gravis ever identified. The sources for this topic are historical publications derived from colonial correspondence with England. This is the only essay I'm aware of in the medical history literature that discusses this well-known and significant Indian [5]. Myasthenia gravis (MG) was shown to have a steady incidence rate throughout time, with an estimated yearly incidence rate of 4.6 per million people. Both sexes had a bimodal appearance according to age- and sex-specific incidence rates. The age boundary between MG cases with early onset and those with late onset should be fixed at 50 years old based on epidemiological evidence [6]. Treatment for MG in early infancy presents unique issues related to the immune system and general growth and development [7]. The phenotype of MG linked with MuSK antibodies is distinct from that of MG not connected with MuSK [8].

Patients diagnosed with MG should always be evaluated for immunoactive medication treatment in addition to symptomatic treatment. Treatment is almost always required for patients, at least while the condition is exhibiting clinical activity in the form of persistent or sporadic muscular weakness [9]. It is recommended that all MG patients have a discussion about physical training, weight control, and prudent lifestyle improvements [10].

As opposed to most alternative treatment choices, the clinical response happens quickly – it usually happens within two to three days – and frequently has a significant impact. For MG crises or potentially dangerous crises, this therapy must be administered, and it should be provided for severe exacerbations. When treating less severe exacerbations, immunosuppressive medication can be started concurrently with plasma exchange or IvIg, but the effects will be delayed. These treatments can be utilized prior to surgery [11].

Early treatment with immunoactive medications and/or thymectomy improves the prognosis over the long run. Trying two or three different medications is insufficient if there is no first response. It is possible to mix medications. The ability to distinguish between MG and non-MG symptoms that a patient may be experiencing can be aided by a longitudinal assessment of AChR antibodies [12].

Treatments for autoimmune diseases may use antigen-presenting cell strategies; this process may be altered in an antigen-specific manner. T-cell receptor immunization may be less effective in humans with MG due to their relatively unrestricted usage of T-cell receptors [13]. Ideally, in the future, a thorough assessment of every MG patient will lead to unique therapeutic outcomes, meaning that the course of treatment will be customized based on the individual autoimmune dysfunction.

## METHODOLOGY

### Ligand Extraction

Potential ligands were looked through utilizing the IMPPAT (Indian medicinal plants, phytochemistry and therapeutics) database (https://cb.imsc.res.in/imppat/). The creation of natural product-based medications will be made possible by computational methods made possible by an extensive online library on the phytochemistry of Indian medicinal plants [14]. Every ligand that was chosen for the current experiment had a canonical grin that was captured on camera. SDF formatted data on PubChem was the source of the top 46 ligands (https://pubchem.ncbi.nlm.nih.gov/) [15].

### Proteins Extraction

Muscle-specific kinase (MuSK) with PDB ID 1LUF is the protein that must be targeted in myasthenia gravis. It was obtained from the PDB database (https://www.rcsb.org/structure/1LUF). For the protein, PDB format was obtained. X-ray diffraction was used to recover protein at a resolution of 2.05Å [16].

### Homology Modeling

Compared to other methods, the only technique that can correctly create a three-dimensional (3-D) protein model constructed using the amino acid content is comparative homology modeling. Muscle-specific kinase (MuSK) protein 3D model building was done using Swiss Model (https://swissmodel.expasy.org/interactive/2fPUee/models/) [17]. The UniProt database(https://www.uniprot.org/) provided the protein's FASTA sequence.

### Protein Purification

Before docking, all water molecules were eliminated since they might affect docking scores. To enable quicker binding with the ligands selected for the investigation, prebound ligands are eliminated from the crystal structures (Figure 1). The protein structures retained their chains despite removing extra chains for analysis. DS Biovia Discovery Studio was utilized to carry out the protein purification. To make enhanced structures better, polar hydrogen atoms are added [18].

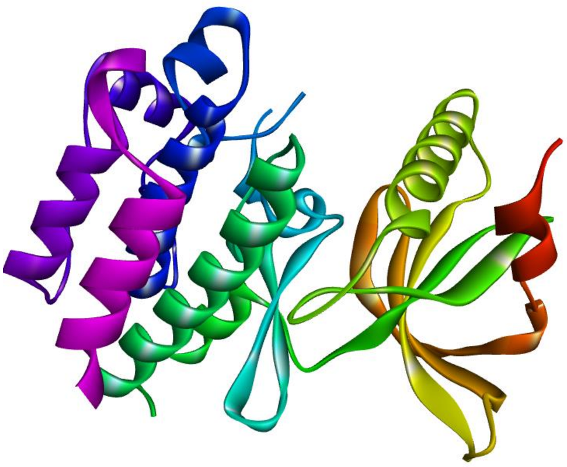


**Figure 1.** Purified protein stucture of protein MuSK-1LUF.

**Pharmacological Studies**

Using SwissADME analysis, the ligands' pharmacological properties were evaluated (http://www.swissadme.ch ). The assessment covers the following physicochemical properties: size, flexibility, polarity, insolubility, and lipophilicity (Tables 1 and 2). Then, the application of the LIPINSKI rule of five to choose the best ligand candidates. ADMETLAB 2.0 (https://admetmesh.scbdd.com ) was applied to evaluate the ligands' toxicity [19].

**Molecular Docking**

PyRx was first loaded with phytocompounds from the plant, which were then uploaded as macromolecules together with the purified proteins (MuSK-1LUF). The OPENBABEL was used to translate the ligands from SDF format to PDB format [20]. The active site's grid dimensions were determined to be center X = 121.894, center Y = 90.3785, and center Z = –0.8872 (1LUF) [21].

The ligands were separately docked against 1LUF, and energy reduction was performed using the PyRx web server. Based on the target protein's binding affinity, the most effective compounds Rhein, anthraquinone, chrysophanic acid, aloe emodin, and aromadendrin, were selected for more investigation after the docking results (Table 3).

**Visualization**

Dassault Systems BIOVIA Discovery Studio Visualizer was used to create 2D and 3D models after downloading the conformations in PDB format with the greatest binding scores [22].

## RESULT

**Pharmaceutical Research**

An essential medicinal plant utilized in many traditional medical systems, such as Chinese traditional medicine and Ayurveda, is *Cassia fistula* (Figure 2(a)). 48 phytocompounds were taken from the IMPPAT database according to the 2D structures of the first six ligands, and the docking results closely corresponding to protein 1 were obtained from PubChem (Table 1).

**Hydrophobicity Plot**

The protein 1LUF hydrophobicity plots were examined with the BIOVIA discovery studio program, as indicated in Figure 2(b), respectively.

The Ramachandran map is accustomed to identify the zones where energy use is allowed in protein structures when amino acid torsions are orientated in opposition to one another. The Ramachandran plot of 1LUF-MuSK is seen in Figure 2(c) and was created using PDBsum generate.

**Protein Structure Analysis**

***Ramachandran Plot***

Every residue in the structure, except for those at the chain termini, has its phi-psi in the Ramachandran's torsion angle display plot [23]. Triangles are used to distinguish lycine residues from other sidechain types, as they are not limited to the plot area designated for those sidechain kinds. The plot's coloration and shading correlate to the several zones (see below) that Morris et al. (1992) described: the "core" regions; those are the darkest regions and represent the most favorable combinations of phi-psi values. (shown in red).

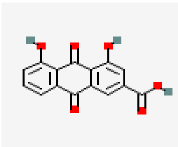
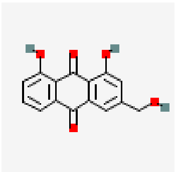
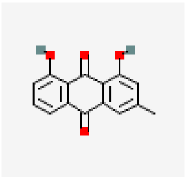
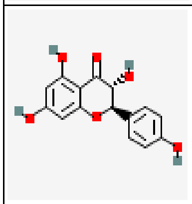
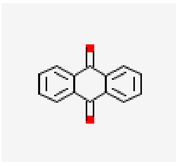
Having more than 90% of the residues in these "core" areas is the ideal situation. Indicators of stereochemical quality that are more precise include the percentage of residues found in the "core" regions.

The degree of favorability of each plot's regions is shown by their shading, the deeper the shade, the more favorable the area. Based on structures determined by the shade was produced using a data set of 163 non-homologous, high-resolution protein chains using X-ray crystallography to 2.0Å resolution or greater and with an R-factor not exceeding 20%.

The numbers that follow each residue name in brackets indicate the total number of data points on that graph. The red numbers above the data points indicate the residues that are of concern, which indicate which residues are in unfavorable areas of the plot.

**Table 1.** The top six ligands' canonical smiles, names, PubChem ID and 2D structures.

| 2D Structure | Metabolites | PubChem CID | Canonical Smiles |
|---|---|---|---|
|  | Rhein | 10168 | C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)C(=O)O |
|  | Aloe emodin | 10207 | C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)CO |
|  | Chrysophanic acid | 10208 | CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=CC=C3O |
|  | Aromadendrin | 122850 | C1=CC(=CC=C1C2C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O |
|  | Anthraquinone | 6780 | C1=CC=C2C(=C1)C(=O)C3=CC=CC=C3C2=O |

## Secondary Structure

The secondary structure of the chosen proteins, 1LUF-MuSK, was examined using PDBsum, as seen in Figure 2(d).

### 1LUF

The PDBsum results for the prediction of protein secondary structure include two sheets, fifteen beta turns, one gamma turn, sixteen helices, twelve helix-helix, seven strands, four beta hairpins, and four beta bulges. There are 275 residues in all in the structure.

## ADMET Analysis

Using a web tool called ADMETlab 2.0, five ligands – Rhine (PubChem ID: 10168), Aloe emodin (PubChem ID: 10207), Chrysophanic Acid (PubChem ID: 10208), Aromadendrin (PubChem ID: 122850), and Anthraquinone (PubChem ID: 6780) – were screened for their physiochemical properties, medicinal chemistry, absorption, distribution, and toxicity.

The best guideline for pharmacologically assessing potential medication candidates is the Lipinski Rule of 5. The Lipinski Rule states that a medicine must have a molecular weight between 150 and 500 Daltons, a lipophilicity of less than 4.15, a molar refractivity ranging from 40 to 130 Å2, and less than five hydrogen bond acceptors and hydrogen bond donors.

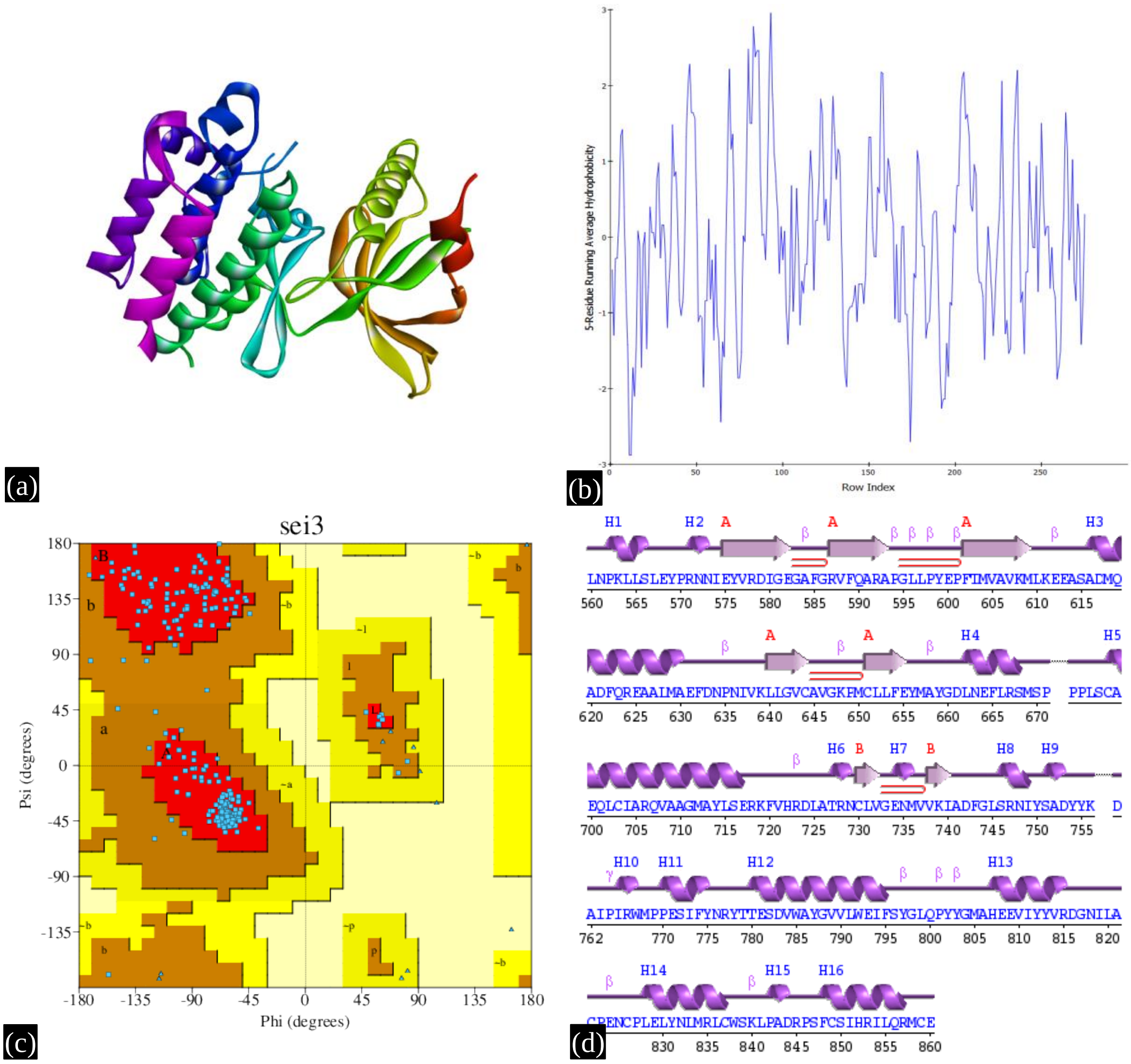



**Figure 2.** Ramachandran plot of 1LUF-MuSK protein using PDBsum. (a) Check out the structure of the purified 1LUF protein, in (b) as we can see, the hydrophobicity plot, in (c) Ramachandra plot, and (d) depicts the secondary structure of 1LUF.

**Table 2.** Physicochemical property parameters.

| Properties | Properties | Optimal Range |
|---|---|---|
| Lipophilicity | xLogP | –0.7 to +5.0 |
| Size | MW | 150–500 g/mol |
| Polarity | TPSA | 20–130 |
| Saturation | Sp3 hybridization | Not less than 0.25 |
| Flexibility | Rotatable bonds | Not more than 9 |

**Table 3.** Physio-chemical properties of the ligand molecules.

| Ligands | Molecular Weight | Fraction Csp3 | Rotatable Bonds | TPSA | Lipophilicity |
|---|---|---|---|---|---|
| Rhein | 284.22 | 0.00 | 1 | 111.90 Å² | 2.23 |
| Aloe emodin | 270.24 | 0.07 | 1 | 94.83 Å² | 1.82 |
| Chrysophanic acid | 254.24 | 0.07 | 0 | 74.60 Å² | 3.53 |
| Aromadendrin | 288.25 | 0.13 | 1 | 107.22 Å² | 1.31 |
| Anthraquinone | 208.21 | 0.00 | 0 | 34.14 Å² | 3.39 |

After undergoing Lipinski review, the top five ligands met all the requirements without failing to do so (Table 4).

**Table 4.** SwissADME was used to acquire information on the Lipinski rule's characteristics.

| Ligands | Molecular Weight | Hydrogen Donors | Hydrogen Acceptors | MLogP | Molar Refractivity |
|---|---|---|---|---|---|
| Rhein | 284.22 | 3 | 6 | 0.29 | 70.75 |
| Aloe emodin | 270.24 | 3 | 5 | 0.10 | 69.92 |
| Chrysophanic acid | 254.24 | 2 | 4 | 0.92 | 68.76 |
| Aromadendrin | 288.25 | 4 | 6 | -0.10 | 72.73 |
| Anthraquinone | 208.21 | 0 | 2 | 1.86 | 59.75 |

## ADME Analysis

The ADME investigation examines the drug's solubility, glycoprotein permeability, human gastrointestinal absorption, and blood-brain permeation degree. The Blood-brain barrier (BBB) assesses a medication candidate's ability to cross the blood-brain barrier. This information is essential to produce pharmaceuticals. The efficacy of the medication can only be increased by significant gastrointestinal (GI) adsorption. For the oral medications to work as best they can, they should in fact have good gastrointestinal absorption and solubility (Table 5).

**Table 5.** ADME data obtained using Swiss ADME.

| Ligands | GI Absorption | Blood Brain Barrier Penetration | PGP Substrate | Solubility (LOGSw-SILICOS IT) |
|---|---|---|---|---|
| Rhein | High | No | No | –3.46 |
| Aloe emodin | High | No | No | –3.92 |
| Chrysophanic acid | High | Yes | No | –4.49 |
| Aromadendrin | High | No | No | –2.61 |
| Anthraquinone | High | Yes | No | –5.25 |

## Toxicity Prediction

The following constitute the fundamental components of toxicity prediction: Considerations included hERG blockers, H-HT, DILI, skin sensitivity, carcinogenicity, pulmonary toxicity, AMES toxicity, and rat oral acute toxicity (Table 6).

**Table 6.** Classification of toxicity.

| Ligands | Respiratory | hERG | Carcinogenicity | H-HT | DILI | Ames | ROA |
|---|---|---|---|---|---|---|---|
| Rhein | 0.069 | 0.028 | 0.62 | 0.297 | 0.989 | 0.909 | 0.029 |
| Aloe emodin | 0.925 | 0.006 | 0.114 | 0.033 | 0.32 | 0.592 | 0.023 |
| Chrysophanic Acid | 0.072 | 0.027 | 0.908 | 0.046 | 0.942 | 0.886 | 0.23 |
| Aromadendrin | 0.367 | 0.068 | 0.039 | 0.253 | 0.94 | 0.154 | 0.341 |
| Anthraquinone | 0.043 | 0.041 | 0.901 | 0.077 | 0.855 | 0.734 | 0.134 |

## Molecular Visualization and Docking Systems

Fifty ligands were docked against the target protein, 1LUF-MuSK, in this docking investigation using the PyRx program. The conformation that had the strongest affinities and the root mean square deviation (RMSD) that is lowest following docking was finished was chosen as the ideal docking parameter.

After binding our ligands to target proteins, binding affinity, RMSD/ub, and r/lb were written. First 6 of 48 ligands shown are low 1LUF-MuSK, i.e., Binding affinities for each protein as shown in Table 7.

**Table 7.** Target protein binding affinity of ligand derivatives.

| **Ligands** | **Binding Affinity** |
|---|---|
| Rhein | –10.7 |
| Aloe emodin | –9.9 |
| Chrysophanic acid | –9.7 |
| Aromadendrin | –9.6 |
| Anthraquinone | –8.9 |

Using the Dassault Systems BIOVIA Discovery Studio Visualizer, the chosen ligands were visualized, and both two- and three-dimensional models were obtained. Additionally, along with details on the kind and category of interaction, the bond distance for the pertinent amino acid residues in the ligand was obtained Figures 3, 4, 5, and 6(a–d).

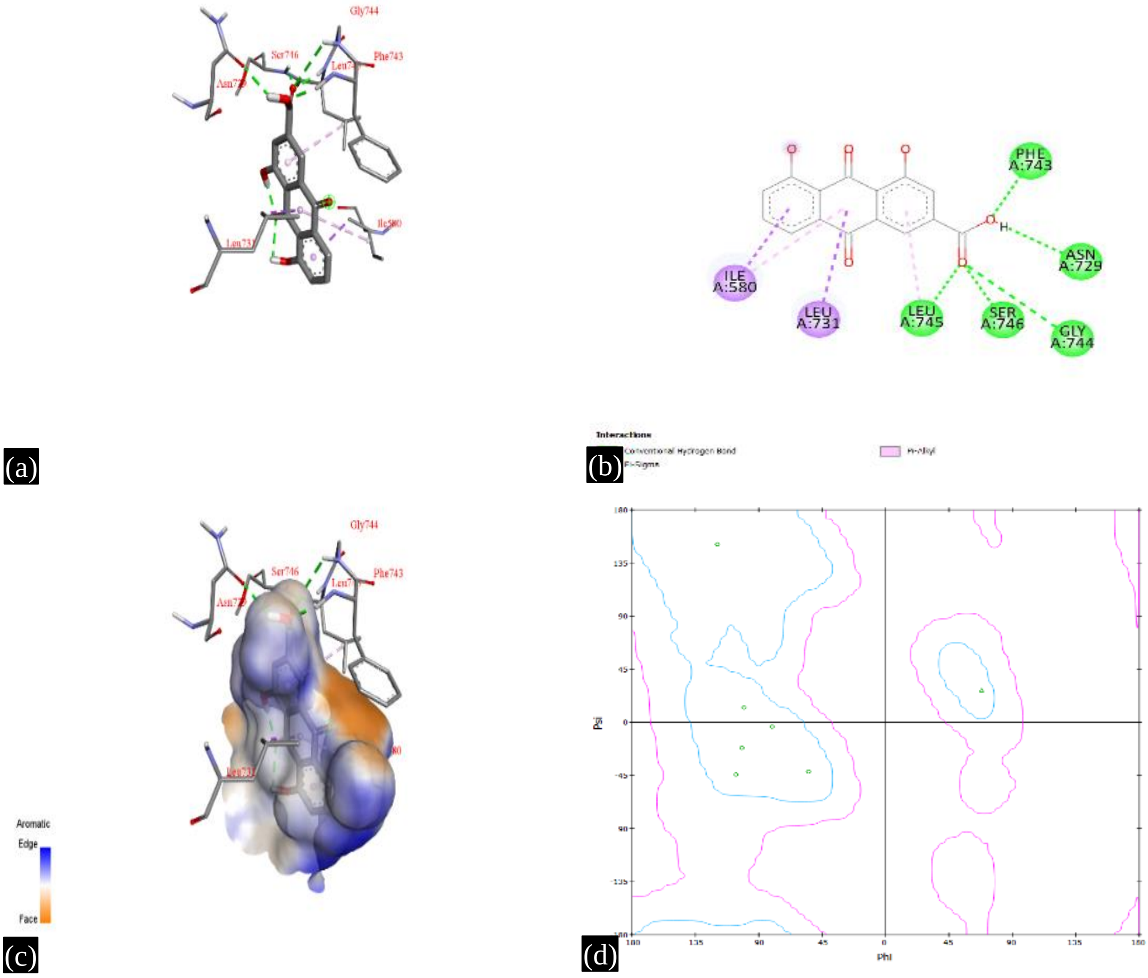



**Figure 3.** Visualisation of Rhein interacting with Musk-1LUF. (a) 3D interaction, (b) 2D interaction, (c) Aromatic structure, (d) Ramchandran plot.

## DISCUSSION

ADME (absorption, distribution, metabolism, and excretion) in conjunction with molecular docking analytical methods for the search for promising phytochemicals for treatment of Myasthenia gravis (MG) is a novel technique in drug development. The goal of this strategy is to find new therapy options for MG by using computational techniques to evaluate and rank phytochemicals with therapeutic potential.

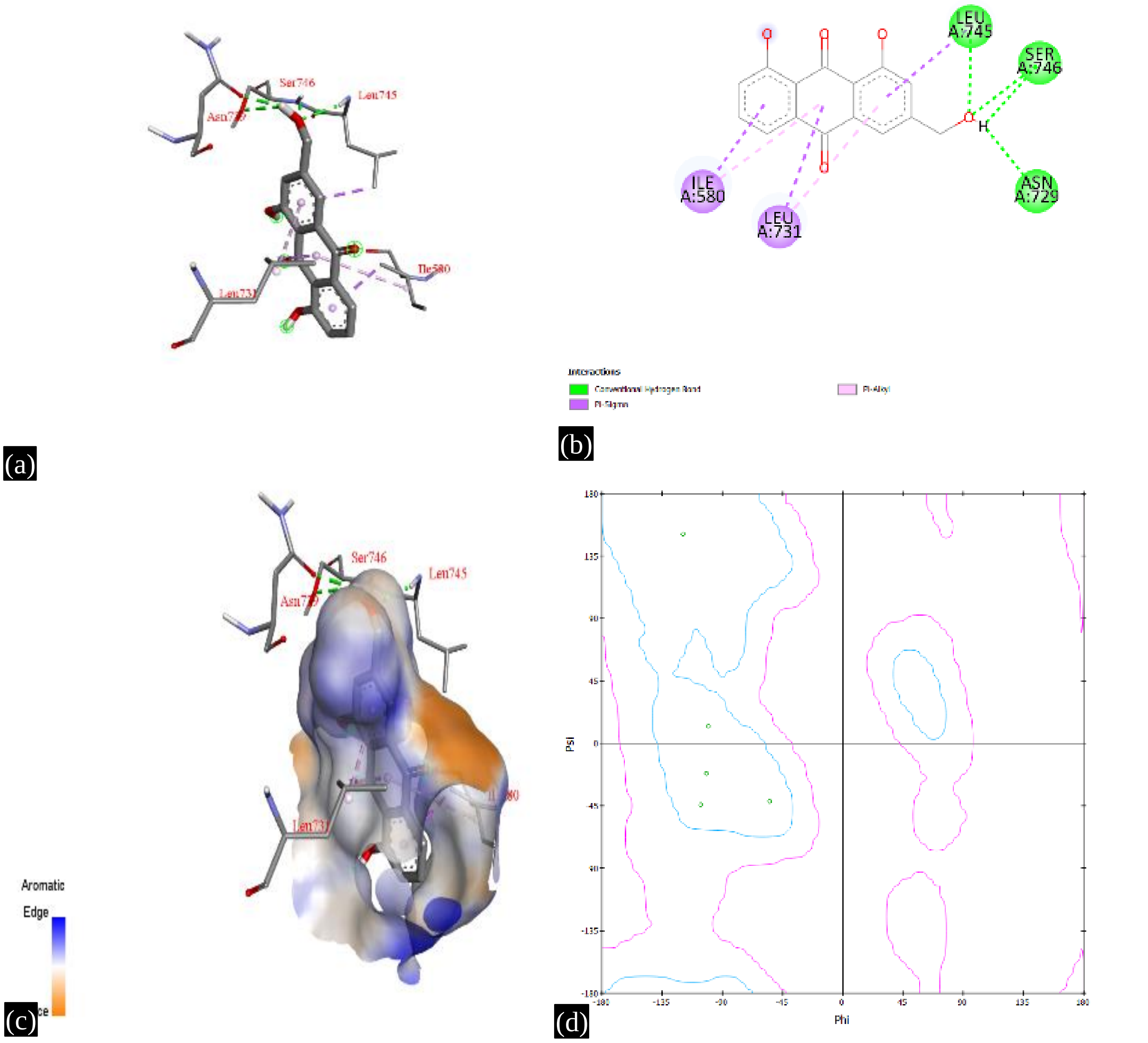



**Figure 4.** Visualisation of Aloe-emodin interacting with Musk-1LUF. (a) 3D interaction, (b) 2D interaction, (c) Aromatic structure, (d) Ramchandran plot.

Target protein interactions are mimicked by molecular docking, making it a valuable tool that acetylcholine receptors or enzymes involved in neuromuscular transmission have with phytochemicals during the pathogenesis of MG. Selecting phytochemicals with a high probability of biological action against MG targets is guided by the docking procedure, which also predicts binding affinities and clarifies possible binding mechanisms.

ADME analysis also plays a key role in assessing the pharmacokinetic characteristics of discovered phytochemicals. This research evaluates important factors, such as excretion rates, distribution in tissues, metabolism, and bioavailability to offer insights into the overall appropriateness of phytochemicals as possible MG treatment options.

By selecting the phytochemicals that have the best potential for both therapeutic effectiveness and advantageous pharmacokinetic profiles, the combination of molecular docking and ADME analysis enhances the drug development process. This method offers a time- and money-efficient way to screen a wide variety of natural chemicals for MG therapy. In addition, it supplements conventional experimental approaches.

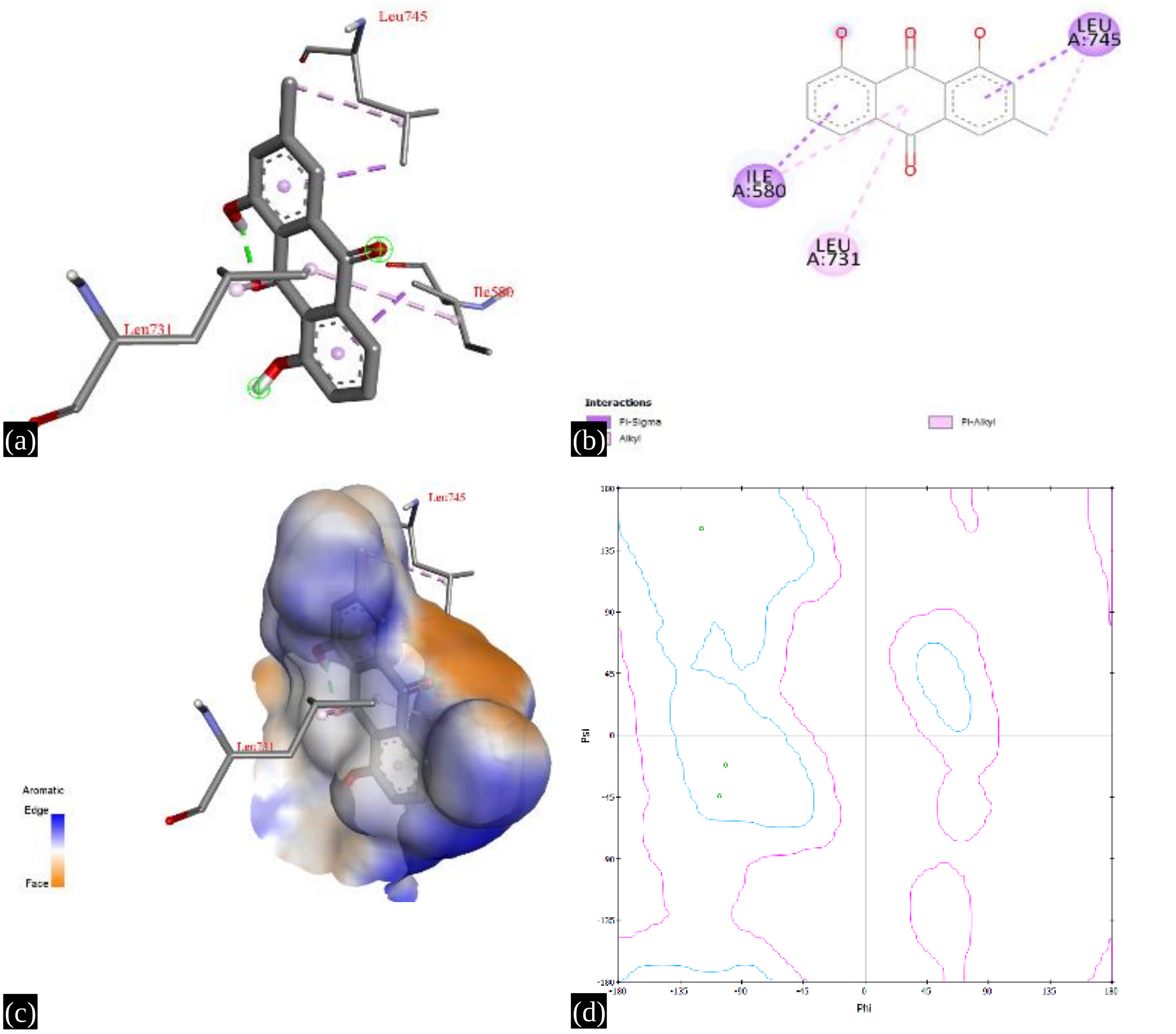
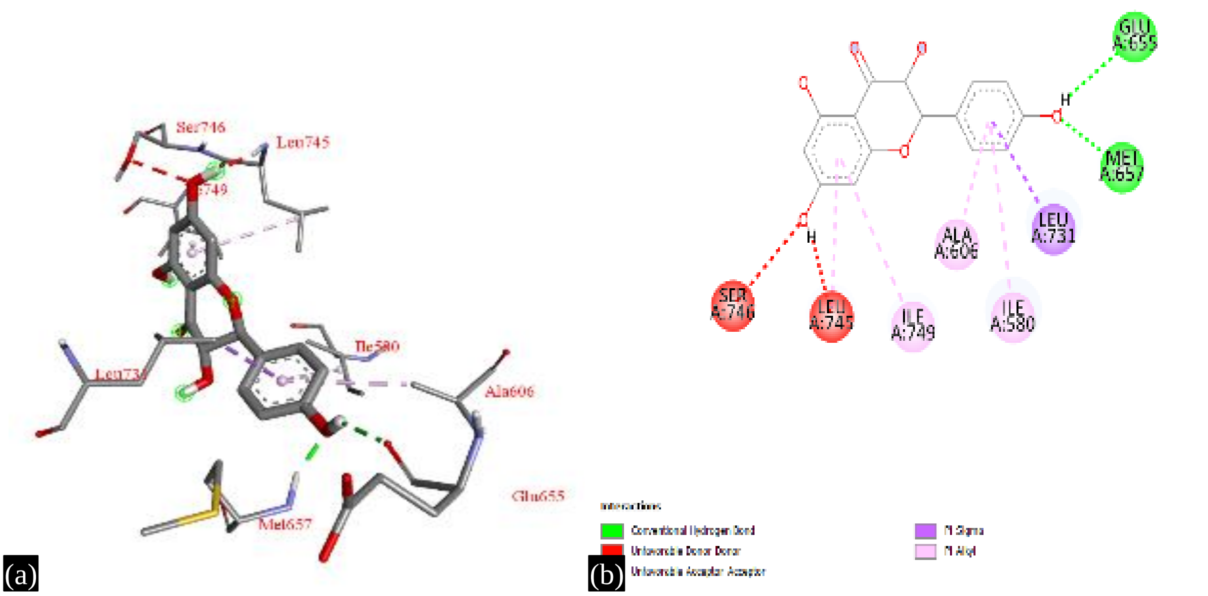



**Figure 5.** Visualisation of chrysophanic acid interacting with Musk-1LUF. (a) 3D interaction, (b) 2D interaction, (c) Aromatic structure, (d) Ramchandran plot.



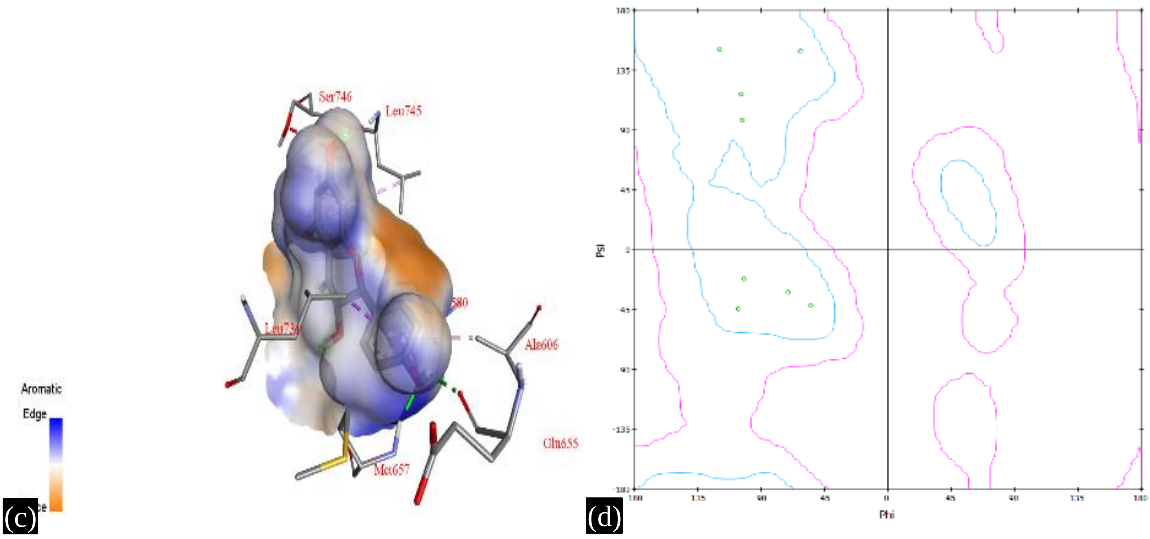



**Figure 6.** Visualisation of aromadendrin interacting with Musk-1LUF. (a) 3D interaction, (b) 2D interaction, (c) Aromatic structure, (d) Ramchandran plot.

Two effective programs that are frequently used for molecular docking investigations are PyRx and Biovia. In this context, molecular docking entails essentially screening phytochemicals against certain target proteins linked to MG, including crucial enzymes involved in neuromuscular transmission or acetylcholine receptors. By predicting how phytochemicals would interact and attach to various targets, the docking technique can find compounds with high binding affinities and offer insights into possible therapeutic actions.

The combination of PyRx and Biovia makes it possible for researchers to quickly screen and rank a wide variety of phytochemicals, which speeds up the drug development process. By finding possible drug candidates with the best binding interactions and pharmacokinetic characteristics, computational techniques improve decision-making and lessen the need for resource-intensive experimental screening.

Research conducted in vivo and in vitro will eventually be able to confirm the efficaciousness, safety, and mechanisms of action of potential phytochemical candidates found by computational screening for the treatment of MG. The creation of nature-inspired medicines with higher efficacy and fewer side effects than traditional MG treatments may be made possible via a successful validation process.

One of the many benefits of using Biovia and PyRx for molecular docking and ADME analysis in screening huge chemical libraries is that it’s fast, scalable, and economically viable. In the future, to verify the safety and effectiveness of phytochemical hits found through computational research for MG therapy, additional validation can be achieved by experimental testing.

## CONCLUSIONS

In conclusion, the search for phytochemicals for MG treatment by molecular docking and ADME analysis represents a promising strategy to discover natural compounds with therapeutic potential. This approach uses computational methods to prioritize candidate compounds for further preclinical and clinical evaluation, ultimately aiming to address the unmet medical needs of MG patients. The application of computer methods like molecular docking and ADME analysis with PyRx and Biovia shows great potential in the discovery of new phytochemical-based treatments for MG. By using an integrated approach, it is possible to find possible medication candidates that have lower side effects and increased efficacy, which will ultimately lead to more individualized therapy options for MG patients.

To summarize, the utilization of Biovia and PyRx in investigating phytochemicals for the treatment of MG highlights the significance of computational techniques in expediting the identification and advancement of novel medicines sourced from natural sources.

**Acknowledgment**

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**Authors Contribution**

The manuscript has been equally contributed to by each author.

**ABBREVIATIONS**

| | | |
|---|---|---|
| MG | : | Myasthenia gravis |
| AChR | : | Acetylcholine receptor |
| MuSK | : | Muscle-specific tyrosine kinase |
| SMILES | : | Simplified molecular input line entry system |
| IMPPAT | : | Indian medicinal plants, phytochemistry and therapeutics |
| GI | : | Gastrointestinal |
| BBB | : | Blood brain barrier |
| hERG | : | Human ether-a-go-go-related gene |
| DILI | : | Drug-induced liver injury |
| H-HT | : | Hereditary haemorrhagic telangiectasia |
| TPSA | : | Topological polar surface area |
| ROA | : | Route of administration |

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