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Using Multitarget Molecular Docking to Examine the Antiviral Potential of *Clerodendrum Phlomidis* against Measles

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Abstract

Objective: Measles, a viral disease caused by a member of the Paramyxoviridae virus family, is highly contagious and characterized by a respiratory illness and a maculopapular rash on the skin. Children are the main victims of the illness. In the context of drug development, this study investigates the efficacy of phytocompounds derived from Clerodendrum phlomidis against the target protein of the measles virus. Methods: The 7SKS protein was retrieved from the Protein Data Bank (PDB) database. Molecular docking studies were conducted systematically using PyRx and BIOVIA Discovery Studio Visualizer to assess the binding affinities of phytocompounds to the target protein. To evaluate the pharmacological properties of the phytocompounds, Swiss-ADME and ADMET lab were employed. Results: The docking results indicate that among the phytocompounds tested, Pectolinarin, beta-sitosterol, Clerodendrin A, Clerodin, Clerosterol, Daucosterol, Scutellarein, and Sterol exhibited the highest binding affinities to the target protein. However, based on the ADMET profile and drug-likeness prediction analysis, Clerodin and Scutellarein were found to have drug-like properties among the eight compounds evaluated. Conclusions: The results of this study indicate that Clerodin and Scutellarein possess specific binding affinity and therefore may be effective against the matrix protein. As such, these phytocompounds hold potential for use in therapeutic strategies against measles disease.

Keywords: Paramyxoviridae**,** Measles disease, 7SKS protein, *Clerodendrum phlomidis,* phytocompounds, Molecular docking, ADME.

INTRODUCTION

The virus-based disease measles is serious and extremely contagious [1]. The disease can be transmitted through both aerial dispersal and person-to-person contact. Measles can spread in public places even when there isn't direct person-to-person contact because infectious droplets from a patient's respiratory secretions can linger in the air for up to two hours. Measles outbreaks can occur in crowded settings such as schools and densely populated areas, and there have been reports of transmission on airplanes and in airports. The incubation period for measles typically lasts 6 to 21 days (median 13 days), and subclinical disease is rare. According to estimates, the contagious period lasts from five days before the rash shows to four days after. The greatest period of contagiousness is thought to be the late prodrome phase, when the patient exhibits fever and respiratory symptoms. Patients with measles-related subacute sclerosing panencephalitis are not contagious [2].

Measles continues to be a major cause of child morbidity and mortality globally despite the existence of a safe and effective vaccine. In

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addition, measles is associated with several neurologic disorders, including acute disseminated encephalomyelitis (ADEM), measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE) [3, 4]. The measles virus (MV) infects immune cells, resulting in acute immune suppression. Infection with measles can significantly impair pre-existing immunological memory, making individuals more susceptible to other infections. Every year, the virus causes more than 100,000 fatalities, many of which are brought on by secondary infections because it interferes with immune cell function. It is currently unclear if measles infection results in permanent damage to the immune system's memory [5].

Systemic sickness is brought on by the MV, a highly contagious negative strand RNA virus that affects both humans and non-human primates. The respiratory route is the main method of transmission. Fever and a skin rash, together with coughing, coryza, and conjunctivitis in many cases, are the main symptoms of measles. Transient immune suppression, which increases vulnerability to opportunistic infections, is another feature of measles. Paradoxically, the illness also triggers a robust immune response that is specific to the virus and confers lifetime immunity against measles. Recent studies have uncovered fresh information about the tropism and pathogenesis of MV, including the finding that CD150 and nectin-4 are the virus's cellular receptors [6].

The Rigveda and Atharvaveda, two of the oldest Indian Vedic writings, are the sources of the holistic medical system known as Ayurveda. This system of traditional Indian medicine has a long history that spans several millennia and has been used to manage a wide range of human illnesses. Since ancient times, various medications have been produced and used from Ayurveda as a "tradition to trend." The potential of Ayurvedic medicine needs to be further explored using cutting-edge scientific validation methodologies for improved therapeutic leads [7]. Ayurveda's essential principles place a high priority on preventing unneeded suffering and encouraging a long, healthy life. By restoring harmony and creating a healthy lifestyle to prevent imbalances from recurring, ayurvedic practise involves using natural ingredients to treat ailments at their source [8].

The Lamiaceae family includes the shrub *Clerodendrum phlomidis* L., which is widely dispersed in Southeast Asia. In Sanskrit, it is referred to as Agnimantha. This genus is at the forefront of ethnomedicine in numerous indigenous medical systems, including Indian, Chinese, Thai, Korean, Siddha, Unani, and Japanese, due to the wide range of medicinal uses attributed to this plant, including the treatment of ailments like syphilis, typhoid, cancer, jaundice, hypertension, constipation, gonorrhoea, piles, urinary diseases, fearful disorders, inflammation, and measles [9, 10]. The plant's leaves, roots, and stems contain specific phytochemical compounds that have been utilized for the treatment of measles. These compounds possess anti-inflammatory, antibacterial, and antiviral properties, enabling them to impede the growth of microorganisms, combat infections, and mitigate inflammation [11]. This study investigated ten bioactive phytochemicals present in *Clerodendrum phlomidis* for their potential as inhibitors of measles core protein 7SKS, with a focus on identifying compounds that are both stable and active (Figure 1).

METHODS

Protein Preparation

In order to strengthen hydrogen bonds and minimise atomic collisions, hydrogen atoms are frequently added to protein crystal structures prior to docking. Prior to the virtual screening, ligands must be prepared to establish three-dimensional geometries, assign appropriate bond ordering, and produce accessible tautomer and ionisation states [12].

The PDB (Protein Data Bank) of the RCSB (Research Collaboratory for Structural Bioinformatics) (https://www.rcsb.org/) [13] was used to get the three-dimensional crystal structure of the matrix protein (Crystal structure of measles virus matrix protein) (PDB ID: 7SKS) [14]. There are 376 amino acids altogether in its 2 chains, A and B. The crystal solution of it is 2.54. Using Discovery Studio

visualizer 21.1's standard technique, protein preparation was carried out. Proteins were stripped of their heteroatoms and water molecules.

Figure 1. (a) *Clerodendrum phlomidis* tree, (b) Structure of 7SKS protein

Ramachandran Plot

The polypeptide chain conformation angles phi and psi of a protein molecule are shown on the Ramachandran plot. Ramachandran plot evaluation (https://swift.cmbi.umcn.nl/servers/html/ramchk.html) [15] and the MolProbity Server (http://molprobity.biochem.duke.edu/index.php) [16] were used to conduct the analysis. The PDB file for matrix protein (7SKS) was uploaded in order to examine the Ramachandran plot with outliers that are marked by residue type, residue number, and chain and display all the labels.

Ligand Selection

Indian Medicinal Plants, Phytochemistry, and Therapeutics (IMPPAT) provided 10 phytocompounds from Clerodendrum phlomidis for the identification of effective matrix protein inhibitors. The PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/) [17], which contains the structures of phytocompounds, was used to retrieve three-dimensional structural data files (3D SDF). The PyRx tool was used to prepare the ligands, which included ligand optimisation, energy minimization, and conversion to 3D PDB format [18].

Molecular Docking

A crucial technique in structural molecular biology and computer-assisted drug design is molecular docking. The goal of ligand-protein docking is to foretell the main binding mode(s) of a ligand with a protein with a known three-dimensional structure [19]. PyRx, a computer programme for virtual screening, was applied during the molecular docking investigation [20]. According to the data on the IMPPAT, the PyRx tool was utilised to dock the chosen ligands with matrix protein (7SKS). Target selection for the docking investigation involved choosing prepared receptors and ligand files. Using the open-babel tool tab, a protein was loaded and transformed into macromolecules [21]. To check all potential combinations of ligand and protein binding, the grid box was formed by maximisation after the protein and ligand molecules were specified. The forward button was pressed to start docking after the necessary modifications had been made. After docking was finished, a table containing each ligand's binding affinity was produced. Eight of the ligands with the highest binding affinities were chosen, and their data were recorded in PDB format. The top 8 ligands with the highest binding affinities in PDB file format were selected. A 2D–3D interactive visualisation study using Discovery Studio Visualizer 21.1 was carried out [22].

ADME Analysis

ADME stands for Absorption, Distribution, Metabolism, and Excretion. The goal of ADME research is to understand how a substance is metabolised by a living being. Toxicology tests are

widely used in this procedure, hence the acronym ADMET [23]. The concept of ADME is typically used to explore chemical effects on health. be eliminated, others might not. The toxicity of a chemical can be evaluated by taking into account all aspects of how chemicals enter the body, move through the body, and leave the body [24]. In this study, the top 8 compounds with the highest binding affinities were chosen for the drug likeliness test and ADMET (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) analysis. Drug likeliness and ADMET analysis were carried out by uploading the ligand file in canonical smile format to SWISS-ADME (http://www.swissadme.ch/) and ADMETLAB (https://admetmesh.scbdd.com/) for analysis [25, 26]. The Swiss-ADME tool was also used for the study of boiled eggs [27]. The Lipinski rule was used in the ADME analysis. When a molecule meets two or more of the following requirements, this rule predicts whether a medicine is likely to be effective or not: fewer than 500 Daltons for molecules, high lipophilicity (log P<5), less than 10 hydrogen bond acceptors, less than 5 hydrogen bond donors, molar refractivity should range from 40 to 130.

RESULTS

Ramachandran Plot

Consider the following protein geometry in the Ramachandran plot (Figure 2) (Table 1).

Table 1. Protein geometry obtained from Ramachandran plot analysis.

Poor rotameters	4	0.83%
Favored rotameters	456	94.80%
Ramachandran outliers	0	0.00%
Ramachandran favored	515	96.62%
Rama distribution Z score	-1.24 ± 0.32	
Cβ deviations > 0.25 Å	0	0.00%
Bad bonds:	1/4423	0.02%
Bad angles:	0/5993	0.00%
Chiral volume outliers	0/705	

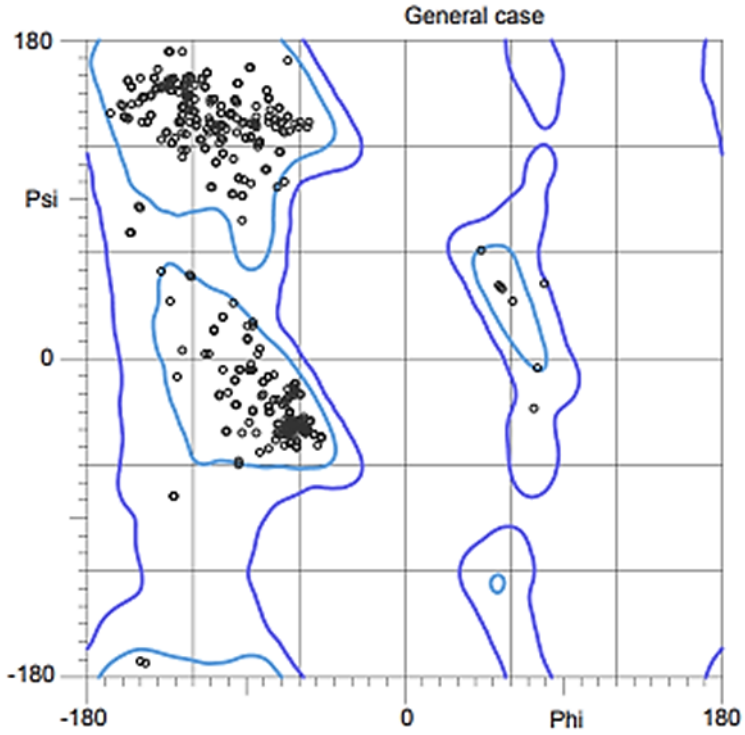


Figure 2. Ramachandran plot of protein 7SKS for general case.

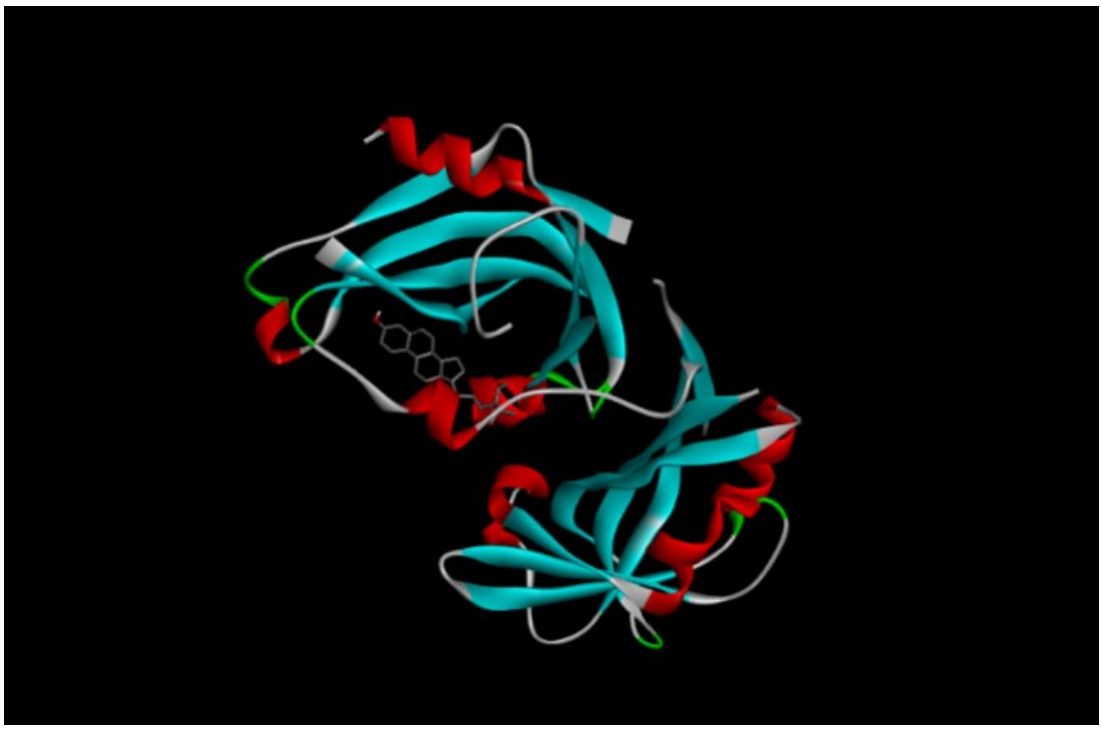
Molecular Docking

The results of the molecular docking study revealed that the active phytocompounds from *Clerodendrum phlomidis* have a high affinity for 7SKS. Further study on identifying the active phytocompounds with the highest binding affinities was strengthened by molecular docking using PyRx. Table 2 displays the binding energies of the top eight phytochemicals from *Clerodendrum phlomidis* that have the greatest affinity for 7SKS.

Using PyRx software, the results of the molecular docking analysis showed that 8 out of the 10 compounds present in the leaf, root, and stem portions of Clerodendrum phlomidis demonstrated a strong affinity for the 3T4G protein (>7 Kcal/mol) [28–35]. Following this initial screening, the top 8 compounds were selected for further investigation, including drug likeliness prediction and ADME analysis based on the molecular docking data. The results of this analysis identified Pectolinarin, beta-Sitosterol, Clerodendrin A, Clerodin, Clerosterol, Daucosterol, Scutellarein, and sterol as the compounds with the highest binding affinities. Conversely, 1-Hexacosanol and Mannitol exhibited the least binding affinities, as reported in Table 2. Figure 3 shows 2D and 3D diagram of interactions between ligand and target protein.

Table 2. Clerodendrum phlomidis' top 8 phytochemicals with the highest binding affinity for the 7SKS Protein.

S.N.	PubChem Compound ID	Phytocompound Name	Binding energy (Kcal/mol)
1.	16884	Pectolinarin	-7.1
2.	5281697	Scutellarin	-7.4
3.	442013	Clerodendrin A	-7
4.	442014	Clerodin	-6.4
5.	1107	Sterol	-6.9
6.	5283638	Clerosterol	-7.3
7.	222284	beta-Sitosterol	-8.1
8.	5742590	Daucosterol	-7.8



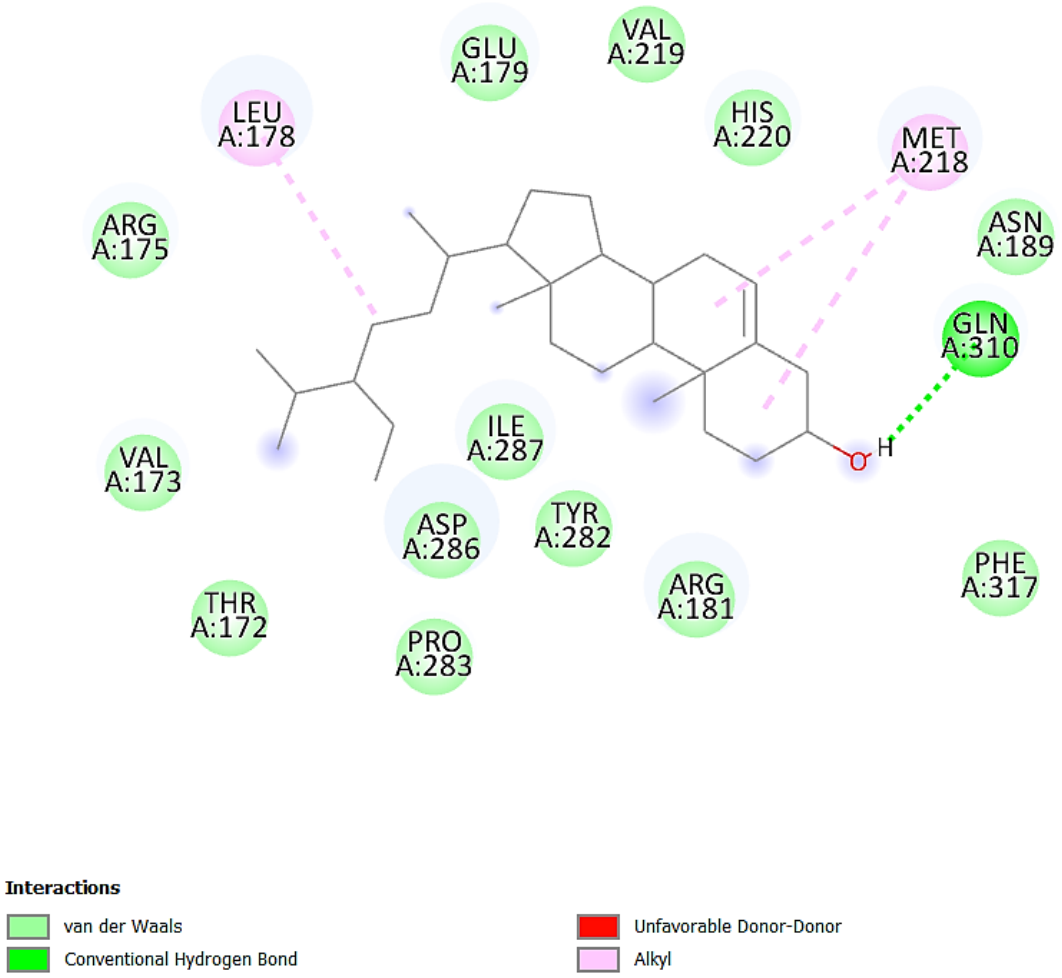


Figure 3. 2D and 3D diagram of interactions between ligand and target protein.

ADME analysis and Drug-likeliness Prediction

After molecular docking analysis, the active phytochemicals with the best binding values, interactions, and affinities were found and subsequently assessed for their ADME parameters using the online tool Swiss ADME.

Lipinski's rule of five was used in this study to differentiate between molecules that are similar to drugs and those that are not. The best-docked compounds' drug-likeness was calculated using Lipinski's rule of five (Table 3).

The results obtained from ADME analysis (Table 3) indicated that phytocompounds Clerosterol, beta-Sitosterol, Daucosterol were found to have one violation each of Lipinski's rule. Additionally, Clerodendrin A and Pectolinarin exhibited 3 and 2 violations of Lipinski's rule, respectively. These substances demonstrated no Blood Brain Barrier (BBB) penetration and low gastrointestinal (GI) absorption. Sterol, however, only displayed one exception to Lipinski's rule—its MLOGP value was higher than 4.15—but it had high GI absorption and was BBB permeable. The remaining two compounds, Scutellarein and Clerodin, were found to have zero violations of Lipinski's rule. Additionally, they both demonstrated high potential for GI absorption, making them suitable for use as oral drugs.

Additionally, a boiled egg analysis was performed using the SWISS ADME tool to forecast the BBB permeate and GI adsorption of particular phytocompounds (Figure 4). Points positioned inside

the yellow of the BOILED-Egg are the analogues that are anticipated to passively infiltrate the BBB. Points within the egg white are relative to the analogues anticipated to stand passive absorption with the aid of using the gastrointestinal tract. Red dots indicate that the molecules are predicted not to be affected by Pglycoprotein mediated extrusion from the central nervous system.

Table 3. ADME analysis of top 8 phytocompounds.

S.N.	Ligand Name	Molecular weight (g/mol)	H-Bond Donor	H-Bond Acceptor	Molar Refractivity	Lipinski's rule
1	Pectolinarin	622.57	15	7	148.29 No	3 violations
2	Scutellarein	286.24	6	4	76.01 Yes	0 violation
3.	Clerodendrin A	606.66	12	1	148.73 No	2 violations
4.	Clerodin	434.52	7	0	111.78 Yes	0 violation
5.	Sterol	248.4	1	1	76.54 Yes	1 violation
6.	Clerosterol	412.69	1	1	132.75 Yes	1 violation
7.	beta-Sitosterol	414.71	1	1	133.23 Yes	1 violation
8.	Daucosterol	576.85	6	4	165.61 Yes	1 violation

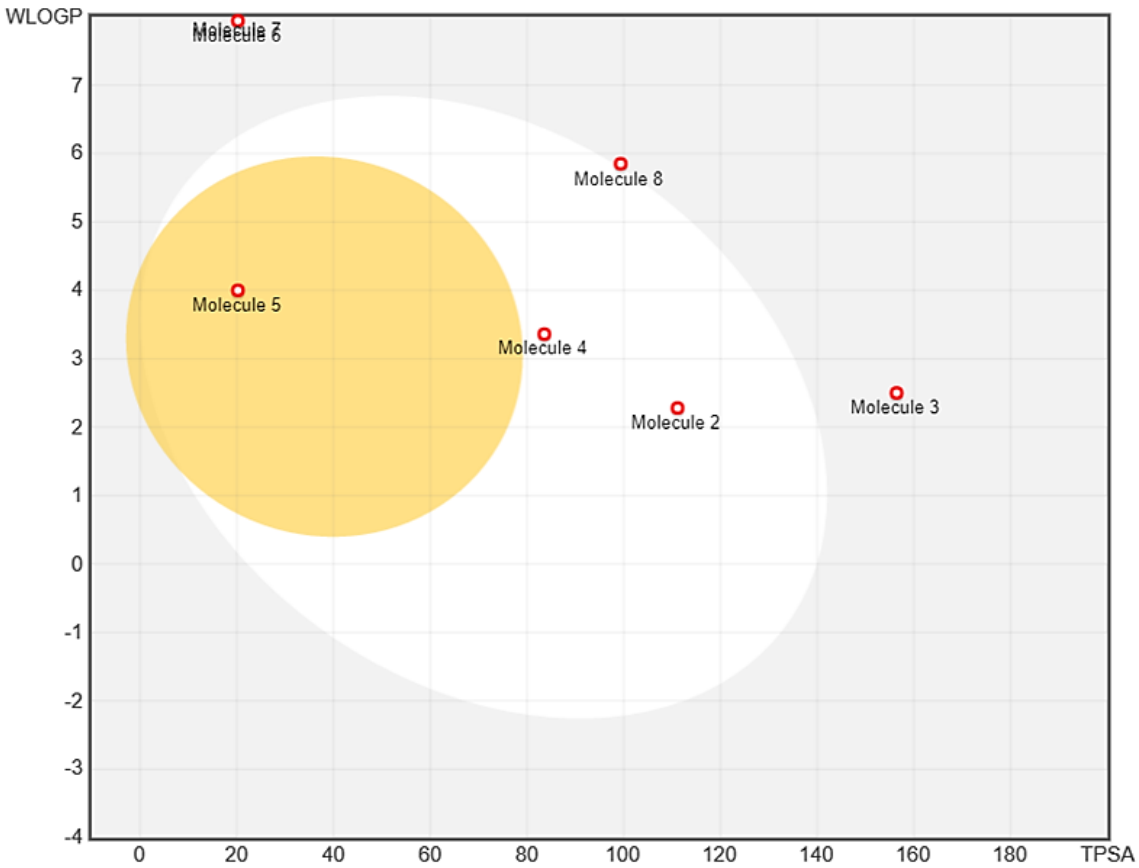


Figure 4. BOILED Egg analysis. (1) Pectolinarin, (2) Scutellarein, (3) Clerodendrin A, (4) Clerodin, (5) Sterol, (6) Clerosterol, (7) beta-Sitosterol, (8) Daucosterol.

DISCUSSION

Measles can be avoided with the MMR vaccine in contemporary medicine. The MMR vaccine has a very high level of dependability and security. The effectiveness of the MMR vaccine to prevent measles is approximately 97% after two doses and 93% after one. The MV that causes the measles is contagious. Even though there is a safe vaccine to prevent measles, 30 to 40 million people around the world still catch the illness each year. Over 500,000 people per year pass away from the measles,

which accounts for 44% of the 1.7 million child deaths that could have been avoided by vaccination. Conjunctivitis, pneumonia, ear infections, throat infections, and diarrhoea are a few of the adverse effects that measles can cause. It was discovered that giving antibiotics to kids with measles led to a lower incidence of pneumonia, ear infections, and tonsillitis in clinical research that was carried out in May 2013 with 1263 kids [36].

The binding affinities of the phytocompounds used for this investigation were discovered by molecular docking experiments. Therefore, molecular docking is crucial in selecting the substances or ligands for additional investigation.

To assess the possibility of the compounds under research being used as a direct or indirect measles treatment strategy, this study used a variety of investigative techniques, such as molecular docking and ADME analysis. In order to precisely predict the interaction between receptors or proteins and ligands or phytocompounds as well as their relative binding affinities, the computational method known as "molecular docking" is used. It has proven to be an extremely efficient method for screening a variety of compounds and finding brand-new medications against target proteins. Among the various types of docking, protein-ligand docking is of particular interest because of its applications in the pharmaceutical industry [37, 38].

The discovery of relationships between proteins and ligands alone cannot be used to infer that these phytocompounds are prospective pharmaceuticals. It is important to look into the ligands' stability, interactions, and binding affinities with targets. In silico methods that have proved successful for this goal include toxicity prediction, ADME analysis, and molecular docking [39]. The ADME test evaluates a putative medicinal chemical's lipophilicity, solubility, pharmacodynamic, and pharmacokinetic properties inside the biological system. The success of the search for novel medications depends on it. A toxicology study is essential to determining the effects and dangers of these substances on the human body.

In this study, it was discovered that eight phytocompounds, namely Pectolinarin, beta-Sitosterol, Clerodendrin A, Clerodin, Clerosterol, Daucosterol, Scutellarein and sterol, had significantly good binding affinity with the target protein. When these compounds were further studied in detail, Pectolinarin and Clerodendrin A had 3 and 2 violations, respectively, of Lipinski’s rule. Beta-Sitosterol, Clerosterol, Daucosterol, and sterol, had 1 violation each, and Scutellarein and Clerodin had 0 violations each for Lipinski’s rule. An active oral medication should not have more than one infraction in accordance with the Lipinski rule of 5.

These results imply that Pectolinarin and Clerodendrin A cannot be used as oral drugs. While Sitosterol, Clerosterol, Daucosterol, and Sterol could be considered for use as oral drugs with the necessary modifications done after further in-depth studies, Scutellarein and Clerodin could be clearly used as potential oral drugs with high solubility and GI absorption. The compounds that obeyed Lipinski’s rule also showed good results against toxicity. The likelihood of failure as a result of medication similarity is also quite low. The success or failure of a medication is a critical factor that must be taken into consideration before progressing further in its development. Pharmaceuticals often fail in clinical trials due to the occurrence of harmful side effects, which can be both costly and hazardous during the production and use of the drug. Therefore, it is essential to assess the safety profile of a drug candidate early on in the drug discovery process to minimize potential risks and ensure the development of safe and effective medications.

According to the investigation's findings, it can be said that the phytochemicals derived from *Clerodendrum phlomidis*, especially the molecules Scutellarein and Clerodin anticipated by the Swiss ADME approach, have proven to be effective therapeutic agents with desirable ADME properties. Even though more investigation is always required, this study offers an analytical framework for the creation of a potential measles medication.

CONCLUSION

Clerodendrum phlomidis is the subject of this investigation in order to find any potential natural phytocompounds that may exist that could serve as therapeutic agents for the treatment of measles. The measles virus (MV) is responsible for this disease, which infects immune cells and causes acute immunosuppression. According to ADME data, two out of the eight compounds investigated in this study show potential for targeting the matrix protein. The development of a successful measles medication may benefit from the use of the best-docked phytocompounds, which show drug-like characteristics, appropriate ADMET profiles, toxicity predictions, and efficacy. However, additional investigation is imperative to modify these phytochemicals in order to optimize their safety and efficacy for the treatment of measles.

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Authors Contribution

The contribution of all the authors to the manuscript has to be clearly stated.

Conflict of Interest

The authors declare no conflict of interest.

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Abbreviations

ADMET	Absorption, Distribution, Metabolism, Excretion, Toxicity
BBB	Blood Brain Barrier
IMPPAT	Indian Medicinal Plants, Phytochemistry, And Therapeutics
MV	Measles Virus
PDB	Protein Data Bank
RCSB	Research Collaboratory for Structural Bioinformatics
SDF	Three-Dimensional Structural Data File

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