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Research Article

Anti-Measles Potential of Selected Compounds from *Uvaria chamae* P. Beauv: A Molecular Docking Approach

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Abstract

Measles is an extremely contagious viral infection, reported to be responsible for most global childhood death. Plants have been proven to be very effective against viral diseases with an added advantage of less toxicity. Previous studies have reported the activities of *Uvaria chamae* extracts against measles virus. This study investigated bioactive compounds in silico anti-measles activities from *Uvaria chamae* leaves extract. The in silico docking studies were carried out using four compounds isolated from *U. chamae* (stigmasterol, chrysin, chalcone, and dihydrochalcone) reported in literature. The pharmacokinetic properties of these selected compounds were also evaluated using ADMET studies. The compounds were docked to the measles virus nucleoprotein (PDB ID: 5E4V) and they had binding affinities ranging from -6.4 to -8.2 kcal/mol. Stigmasterol (-8.2 kcal/mol) and Chrysin (-8.0 kcal/mol) showed the greatest affinities for the protein target. These two compounds passed the Lipinski's Rule of Five for leadlikeness. Stigmasterol and Chrysin showed promising pharmacological properties that indicate that they could be investigated as viable lead candidates for further anti-measles drug development studies.

Key Words: *Uvaria chamae*, *in silico*, Measles, Stigmasterol and Chrysin.

INTRODUCTION

Measles, also known as Rubeola, is an extremely contagious viral infection, and it is reported to be one of the most important global cause of deaths and sicknesses (Oluremi and Adeniji, 2015), even though it is a vaccine-preventable disease. It is more prevalent in children under the age of five (Adekola *et al*., 2021) and as such, a live attenuated vaccine is given to children as part of the Measles, Mumps, Rubella (MMR) vaccine at the age of one, and a subsequent booster dose at the age of 5 (Di Pietrantonj *et al*., 2021). The reservoir for this virus is the human respiratory tract and transmission occurs through the inhalation of droplets produced by infected individuals (Qureshi and Jan, 2021). Despite the availability of vaccines for the disease, in recent times a global increase in measles cases has been reported. In 2019, in the US, the highest number of measles cases in a single year since 1992, with nearly 1,300 confirmed cases was reported (Smith, 2022). Data worldwide in the same year have shown that measles cases have tripled, with countries in Europe and Africa the most affected. In December 2021, a measles outbreak was reported in Anambra community of Ifite-Ogwari, Anambra state in Nigeria, where 13 children were reported dead (NCDC, 2021; Qureshi, 2021) due to measles.

Medicinal plants have been proven to be very effective against certain viral infections (Olumese *et al*., 2016). The discovery of antiviral drugs of plant origin appears promising (Oluremi and Adeniji, 2015). *Uvaria chamae* known as 'Oko aja' amongst the Yorubas, is a member of the Annonaceae family and is an evergreen plant whose parts are used widely in traditional medicine in Western Africa (Olumese *et al*., 2016). Antimicrobial (Ogbulie *et al*., 2007; Oluremi *et al*., 2010; Monon *et al*., 2015), antioxidant (Monon *et al*., 2015), antidiabetic (Emordi *et al*., 2015), antimalarial (Okokon *et al*., 2006; Adepiti and Iwalewa, 2016) and toxicological studies (Olumese *et al*., 2016) have been carried out on various parts of the plant. Oluremi and Adeniji (2015) reported that *Uvaria chamae* root and stem bark extract showed in vitro anti-measles virus activity, In addition, Popoola *et al.* (2021) reported that chalcone, a compound isolated from *Uvaria chamae* demonstrates antiviral and antioxidant activity and has been evaluated for severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2)/coronavirus disease 2019 (Covid-19).

The process of isolating potential bioactive compounds and translating them into potential leads for drug discovery and development is an intense, lengthy, and multidisciplinary task (Chen *et al*., 2018). The conventional procedure for medicinal chemists to design and synthesize a new bioactive molecule involves trial and error screening method (Weng *et al*., 2018), which is very expensive as biological testing expenses have gone up exponentially. Thus, in silico method, which is a virtual computational drug screening method that uses a wide range of software like, PyRx, PubChem, Grid Computing, and Python can be used to accelerate the process of drug discovery and development (Kondapuram *et al*., 2021; Macalino *et al*., 2020). This study evaluated the anti-measles activity of some

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selected bioactive compounds from *U. chamae* using in silico methods.

MATERIALS AND METHODS

Identification of bioactive compounds from *Uvaria chamae* plant fractions: Four bioactive compounds from *Uvaria chamae* stigmastetol, chrysin, chalcone, and dihydrochalcone were obtained from the literature following the establishment of their activities against the measles virus (Oluremi and Adeniji, 2015; Thomas *et al*., 2018; Stompor *et al*., 2019; Popoola *et al* 2022).

Ligand Selection and Preparation: The structures of the bioactive compounds obtained from literature on *Uvaria chamae* leaves were retrieved from Pubchem database (https://pubchem.ncbi.nlm.nih.gov/). The structure of the molecules was exported in SDF format to PyRx virtual screening tool for docking with the macromolecule of interest.

Preparation of Target Protein: The RCBS Protein data bank (RCBS PDB) database (https://www.rcsb.org/) was used to obtain the 3D structure of the enzyme receptor (Measles Virus Nucleoprotein Core in Complex with an N-Terminal Region of Phosphoprotein), PDB Code: 5E4V (Abdulrahman *et al*., 2022). UCSF Chimera software (Butt *et al*., 2020), was used to prepare the protein by removal of co-ligands and adding of polar hydrogen prior to the docking. The cleaned protein was saved in the pdb file format.

Molecular Docking: The ligands and the target measles protein were predicted to interact with one another to elicit a biological response. PyRx virtual screening tool was used for the molecular docking analyses. The compounds were docked into the crystal structure of the nucleoprotein, the resulting binding affinities recorded and the highest docking pose for each ligand was selected. Post docking analysis was carried out using the USCF Chimera and Discovery Studios software where further information like bonding angle, types of bonding, receptor's active site and other characteristics in the relationship were determined.

Pharmacokinetics and Toxicology (ADMET) Predictions: The online software SwissADME (http://www.swissadme.ch/index.php), admetSAR 2 (http://lmmd.ecust.edu.cn/admetsar2) and ADMETlab 2.0 (https://admetmesh.scbdd.com) were used to assess the pharmacokinetic and toxicological properties of the ligands. The canonical smiles of each ligand were obtained from the PubChem database and used to evaluate the druggability of each ligand. Parameters such as absorption, distribution, metabolism, excretion and toxicity were evaluated.

RESULTS

Molecular docking analysis: PyRx was used to dock the four ligands to the measles virus nucleoprotein core in complex with an n-terminal region of phosphoprotein to study their interactions with the protein and determine their viability as potential drug targets. Table 1 shows the binding affinities of the complexes formed between the ligands and the target protein. The binding energies of the interactions ranged from -6.4 to -8.2 kcal/mol.

Table 1:
Binding energies and interactions of the investigated compounds

Ligands	PubChem ID	Binding Affinity (kcal/mol)	Hydrogen bonds and bond length	Hydrophobic interactions
Stigmasterol	5280794	**-8.2**	SER 99, 1.914 A	LEU 83, PHE 97, MET 104, ILE 17, LYS 49, TYR 111
Chrysin	5281607	**-8.0**	TRP 127, LYS 131	ARG 38, PHE 125
Chalcone	637760	**-7.3**	ASN 42, 2.402 A	PHE 125. ARG 38
Dihydrochalcone	64802	**-6.4**	LYS 49, 1.791 A	PRO 48, 1LE 17, TYR 111

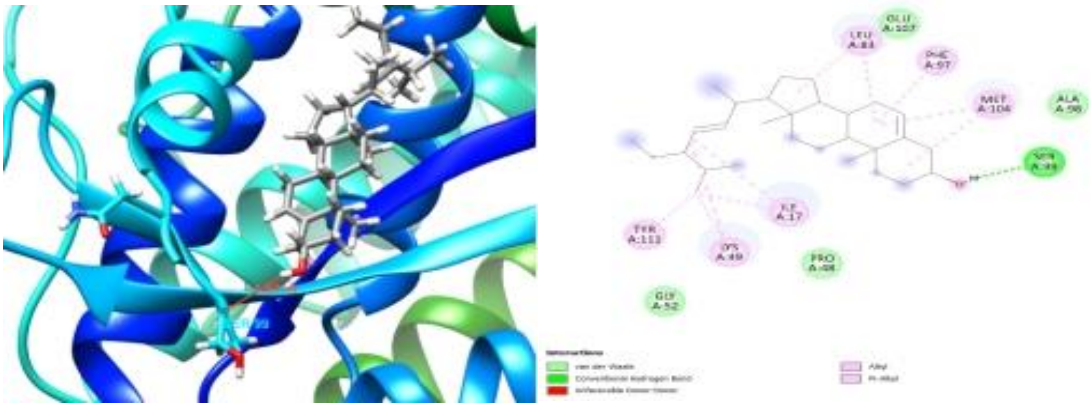

Fig 1:
Interactions between stigmasterol and the residues within the active site of the nucleoprotein in 3D and 2D

All the compounds that interacted with measles virus nucleoprotein via a hydrogen bond to the amino acid residue SER 99, however, the binding energies of stigmasterol and chrysin were significantly ($p<0.05$) higher compared to

dihydrochalcone (-6.4 kcal/mol). In addition, dihydrochalcone formed a hydrogen bond at the amino acid residue LYS 49, while stigmasterol interacted with the same amino acid residue via a pi-alkyl bond (Figure 1).

The interaction of the compound chalcone with measles virus nucleoprotein was observed to be via hydrophobic interactions and a hydrogen bond at the amino acid residue LYS 49 with a bond distance of 1.791 A (Figure 2). Analysis of the 2-D of chrysin-nucleoprotein interaction showed the presence of two hydrogen bonds between the ligands and two amino acid residues (TRP 127 and LYS 131) with hydrophobic interactions with ARG 38 and PHE 125 residues (Figure 3).

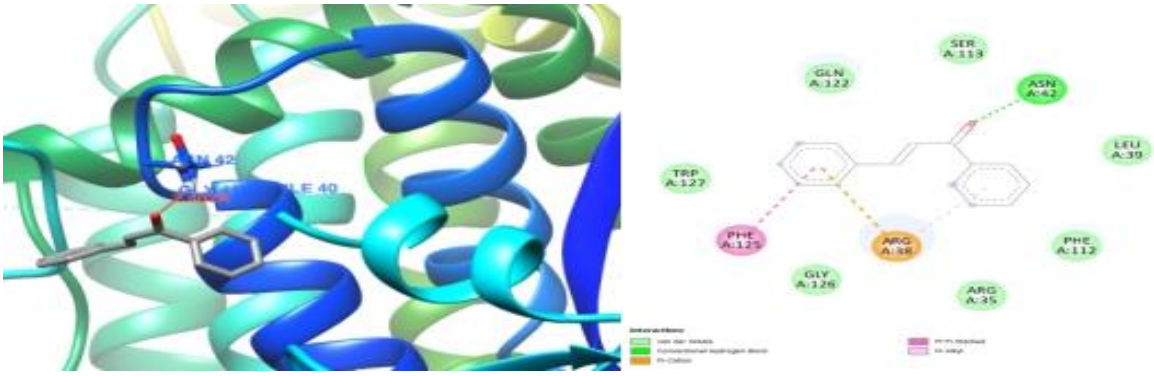

Fig 2:
Interactions between chalcone and the residues within the active site of the nucleoprotein in 3D and 2D

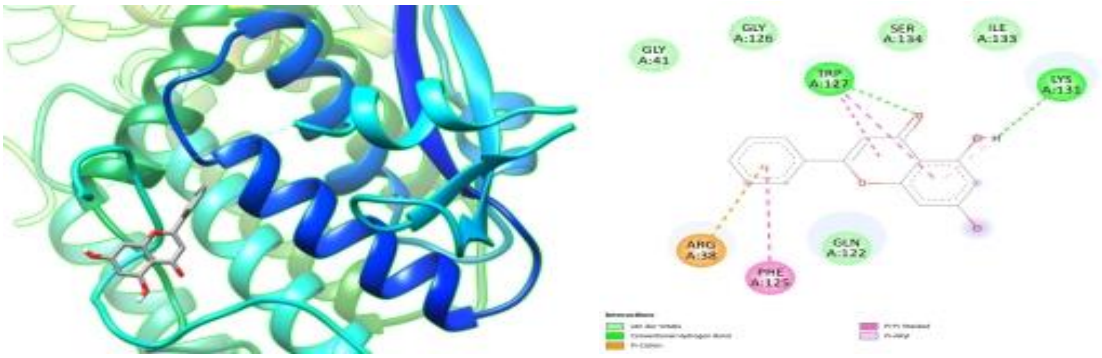

Fig 3:
Interactions between Chrysin and the residues within the active site of the nucleoprotein in 3D and 2D

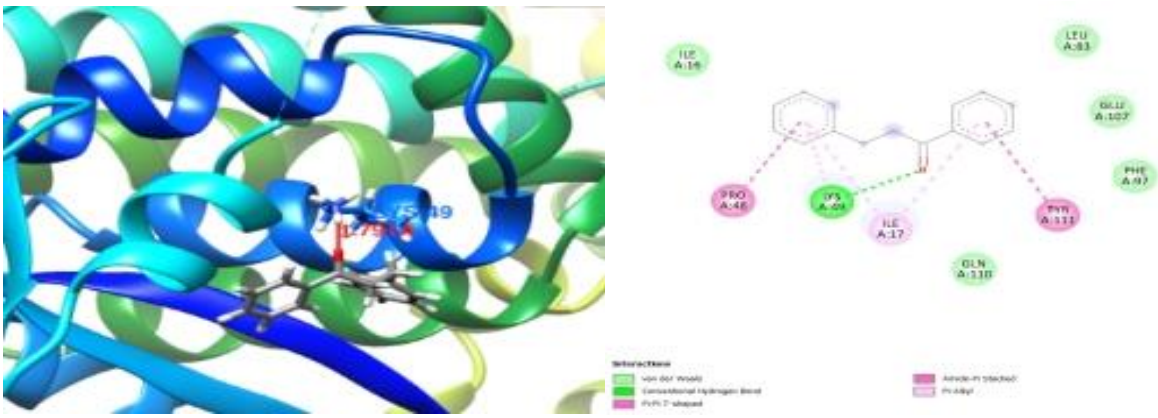

Fig 4:
Interactions between dihydrochalcone and the residues within the active site of the nucleoprotein in 3D and 2D

Pharmacokinetics (ADME) and Toxicity analysis: The ADMET - predictions for the four selected compounds of *Uvaria chamae* is presented in Table 2. Chrysin, chalcone and dihydrochalcone all passed the Rule of Five and also showed good solubility. Table 3 shows the behaviours of these ligands against some selected parameters.

DISCUSSION

Measles is a viral infection that is extremely contagious and leads to serious health complications, yet there are no known definitive antiviral treatments. It is currently managed using vaccines that help develop lifelong antibodies as well as treatment of complications that arise from those being infected by the virus (Bester, 2016). Medicinal plants are often used in traditional medicine to treat measles, and many scientific investigations have been carried out on these claims. *Uvaria chamae* is a plant whose antiviral properties have been reported (Oluremi and Adeniji, 2015).

Table 2:
ADMET properties of the ligands

Categories	Types of Parameters	Stigmasterol	Chrysin	Chalcone	Dihydrochalcone
Drug likeliness (Lipinski's rule of five)	Molecular Formula	$C_{29}H_4O_8$	$C_{15}H_{10}O_4$	$C_{15}H_{12}O$	$C_{15}H_{14}O$
	Molecular weight (g/mol)	412.693	254.244	208.26	210.27
	No. of H bond donors	1	2	0	0
	No. H bond acceptors	1	4	1	1
	iLogP	5.01	2.27	2.53	2.58
	Lead likeliness (Violation)	2	1	1	1
	Topological polar surface area (A)	20.23	70.67	17.07	17.07
	Solubility	Poorly Soluble	Moderately Soluble	Soluble	Soluble
Absorption	GI Absorption	Low	High	High	High
	$CaCO_2$ Permeability	Yes	Yes	Yes	Yes
	Human Intestinal Absorption	Yes	Yes	Yes	Yes
Distribution	BBB Permeability	Yes	No	Yes	Yes
	Plasma Protein Binding	1.044	0.948	0.774	0.857
Metabolism	CYP2D6 inhibitor	No	No	No	Yes
	CYP3A4 inhibitor	Yes	Yes	No	No
	CYP2C9 inhibitor	Yes	Yes	No	No
	CYP2C19 inhibitor	No	Yes	Yes	Yes
	CYP1A2 inhibitor	No	Yes	No	Yes
Excretion	Total Clearance (log mL/min/kg)	15.958	5.131	5.327	7.483
	Half-life (T½)	0.014	0.787	0.736	0.723
Toxicity	Human Hepatotoxicity	Yes	No	No	No
	Acute Oral Toxicity (LD_{50}) (moL/kg)	2.626	1.925	1.482	1.984

Molecular docking was carried out to predict the nature of interactions of compounds previously isolated and reported from the extracts of *U. chamae* to a target protein receptor. The protein of interest (Measles Virus nucleoprotein Core in Complex with an N-Terminal Region of Phosphoprotein), is an essential part of the RNA of the measles virus RNA polymerase and is also a necessity of the synthesis of the RNA (Guryanov *et al*., 2016). Therefore, finding compounds that interfere with this enzyme could be a potential target for inhibition of viral replication. The binding affinities of the docked compounds to this receptor is an indication of the stability of the complex formed between the ligand and protein. Out of the four compounds docked, stigmasterol had the highest binding affinity (-8.2 kJ/mol). The specificity of ligand binding is significantly influenced by hydrogen-bonds (Elekofehinti *et al*., 2018) and all the ligands interacted with the nucleoprotein via both hydrogen bonds and hydrophobic bonds. Stigmasterol formed one hydrogen bond (SER 99) with its OH group and six other hydrophobic alkyl and pi-alkyl interactions (LEU 83, PHE 97, MET 104, ILE 17, LYS 49, TYR 111). Dihydorchalcone was observed to also form a complex at this same active site, forming an hydrogen bond with its carbonyl functional group with the amino acid residue LYS 49. Chrysin and Chalcone were also observed to interact with the nucleoprotein around the same active sites, forming hydrogen bonds at residues TRP 127, LYS 131 and ASN 42 . The complexes formed were further stabilized by pi hydrophobic interactions at residues PHE 125 and ARG 38 similarly.

An evaluation and understanding of ADMET properties of potential lead compounds is crucial for discovery and development of new drugs (Chandrasekaran *et al*., 2018). The four compounds were subjected to the parameters for the Lipinski's Rule of Five, and Chrysin, Chalcone and dihydrochalcone all passed the test, while stigmasterol had one violation (iLogP > 5). Lipophilicity (LogP) is a factor that influences the absorption, permeability and total clearance of a test compound (Chandrasekaran *et al*., 2018). The result showed that stigmasterol displayed poorer ADME suggesting that the compound may not be a lead compound. Chalcone and its analogue showed better solubility and absorption properties. The ability of the compounds to penetrate the blood-brain barrier was also evaluated and stigmasterol, chalcone and dihydrochalcone showed potential.

CONCLUSION

Four compounds previously isolated from the plant were evaluated using in silico techniques against a measles virus nucleoprotein. They can be further analyzed as drug target candidates for measles virus in vitro for new drug synthesis against measles disease.

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