

In silico studies of viral protein inhibitors of Marburg virus using phytochemicals from *Andrographis paniculata*

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ABSTRACT

The Marburg virus is a causative agent of Marburg hemorrhagic fever, which was discovered in Marburg, Germany, in 1967. It is a highly contagious and fatal disease transmitted by body fluids. The reservoir host is African fruit bats. Currently, there is no vaccine available to control this disease. Medicinal plants possess many phytochemicals of great therapeutic value. Many have antiviral properties and have been identified as promising drug molecules against various viral diseases proven with an *in silico* approach. The current research uses the *in silico* approach to identify the phyto-derived drugs from *Andrographis paniculata* to treat the Marburg virus. Twenty-four bioactive molecules from the *A. paniculata* plant were investigated against the targets VP35 and VP40 of Marburg viral proteins using the AutoDock Vina 1.1.2 tool. Out of 24 compounds, Andrographidine C, Andrographidine A, Andrographolactone, and 7-O-methylwogonin showed best docking scores for the target VP40 dimer while Bisandrographolide A, Luteolin Andrographolide, and Andrographiside showed best docking scores with VP35 protein. To determine the druglikeness, pharmacokinetic and pharmacodynamic properties and toxicity for each target's highest docking score compound was assessed using the Swiss absorption, distribution, metabolism, and excretion (ADME) and pkCSM tool. Andrographidine C and Andrographolide performed well in all the parameters of ADME and toxicity. These compounds are recommended as effective inhibitors of VP35 and VP40 of Marburg virus and potential antiviral drugs to treat the hemorrhagic disease. Furthermore, *in vitro* and *in vivo* studies can be used to examine the effectiveness and mode of action against the proteins of the Marburg virus.

1. INTRODUCTION

Marburg virus is considered to be virulent pathogen that can result in infectious diseases and hemorrhagic fever in humans and nonhuman primates [1]. It is a part of the genus Marburg virus and belongs to the family Filoviridae. Its structural and functional aspects are closely linked to the Ebola virus. Both Ebola and Marburg viruses belong to the same family and are native to Africa [2]. The fatality rate ranged from 25% in the first outbreak reported in a laboratory in 1967 to more than 80% between 1998 and 2000 in the Democratic Republic of the Congo during the 2005 outbreak in Angola [3]. The genome of the virus is a negative-stranded RNA virus, filamentous, nonsegmented, and the viral replication and transcription are similar to rhabdoviruses. Globally,

Filoviruses are listed as category A priority pathogens owing to their high morbidity and mortality [4]. It contains different protein molecules, such as matrix proteins VP40 Dimer, transcriptional factor VP30, nucleocapsid VP35, glycoproteins (GPs) (G1 and G2), nucleoproteins (NPs), which are considered to be potential target molecules for the studies [5]. Nucleoprotein is the principal component of the viral ribonucleoprotein, and it directly affects the viral RNA genome replication and transcription. A single surface protein possessed by the Marburg virus is named envelope GP. It regulates the attachment and entry of virus particles into the target cells and favors immune evasion. Protein VP24 is another kind of protein in the Marburg virus. It plays a notable role in forming the nucleocapsid layer, virion assembly, and recruits into the inclusion body in the presence of NPs [6]. In Marburg virus minigenome system, VP30 upsurges the reporter gene's activity by twofold for viral replication [7,8]. The intrinsic function of the matrix protein VP40 is to mediate the budding of viral particles that are localized to the cell membrane. Thus, playing a significant role in virus

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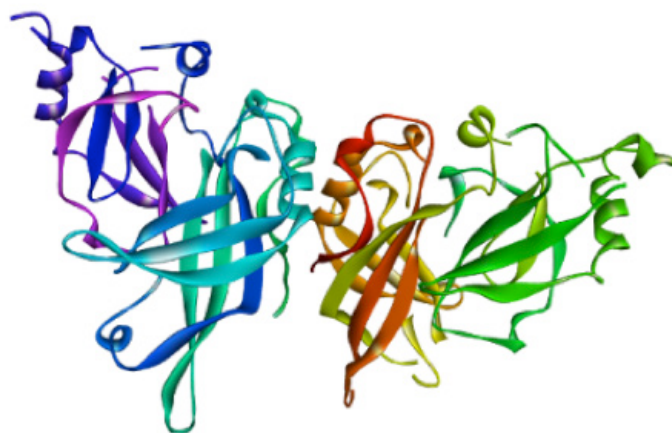


Figure 1: 3D structure of protein VP40 dimer.

progress and replication [5]. VP35 is a protein produced by both Marburg and Ebola viruses; it serves as a significant cofactor for polymerase and inhibits with RNAi pathway and contender of the innate immune response. At various stages of the signaling pathways in retinoic acid-inducible gene-I-like receptors downstream, VP35 can inhibit interferon (IFN) production to escape immune response [9]. Despite extensive research, there are no vaccines or effective drugs available to control the Marburg virus. Ribavirin is a wide-spectrum antiviral drug used against hemorrhagic fever viruses such as the Marburg virus. Ribavirin inhibits the enzyme inosine-5'-phosphate dehydrogenase involved in Guanosine-5'-triphosphate biosynthesis, thereby affecting RNA metabolisms such as viral RNA translation, capping, and replication. However, treatments with antiviral drugs are associated with major ill-effects such as hypertriglyceridemia, hepatotoxicity, diarrhea, and anemia in children [10,11]. Thus, there is a need to identify an alternative drug that is effective and safe to use. Also, the tremendous growth in population correspondingly leads to an increased shortage of medicinal products; the high demand ultimately increases the cost of medication, and not to avoid the side effects of many allopathic medicinal products and drug resistance of viral particles, have led to the ultimate focus on plants as an alternate source of medicinal products for a wide range of human conditions [12,13]. *Andrographis paniculata* is one of the popularly used medicinal plants in the world. It stands unique for its traditional and ayurvedic medicinal properties for centuries in Asia, such as Indonesia, India, Malaysia, Thailand, etc., to treat different diseases. The whole plant, including its leaves to the root, contains more than 40 various phytochemical compounds. The active phytochemicals extracted from these parts report variations in phytochemical profile attributed to various reasons such as environmental conditions, age of the plant, genetic factors, different seasons, and locations [14,15]. Several studies have shown that this plant has a wide range of pharmacological properties such as anti-protozoan, anti-microbial, antiplatelet aggregation activity, cytotoxic sex hormone modulatory, anti-inflammatory, anti-oxidant, immunostimulant, antidiabetic, and anti-infective [16–19].

Researchers primarily use bioinformatics tools and computational methods to identify and analyze the efficiency of novel drugs. Molecular docking analysis is carried out to find the energy of

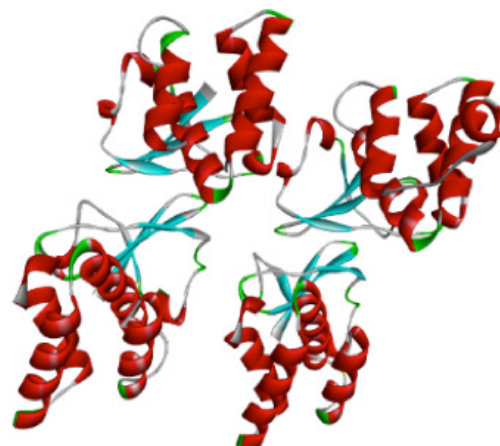


Figure 2: 3D structure of protein VP35.

interaction between the protein and its ligands. This interaction study could be highly used in pharmaceutical industries for drug designing and production [9,20]. In the present study, we carried out molecular docking studies using the AutoDock Vina tool with Discovery Studio v20.1.0.19295 to find the best fitting phytochemical against the Marburg viral proteins VP40 and VP35, for use as a potential treatment against the Marburg virus [21]. By targeting these two proteins, we can stop virus replication and prevent the inhibition of IFN production. In such a way, it could block Marburg virus entry into host cells through VP40 and VP35.

AutoDock Vina is one of the fastest and most accurate computational software employed in docking [22]. In addition, researchers have recently used the AutoDock Vina tool for *in silico* docking research on SARS-CoV-19 [23], SARS-CoV-2 [24], and cancer [25]. Joshi *et al.* [24] conducted an *in silico* docking research on COVID-19. They used 318 phytochemicals against targeting the Mpro and ACE receptor. A total of 10 compounds were identified based on their best affinity and docking score compared with the reference compounds [24]. AutoDock Vina was employed as an effective tool in identifying phytochemical compounds against the main protease (6LU7) of severe acute respiratory coronavirus [23]. Previous studies have also, Qawoogha and Shahiwala [25], identified the potential anticancerous phytochemicals targeting the receptors ERBB2, ERBB3, and VEGFR in colorectal cancer. After screening 18 phytochemicals using AutoDock Vina, they concluded that the phytochemicals yuanhuanin, theaflavin, and genistein have the highest binding affinity compared to the standard drugs [25]. After molecular docking, the evaluation of pharmacokinetics and toxicity properties was required to determine their function inside the human body. Rutwick Surya and Praveen [26] used Swiss absorption, distribution, metabolism, and excretion (ADME) tool to predict the druglikeness of phytochemicals from *Boerhavia diffusa* Linn. as a significant therapeutic agent against the SAR-CoV-2. Umadevi *et al.* [27] used the pkCSM online web tool to predict the ADME and toxicity properties of the six phytochemicals against transmembrane serine proteinase against COVID-19. In our study, we employed Swiss ADME and pkCSM

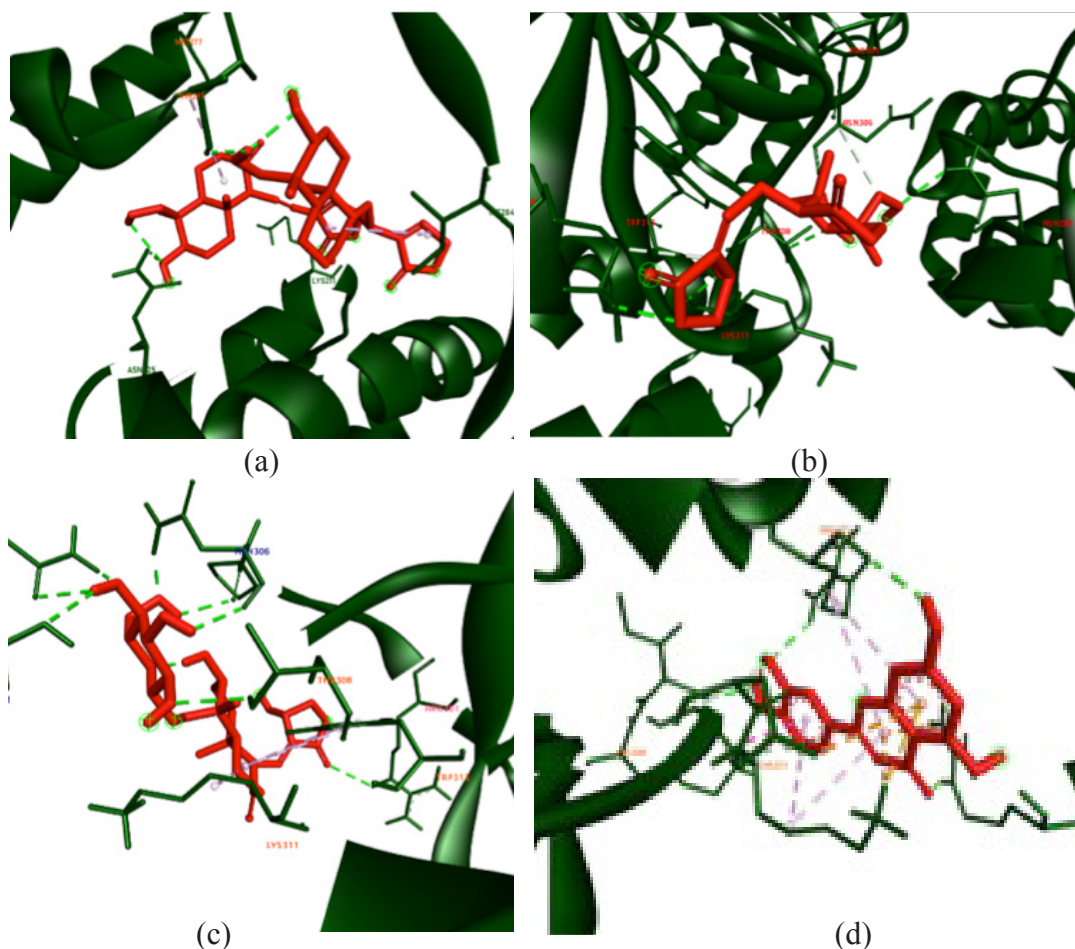


Figure 4: Molecular docking results of four best compounds against VP35 domain of Marburg virus. (a) Three-dimensional binding mode of Bisandrographolide A in the protein active site. (b) Three-dimensional binding mode of Andrographolide in the protein active site. (c) Three-dimensional binding mode of Andrographiside in the protein active site. (d) Three-dimensional binding mode of Luteolin in the protein active site.

was set at $X = 7.697250$, $Y = 40.777750$, and $Z = -19.664500$. The ligands of *A. paniculata* and ribavirin were docked with the binding sites of the two proteins VP40 and VP35. The resulting binding affinities and interactions of the reference compound were compared with those calculated docking results of the phytochemicals in the same protein binding sites using the same dimensions of the grid boxes. Docking results have been expressed in binding energy (Kcal/mol) [21,29,30].

2.4. ADME Test

Evaluation of the pharmacological and druglikeness of the phytochemical compounds was carried out by uploading the ligand file in SDF format or canonical smile format in the Swiss ADME (<http://www.swissadme.ch/>). The Swiss ADME computes physicochemical descriptors and predicts ADME parameters, druglikeness properties, lipophilicity, water solubility, pharmacokinetics properties, and examines medicinal chemistry friendliness of one or multiple small molecules to support drug discovery. The early estimation of ADME at the point of discovery significantly decreases the fraction of pharmacokinetics-related loss during the clinical stages [21,31–33].

2.5. Toxicity Prediction

The toxicity properties of the phytochemicals were predicted by using the web tool called pkCSM. It is one of the *in silico* software which predicts the toxicity caused by molecules to humans [32,34,35]. By using the pkCSM web tool, hepatotoxicity, AMES toxicity, hERG I inhibitor, max. tolerated dose, skin Sensitization, minnow toxicity, oral rat chronic toxicity [lowest-observed-adverse-effect level (LOAEL)], oral rat acute toxicity (LD50), and *Tetrahymena pyriformis* toxicity can be examined [34,35].

2.6. Visualization

The analysis of 3D and 2D hydrogen-bond interactions of the complex receptor–ligand structure was carried out by Discovery Studio v20.1.0.19295 to identify the interactions of an amino acid of a receptor with the ligand [21].

3. RESULTS

3.1. Molecular Docking Analysis

The targets VP40 and VP35 of the Marburg virus were docked with the phytochemical compounds of *A. paniculata* by using AutoDock Vina 1.1.2. The molecular docking results of the

Table 1: Result of Molecular docking of the top four phytochemicals and the targets.

Protein name	PDB ID	Ligand name	Pubchem CID	Interacting amino acid residues	Grid Parameter (center x, y, z)	Covalent H-bond	Binding energy (Kcal/mol)
VP40 Dimer	5B0V	Andrographidine C	5318484	PRO 278, ASN 280, PRO282, ASN148	17.315000, 41.930667, 13.598667	5	-9.4
VP40 Dimer	5B0V	Andrographidine A	13963762	ALA82, VAL150, ILE 151, ASN148, PHE145, PRO 278, TRP 83	17.315000, 41.930667, 13.598667	7	-9.4
VP40 Dimer	5B0V	7-O-Methylwogonin	188316	ASN280, VAL150, PRO278, ILE146	17.315000, 41.930667, 13.598667	4	-8.4
VP40 Dimer	5B0V	Andrographolactone	44206466	PRO282, HIS198, PRO278, ASN200, ILE146	17.315000, 41.930667, 13.598667	2	-8.8
VP40 Dimer	5B0V	Ribavirin (Reference compound)	37542	ASN 200, VAL150, TRP 83, ASN 148	17.315000, 41.930667, 13.598667	5	-6.6
VP35	4GHL	Bisandrographolide A	12000062	PRO305, THR308, ASN306, TRP313, LYS311, LYS328, ASN288	7.697250, 40.777750, -19.664500	3	-8.6
VP35	4GHL	Andrographiside	4128470	PRO305, THR291, ASN306, ASN288, THR308, TRP313, LYS311, ARG301	7.697250, 40.777750, -19.664500	9	-7.5
VP35	4GHL	Andrographolide	5318517	LYS311, ASN288, ASN306, LYS328	7.697250, 40.777750, -19.664500	7	-7.5
VP35	4GHL	Luteolin	5280445	ASP310, ARG271, LYS311, GLY312, LYS328, ILE329, ARG294	7.697250, 40.777750, -19.664500	6	-7.7
VP35	4GHL	Ribavirin (Reference compound)	37542	ASN 306, THR 308, ASP 310, THR 291	7.697250, 40.777750, -19.664500	8	-6.1

Table 2: Toxicity properties of the top four compounds for the targets VP40 Dimer and VP35.

Property	Andro-graphidine A	Andro-graphidine C	7-O-methyl-wogonin	Andrographo-lactone	Bisandrogra-pholide A	Andro-graphiside	Andro-grapholide	Luteolin	Ribavirin
AMES Toxicity	Yes	No	No	No	No	No	No	No	No
Max. tolerated dose Log(mg/kg/day)	0.439	0.573	0.058	0.16	-0.626	-0.82	-0.64	0.564	0.508
hERG I inhibitor	No	No	No	No	No	No	No	No	No
hERG II inhibitor	Yes	Yes	No	No	No	Yes	No	No	No
Oral Rate									
Acute toxicity (LD50) (mg/kg_bw/day)	2.918	2.779	2.51	1.817	4.482	2.904	2.589	2.453	1.481
Oral Rat									
Chronic Toxicity (LOAEL) (mg/kg_bw/day)	3.386	3.523	1.376	1.998	1.993	2.57	0.599	1.537	2.559
Hepatotoxicity	No	No	No	No	Yes	No	No	No	No
Skin sensitization	No	No	No	Yes	No	No	No	No	No
<i>T. Pyriformis</i> toxicity Log (µg/l)	0.285	0.285	0.419	2.645	0.285	0.285	0.553	0.428	0.285
Minnow toxicity	1.517	0.43	-0.347	-0.693	0.457	2.098	1.036	1.346	3.726

top four phytochemicals for each target showing significantly higher negative binding energy as shown in Table 1. The binding energy of phytochemicals with target VP40 was -9.4 kcal/mol for Andrographidine C, -9.4 kcal/mol for Andrographidine A, -8.8 kcal/mol for Andrographolactone, -8.4 kcal/mol for 7-O-methylwogonin, and -6.6 kcal/mol for Ribavirin (reference compound). The remaining ligands showed a docking score of less than -8.5 kcal/mol for VP40 protein. The binding energy of phytochemicals with target VP35 was -8.6 kcal/mol for Bisandrographolide, -7.7 kcal/mol for Luteolin A, -7.5 kcal/mol for Andrographolide, 7.5 kcal/mol for Andrographiside, and -6.1 kcal/mol for Ribavirin (reference compound). The rest of the phytochemicals had docking scores less than -7.5 kcal/mol. The Ribavirin (Reference compound) reported lower binding score than the top four phytochemical molecules of *A. paniculata*. Thus, the lower binding energy or highest negative energy of screened compounds shows a higher affinity for VP40 and VP35 proteins. Table 1 illustrates the molecular docking of the targets VP40 and VP35 of the Marburg virus with the top four phytochemicals of *A. paniculata*.

3.2. ADME and Toxicity Analysis

After molecular docking, the phytochemicals with the highest binding score, interactions, and binding affinity were taken to evaluate the ADME properties using the online tool Swiss ADME. The compound Andrographidine C, which has higher negative energy and binding affinity, was evaluated for ADME properties. The physicochemical properties of the compound Andrographidine C were found to have a molecular weight of 460.43 g/mol, 10 H-bond acceptors, 4 H-bond donors, and a topological polar surface area (TPSA) of 148.05 Å². The lipophilicity of the molecule is as follows: iLOGP is 2.7, XLOGP3 is 0.96, WLOGP is 0.66, MLGOP is -1.18 , and SILICO-IT Log P is 1.44. The water-solubility property calculated was Log S/ESOL -3.62 , which belongs to a soluble class of molecules. Pharmacokinetics was found to have low levels of gastrointestinal absorption and no blood–brain barrier permeability. So, using this as an oral drug is not applicable, but on the other hand, it can be delivered by injection. Druglikeness of this phytochemical obeyed the Lipinski's rule with 0 violations and other rules of Ghose, Veber, Egan, and Muegge, which also showed a good druglikeness score. The medicinal chemistry was found to have no lead likeness and zero alerts for PAINS and Brenk; the synthetic accessibility was 5.48. So, Andrographidine C was predicted as a good drug with good pharmacokinetic properties for the target VP40 dimer. For Bisandrographolide A (-8.6 kcal/mol), the compound's physicochemical properties are the molecular weight of 664.87 g/mol, eight H-bond acceptors, four H-bond donors, and a TPSA of 133.52 Å². The lipophilicity of the molecule is as follows: iLOGP is 5.39, XLOGP3 is 6.08, WLOGP is 5.37, and MLGOP is 3.92. The water-solubility property was calculated as Log S/ESOL of -7.26 , thus belonging to a poorly soluble class of molecules. Pharmacokinetics was found to pose a low level of gastrointestinal absorption and showed no blood–brain barrier permeant. On the contrary, the druglikeness properties of this compound obeyed the Lipinski's rule with one violation, Ghose with three violations, Egan with one violation, and Muegge with

two violations. The medicinal chemistry was not a lead likeness with three violations and zero alerts for PAINS and two alerts for Brenk; the synthetic accessibility was 8.00. Bisandrographolide A did not follow several ADME parameters. Therefore, it may have the chance to cause several drawbacks during human consumption. So, Andrographolide was taken into evaluation. It showed better ADME properties profile than Bisandrographolide A. The ADME properties of the phytochemical compounds are shown in Table 3.

Toxicity properties of the compounds were predicted by a pkCSM online tool. The toxicity test analysis of the best four phytochemical compounds against VP40 Dimer and VP35 are shown in Table 2. In toxicity analysis, Andrographidine C showed a better drug profile for the target VP40. Among the chosen phytochemical compounds for VP35, Bisandrographolide A was predicted to show hepatotoxicity, while Andrographolide was negative for toxicity analysis and it was found to be a safe drug. So, it can be supplied as a medication with a tolerance value suitable for human consumption.

4. DISCUSSION

Molecular docking is a computational process that aims to accurately predict the interaction between macromolecules (receptors and proteins) and small molecules (ligands) and to calculate their binding energy. It is proven to be an extremely effective approach to screen a wide range of compounds and discover novel drugs against target proteins. Because of its applicability in the pharmaceutical sector, protein–ligand docking is of particular interest among the several forms of docking [36–38]. In this study, we used open-source tools for molecular docking simulations—AutoDock tools 1.5.6 and AutoDock Vina 1.1.2. This software is a highly accurate program, user-friendly, and easy to access (The Scripps Research Institute) [30,38,39]. The superiority of this software was tested by Tanchuk *et al.* [39], wherein they could evaluate the test size of 313 complexes. In our study, the proteins selected as drug targets are crucial in causing viral infections in the host, such as VP35 and VP40 of the Marburg virus. All phytochemicals are known to have one or more medicinal properties, which were all selected as ligands. The docking aims to find a ligand that binds to a given receptor binding site and to identify its preferred, most potentially beneficial binding poses [40]. The docking score and hydrogen bonds formed with the amino acids from the group interaction atoms are used to predict the binding modes, the binding affinity, and the orientation of the docked ligands in the active site of the protein receptor. In docking, the hydrogen bonding between ligand and receptor enhances interaction specificity and contributes to molecular recognition and overall interaction strength. Depending on the strength of the interaction, all of the ligand molecules formed significant amounts of hydrogen bonds within the interaction site of the receptor proteins [29]. Furthermore, the quality of the docking is determined by the contribution of intermolecular hydrogen bonds in a ligand–protein complex and the scoring function.

After carrying out docking studies, we shortlisted compounds Andrographidine C and Bisandrographolide A, which have higher binding scores and hydrogen bond interaction with the viral target proteins, and we suggested them as natural and effective drugs to inhibit the Marburg virus, which interfere in

virus progress, replication, and transcription of the viral life cycle. Current studies use a web tool called Swiss ADME (<http://www.swissadme.ch/>) for ADME prediction. The ADME test assesses lipophilicity, solubility, and pharmacological and pharmacokinetic properties of a candidate drug molecule inside the biological system. It is a crucial determinant for the success in drug discovery approach [31,32]. In this study, the ADME results were obtained by uploading the small molecules of Andrographidine C, Bisandrographolide, and the rest of the phytochemicals in SDF format. ADME prediction confirmed that compound Andrographidine C possessed good ADME properties for the target VP40, while Bisandrographolide A for the target VP35 had reported certain drawbacks; it had poor water solubility and did not obey the druglikeness score rules. These poor pharmacokinetic properties of the drug make it less effective for *in vivo* application, and there would be a risk of side effects. Due to this, it was considered an inefficient drug for the target VP35 and hence we evaluated the other top compounds for the target. Among the top four compounds, Andrographolide showed good druglikeness properties, pharmacokinetic properties, and solubility. It obeyed all the rules with 0 violations and provided higher GI absorption. Due to the several disadvantages of Bisandrographolide A, Andrographolide was predicted as a promising drug compared to Bisandrographolide A compound for the target VP35 based on the ADME properties.

In recent studies, Andrographolide from *A. paniculata* was used in *in silico* molecular docking studies to inhibit the Ebola virus. The compound Andrographolide was docked with the targets VP40, VP35, and VP24 protein receptors using the AutoDock tool. They found that Andrographolide had a higher binding affinity and exhibited better interactions with the target VP24 of Ebola virus protein [41]. In another study, Enmozhi *et al.* [32] used the same phytochemical Andrographolide extracted from the plant *A. paniculata* for docking against the main target protease of SARS-CoV-2 (Mpro). They predicted the ADME properties of the compound by using the same tool (Swiss ADME). It had shown good solubility, druglikeness, pharmacodynamics properties, and the compound obeyed Lipinski's rule against SARS-CoV-2 viral target and it was proved to be an effective drug. Hiremath *et al.* [33] used 14 phytochemicals from *A. paniculata* and 18 phytochemicals from *Phyllanthus amarus* to inhibit the SARS-CoV-2 proteins (S protein, 3CLpro, PLpro, and RdRp) through *in silico* docking analysis. They used the AutoDock Vina tool for molecular docking and the Swiss ADME tool predicted the ADME property of the compounds. They reported that the phytochemicals present in the medicinal plant extracts of *A. paniculata* and *P. amarus* have a synergistic effect on multiple target sites of SARS-CoV-2 [33]. From these recent studies, we strongly suggest that the phytochemical of *A. paniculata*, especially the compound Andrographolide predicted by the Swiss ADME tool, proved to be an efficient drug compound with good ADME properties.

Toxicity test is a significant study to identify the effects and risks of these compounds on the human body [35]. Drug failure at the clinical trial level due to their toxic effects tends to be very costly, posing life-threatening risks that are dangerous in the phase

of drug production and application. Along with other ADME/Tox instruments, *in silico* druglikeness prediction offers various possibilities that help identify new targets and eventually contribute to substances with expected biological activity and increase preclinical safety testing in the pharmaceutical industry [42,43]. In toxicity analysis, the AMES test is used to predict whether a compound is mutagenic or not. The mutagenic compound may also act as carcinogenic. The hERG inhibitor blocks the potassium channel and triggers prolonged QT syndrome, which leads to ventricular arrhythmia. The hepatotoxicity test also identifies liver-related side effects [42]. Andrographidine C appeared to have no side effects and is negative for all tests except hERG II inhibitor test. This study revealed that Andrographidine C showed a good drug profile for the target VP40. Both Bisandrographolide A and Andrographolide showed good drug profiles for the target VP35 with no adverse effects. But Bisandrographolide A was likely to be associated with an impairment in the liver function. We concluded that the toxicity test results of Andrographidine C and Andrographolide have a good drug profile for the targets VP40 and VP35 of the Marburg viral protein. Also, in a recent study by Enmozhi *et al.* [32], pkCSM online web tool was used to predict the toxicity of the compound Andrographolide, which was extracted from the plant *Andrographis paniculata*. They found that it was a proven to be an effective drug for SARS-CoV-2 viral target [32]. Studies have reported that compound Andrographolide from *Andrographis paniculata* was used to inhibit the various targets (NS3 helicase, NS5, and NS3 protease) of the Japanese encephalitis virus. The ADMET analysis was carried out by using the pkCSM online web tool and the compound was shown to have a good pharmacokinetic and safety profile of Andrographolide. In addition, an *in-vitro* study also confirmed that Andrographolide has inhibitory potential against the NS3 protease of the Japanese encephalitis virus [34]. In these studies, the compound Andrographolide from *Andrographis paniculata* was predicted by the pkCSM tool and showed a negative result for toxicity analysis and was proven to be an efficient antiviral drug for human consumption. Vincent *et al.* [34] used 145 phytochemical compounds from kabasura kudineer (KK) against the target COVID-19. Based on the molecular docking result, the compounds Andrographidine C, Acetoside, Luteolin 7-rutinoside, rutin, Chebulagic acid, Syrigaresinol, Acanthoside, Violanthin, myricetin, Gingerenone-A, Tinosporinone, Geraniol, Nootkatone, Asarianin, and Gamma sitosterol were found to be a potential molecule to inhibit COVID-19 compared to synthetic drugs. Based on the results obtained from the current study with phytochemicals of *A. paniculata*, Andrographolide and Andrographidine C are potential inhibitors of the targets VP35 and VP 40 and are also found to be potent antiviral agents.

5. CONCLUSION

Twenty-four phytochemicals from *Andrographis paniculata* were used in this experiment to explore the potential drug for the treatment of the Marburg virus. Andrographidine C was found to be the best inhibitor for the target protein VP40 and Andrographolide was found to be the best inhibitor for the target protein VP35, considering the docking score, pharmacokinetic and pharmacodynamic properties compared to Ribavirin (reference

Molecule	Physiochemical Properties			Lipophilicity					Water Solubility		Pharmacokinetics			Druglikeness		Medicinal chemistry		
	Molecular Weight(g/mol)	Hydrogen bond acceptor	TPSA A ²	Log P _{ow} (LOGP)	Log P _{ow} (MLOGP)	Log P _{ow} (SILICO-IT)	Log P _{ow} (iLOGP)	Log P _{ow} (XLOGP3)	Log S (ESOL)	ESOL Class	Pharmacokinetics GI absorption	BBB permeant	Pgp substrate	Bioavailability Score	Lipinski# violations	Lead likeness	PAINS	Brenk
Andrographidine C	460.43	6	148.05	0.66	-1.18	1.44	2.70	0.96	-3.26	Soluble	Low	No	Yes	0.55	0	1	0	0
Andrographidine A	463.45	6	144.14	0.26	-0.99	0.97	2.50	0.69	-3.01	Soluble	Low	No	Yes	0.55	0	1	0	0
Andrographolactone	296.4	2	26.30	4.35	4.28	5.87	3.46	4.72	-4.66	Moderately soluble	High	Yes	No	0.55	1	1	0	0
7-O-methylwogonin	298.9	5	68.90	3.18	1.01	3.55	2.99	3.32	-4.12	Moderately soluble	High	Yes	No	0.55	0	0	0	0
Bisandro-	664.8	8	133.52	5.37	3.92	6.49	5.39	6.08	-7.26	Poorly soluble	Low	No	Yes	0.55	1	3	0	2
Andrographolide	350.45	5	86.99	1.96	1.98	2.94	2.62	2.16	-3.18	Soluble	High	No	Yes	0.55	0	1	0	2
Luteolin	286.24	6	111.13	2.28	-0.03	2.03	1.86	2.53	-3.71	Soluble	High	No	No	0.55	0	0	1	1
Andrographiside	512.59	10	166.14	-0.21	-0.29	0.9	2.12	0.02	-2.63	Soluble	Low	No	No	0.17	2	1	0	2
Ribavirin	244.20	7	143.72	-3.34	-2.53	-2.90	0.35	-1.85	-0.21	Highly soluble	Low	No	No	0.55	0	0	0	0

compound). Recently, in August 2021, the WHO identified a case of Marburg disease in the West African nation of Guinea. This emphasizes the need to use phytochemicals as potential antiviral candidates to treat the Marburg virus. These novel molecules could be utilized for further *in vitro* and *in vivo* studies to validate the drug's potential against the Marburg virus.

6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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8. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

10. DATA AVAILABILITY

All data generated and analyzed are included within this research article.

11. PUBLISHER'S NOTE

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