STM JOURNALS

International Journal of
Bioinformatics and
Computational Biology

Volume 1, Issue 2, 2023
DOI (Journal): 10.37628/IJBCB
July–December

https://journals.stmjournals.com/ijbcb/

Research IJBCB

Uncovering the Comparative Efficacy of Antiviral Drugs and *Caricapapaya* Phytocompound as VP2H inhibitors in Ebola virus: An Insilico Molecular Docking Analysis

Sakina Fatima*

Abstract

The Ebola virus is a fatal disease that transmits from wild animals to humans. Infected individuals' body fluids such as spit, blood, perspiration, faeces, blood, saliva, breast milk, sperm, or fomites can transmit Ebola. Adhesion to cell membranes and penetration into the host organism are essential aspects in viral growth. The presence of VP24, as well as nucleoproteins and structural proteins, is necessary for nucleocapsid formation and integration. The inhibition of VP24 activity reduces viral spread. As a consequence, in the current investigation, 25 phytocompounds from Carica papaya and 5 anti-viral FDA authorised oral medicines were assessed for their potential as anti-Ebola virus therapy alternatives. The goal of our research was to use Carica papaya phytocompounds (CPP) to target the VP24 protein of the Ebola virus. VP24 is important in the pathogenesis of the Ebola virus because it suppresses the host immune response, allowing the virus to elude detection and multiply rapidly. Phytocompounds were revealed to have much better binding affinity against the VP24 protein in the current study than the five other FDA-approved antiviral medicines.

Keywords: Molecular docking, Ebola virus disease, ADMET analysis, Phytocompounds, FDA approved drugs, VP24 protein, Carica papaya, Nitazoxanide, Oseltamivir, Sofosbuvir, Acyclovir, Tenofovir.

INTRODUCTION

Ebola, formerly known as Ebola hemorrhagic fever, is a rare and fatal disease caused by infection with an Ebola virus strain. Ebola can infect people as well as nonhuman primates (monkeys, gorillas, and chimps). Infection with a virus of the family Filoviridae, genus Ebolavirus, causes Ebola. In 1976, near the Ebola River in what is now the Democratic Republic of the Congo, Ebola was found [1]. In Africa, outbreaks have occurred infrequently since then. The Ebola virus's natural reservoir host is yet unknown. Researchers believe that the virus is animal-borne and that bats are the most likely reservoir based on data and the nature of comparable viruses. Four of the five viral strains have been identified in an African animal host [2]. Because Ebola is caused by a virus rather than bacteria, researchers have had a more difficult time creating medicines for viral infections than for bacterial ones. Because the virus is so harmful in certain outbreaks, the fatality rate has been as high as 90%.

Seven years after the last Ebola outbreak in Guinea, the virus has resurfaced, with 23 cases and 12 deaths in a new outbreak. They were caused not by a virus spread from animals to humans, but by

***Author for Correspondence**
Sakina Fatima
E-mail: sakinafathima128@gmail.com

Student, Department of Zoology, Christ-deemed to be university, Hosur Main Road, Bengaluru, Karnataka, India

Received Date: May 12, 2023
Accepted Date: July 25, 2023
Published Date: August 05, 2023

Citation: Sakina Fatima. Uncovering the Comparative Efficacy of Antiviral Drugs and *Caricapapaya* Phytocompound as VP2H inhibitors in Ebola virus: An Insilico Molecular Docking Analysis. International Journal of Bioinformatics and Computational Biology. 2023; 1(2): 62–78p.

latent Ebola within surviving patients. The Ministry of Health confirmed an Ebola (Sudan virus) epidemic in Mubende District, western Uganda, on September 20, 2022. This is Uganda's sixth Ebola outbreak. Five of the six cases were caused by the Sudan ebolavirus. On January 11 2023, the outbreak was declared over, with 142 confirmed cases (and 22 probable) and 55 confirmed deaths [3]. There are no FDA-approved medicinal products to prevent or treat this fatal and widespread disease. In a randomised, controlled trial of 72 patients, ZMapp, a mixture of three monoclonal antibodies, failed to satisfy the statistical threshold for efficacy [4]. Following the recent catastrophic outbreak that created global alarm, another outbreak is expected to loom on the horizon given the trend of outbreaks during the last 40 years, and it may be even more lethal as globalisation increases. As a result, it is crucial to our preparation that research and development of effective anti-Ebola medications continue [5]. An epidemic happens when the number of cases of a specific disease increases faster than predicted in a specific region over a specified time period. In many regions of the world, the number of instances of highly transmissible or dangerous infectious diseases such as Zika, Ebola, monkeypox, SARS, etc has grown over the previous three decades. This tendency is predicted to continue, with zoonotic spillover occurrences occurring as a result of city population growth or congestion, unsanitary conditions, pollution, and migration to unoccupied areas, as well as the influence of global warming on vector distribution [6]. The existence of these factors reduces an individual's ability to resist various diseases. In recent years, the global need for pharmaceutical medicines (vaccine) to treat various diseases has increased. However, due to a lack of infrastructure, several countries are unable to make these vaccinations or must purchase them at a higher cost. In these nations, edible vaccines may be a superior option for disease control because they are less expensive and last longer. This emergency circumstance of an Ebola virus outbreak has both warned and pushed researchers to find a vaccine against the highly contagious Ebola virus sickness. Traditional vaccine production methods, on the other hand, have numerous flaws. As a result, a plant-based vaccine strategy combined with viral vectors and the Agro-infection technology is safe, adaptable, and yields a larger production of recombinant protein for vaccination programmes. Another significant development in plant biotechnology is the recent experimental model of tobacco plant generated ZMapp antibody cocktails. This latest round of ZMapp antibody cocktail experiments offers yet another light of hope for the humanization of the vaccination platform [7]. However, there are several regulatory issues that must be addressed before the vaccine may be commercialised.

Carica papaya Linn is a commercially produced tropical plant and one of the most economically important genera in the Caricaceae family. The entire papaya plant has medicinal characteristics and has long been used to treat a range of ailments across the world. Papaya is used in Ayurvedic and traditional medicine to cure a range of diseases, including digestive difficulties, diarrhoea, cutaneous infections, as a contraceptive, and to heal colds. Numerous research have confirmed papaya's anti-cancer effectiveness in colon, prostate, cervix, and mammary gland cancers. Lysates of papaya fruit, seed, and leaf have also been shown to have a significant cytotoxic impact on cancer cells such as breast, hepatic, and haematological cell lines [8–10].

MATERIALS AND METHODS

Retrieval of Ligands

The secondary metabolites of Carica papaya were obtained from the IMPPAT [43] (Indian Medicinal Plants, Phytochemistry, and Therapeutics) database. After learning about their medicinal or anti-viral characteristics, twenty-five phytochemical substances were short-listed and retrieved. For further research, the canonical SMILES [45] (Simplified Molecular Input Line Entry System) and 2D SDF (Standard Data Files) were extracted from the PubChem [44] database.

Protein Retrieval and Modelling

The three-dimensional crystalline structure of VP24 (Ebola viral protein 24) was retrieved in the.pdb format from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). The homology modeling of viral protein 24 (vp24) was conducted utilizing the Swiss Model platform

[46], wherein the crystal structure 4m0q.1.A was employed as the template. the primary sequence of vp24 was first obtained, which was then subjected to a thorough sequence alignment process with the template protein. Following this, numerous structural templates were generated and the best model was selected based on the global quality and sequence identity.

Protein Preparation

The protein was purified before docking through the elimination of the heteroatoms, ligand group, and water molecules from the crystal structure of the proteins and preserving only the A chains, and polar hydrogens were added to the purified structures in the BIOVIA Discovery Studio programme [48]. The protein VP24's purified structure was stored as a.pdb file.

Protein Structure Validation

Understanding the 3-dimensional structures is critical for molecular docking because they affect how the ligands interact with the proteins. Thus, the purified structure of VP24 was validated using web servers such as PDBsum generate, and DS Biovia Discovery Studio, and the results and figures were recorded.

Molecular Docking

Computational tools such as Molecular docking simulation can be used to examine the interaction between a tiny molecule and its protein targets. The virtual screening software PyRx [49] was used in this investigation to investigate molecular docking of Carica papaya phytocompounds with VP24. Because of the existence of torsions in them, the protein is supposed to be stiff while the ligand is assumed to be flexible during docking. The pure protein structures were allocated as macromolecules during docking using PyRx's AutoDock Vina plugin [11]. Using OpenBabel chemical file conversion tools, the ligands' 2D SDF files were treated to energy reduction by using universal force filed (uff). The docking parameters were established by setting the GPF (Grid Parameter Files) files after the generated proteins and ligand files were stored in.pdbqt format. The docking parameters were specified using the GPF (Grid Parameter Files) files and the.pdbqt format. Table 1 lists the GPF parameters for the protein [12]. The entire docking results were downloaded as csv (comma separated values). The data is collated and examined. The conformations with the highest biding energy were recorded in pdb format and investigated further with DS Biovia Discovery Studio. The 3D and 2D interactions between the ligands and the proteins were examined while visualising the proteins in DS Biovia Discovery Studio [13].

GPF parameters for VP24: X= 45.4318, Y= 58.1240, Z= 63.1222.

ADMET analysis of CPP

Phytocompounds have become increasingly popular in the field of drug discovery, owing to their vast structural diversity and potential therapeutic benefits. However, before phytocompounds can be developed into clinically viable drugs, it is crucial to evaluate their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. To this end, ADMET analysis plays a crucial role in predicting the pharmacokinetics and toxicity of potential drug candidates. In the present study, we selected the best CPP based on their docking score for further ADMET analysis using ADMETlab2.0 [47]. The ADMET properties of the selected phytocompounds were evaluated based on various pharmacokinetic parameters, including blood-brain barrier permeability, plasma protein binding, and half-life, as well as toxicological parameters such as mutagenicity and carcinogenicity [14]. The ADMETlab2.0 platform was utilized to carry out this analysis, which employs a comprehensive range of machine learning and data mining algorithms to predict ADMET properties accurately. Overall, the rigorous ADMET analysis performed in this study is expected to provide valuable insights into the pharmacokinetics and safety profiles of the selected CPP and may lead to the development of novel and efficacious drugs [15].

RESULTS

Homology Modelling of VP24

The VP24 has 99.56% sequence similarity, indicating that the sequence's quality score is outstanding. The GMQE shows an overall quality measurement of 0.77. A score close to one suggests that the model is of higher quality. The QMEAN Dis Co Global value is 0.82. It had a mol probability value of 1.57 as well. The Ramachandran plot was used to examine the simulated structures further. VP24 included 93.84% of the proteins found in the Ramachandran preferred area.

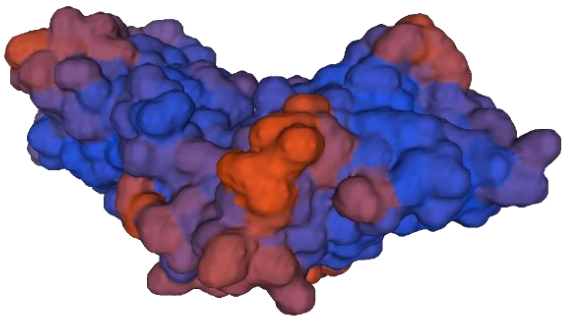

Figure 1. 3D Image of the protein model.

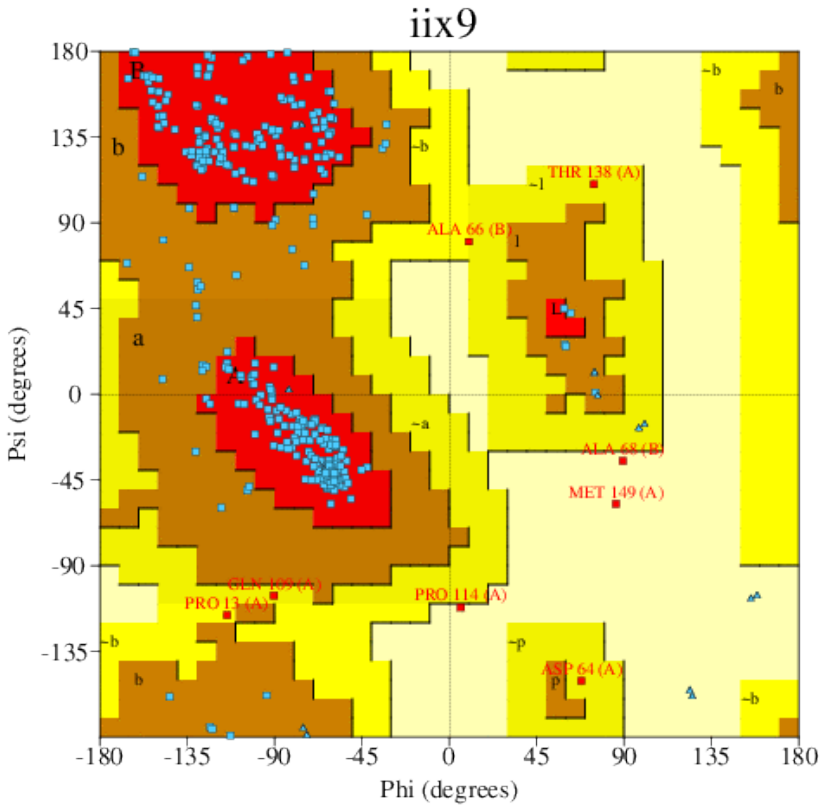

Figure 2. Ramachandran plot.

Retrieval of Ligands

Carica papaya is a medicinal plant that has been used for decades in Ayurveda therapies for its anti-inflammatory and anti-microbial effects due to the plant's main metabolites, which have been shown to have many therapeutic qualities [31, 32]. Current research indicates that the bioactive compounds in Carica papaya have anti-inflammatory, anti-oxidant, and anti-bacterial properties, implying that they might be effective in the treatment of illnesses such as Malaria, Dengue, and Ebola. Bioactive chemicals have also been found to have beneficial effects on the immune system, which may improve overall health and wellness [33–35]. The top 8 Carica papaya ligands were extracted from the IMPPAT database, and the structure of the ligands that showed improved interaction with VP24 is displayed in Figure 3.

Table 1. FDA approved drugs selected for the analysis.

Drug Name	Disease	Mechanism of Action	Side Effects
Nitazoxanide	Ebola	Inhibits viral replication by interfering with pyruvate:ferredoxin oxidoreductase enzyme-dependent electron transfer reaction, which is essential for anaerobic energy metabolism in anaerobic organisms including viruses [17].	Common side effects include headache, abdominal pain, nausea, vomiting, and diarrhea [16]
Oseltamivir	Influenza	Inhibits the neuraminidase enzyme of the influenza virus, preventing the release of viral particles from infected cells and reducing the spread of the virus [18]	Common side effects include nausea, vomiting, diarrhea, abdominal pain, and headache [19, 20].
Sofosbuvir	Hepatitis	Inhibits the RNA polymerase enzyme of the hepatitis C virus, preventing the replication of the virus [21].	Common side effects include fatigue, headache, nausea, and insomnia [22].
Acyclovir	Herpes simplex virus	Inhibits viral DNA polymerase, preventing the replication of the virus [26]	Common side effects include nausea, vomiting, diarrhea, headache, and dizziness [27].
Tenofovir	HIV	Inhibits the reverse transcriptase enzyme of the human immunodeficiency virus (HIV), preventing the replication of the virus [28–30].	Common side effects include nausea, vomiting, diarrhea, headache, and fatigue [23, 25].

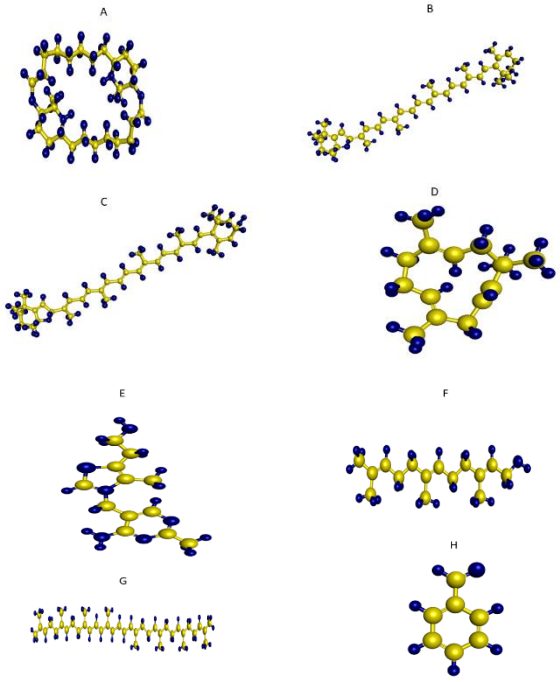

Figure 3. Structure of ligands. A. Carpaine, B. Citroxanthin, C. Cryptoflavin, D. Humulene, E. Thiamine, F. Farnesol, G. Phytofluene, H. Benzaldehyde.

Molecular Docking and Visualization

In this docking research, 25 ligands were docked to the VP24 protein using PyRx software. Upon the completion of docking, the conformation with the lowest binding affinity and root mean square deviation (RMSD) was chosen as the optimum docking posture for the compounds.

The binding affinity, RMSD/ub, and r/lb of our ligands were measured after docking with the targeted protein. The top eight ligands with the lowest binding affinity to the protein were chosen from the 25 ligands evaluated, as shown in the table below.

Table 2. Binding affinity of CPP derivatives towards the target protein VP24.

	Binding affinity	Major Interactions	Bond distance
PHYTOCOMPOUNDS			
Carpaine	-8.5	HIS 78 GLY 174	3.54 3.4
Citroxanthin	-8.4	VAL31 LEU91	4.58 4.82
Cryptoflavin	-7.6	VAL31 LEU91	5.22 4.73
Humulene	-6.2	LEU91 ARG95	2.51 1.99
Thiamine	-5.5	UNK1 UNK1 UNK1 UNK1	2.10 2.22 3.09 2.28
Farnesol	-5.3	PHE29 TRP92	5.15 4.66
Phytofluene	-5.1	LEU75 PRO77	4.05 4.52
Benzaldehyde	-5.0	ASN186 HIS186	1.95 2.07
ANTIVIRALS			
Nitazoxanide	-5.9	VAL31 UNK1 UNK1	2.30 2.79 3.54
Oseltamivir	-5.5	GLN184 ASN185 UNK1 UNK1	2.36 2.15 2.48 2.38
Sofosbuvir	-6.8	ASN171 SER177 SER178 LYS206 UNK1 UNK1 UNK1 TRY172	2.30 2.21 2.97 2.26 2.23 3.09 1.84 3.49
Acyclovir	-5.4	UNK1	2.89
Tenofovir	-5.4	UNK1 UNK1	2.89 3.64

The chosen ligands were visualised using Dassault Systems BIOVIA Discovery Studio Visualizer, and two-dimensional and three-dimensional models were obtained. Additionally, the category and type of contact, as well as the bond distance for the relevant amino acid residues in the ligand, were derived.

ADMET analysis of CPP

Physicochemical properties

Determining the physicochemical properties of phytocompounds is crucial for their development as potential drug candidates. The physicochemical properties of phytocompounds, such as solubility, lipophilicity, and molecular weight, [36–40] can greatly affect their absorption, distribution,

metabolism, excretion, and toxicity (ADMET) profiles. For instance, compounds with poor solubility may have limited bioavailability and require higher doses, while highly lipophilic compounds may accumulate in adipose tissue, leading to toxicity. Therefore, evaluating the physicochemical properties of phytocompounds is essential to assess their ADMET profiles accurately.

In the present study it was found that the CPP were having relatively better physicochemical attributes than the FDA approved antivirals. The CPP (except 5281246 and 6436722) had molecular weight less than 500 and had lesser TPSA than the FDA approved drugs.

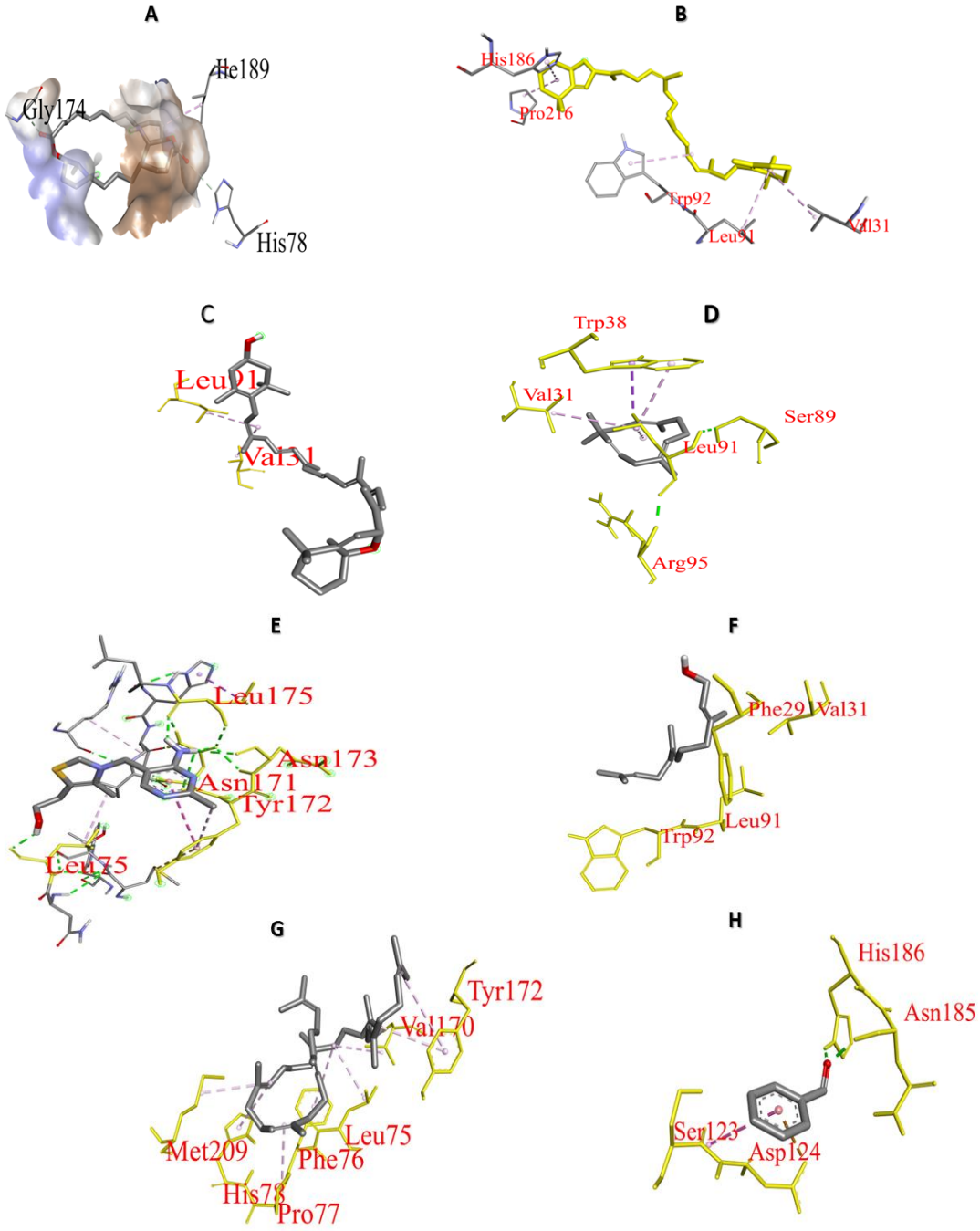

Figure 4. 3D structures of the selected ligands. A. Carpaine, B. Citroxanthin, C. Cryptoflavin, D. Humulene, E. Thiamine, F. Farnesol, G. Phytofluene, H. Benzaldehyde.

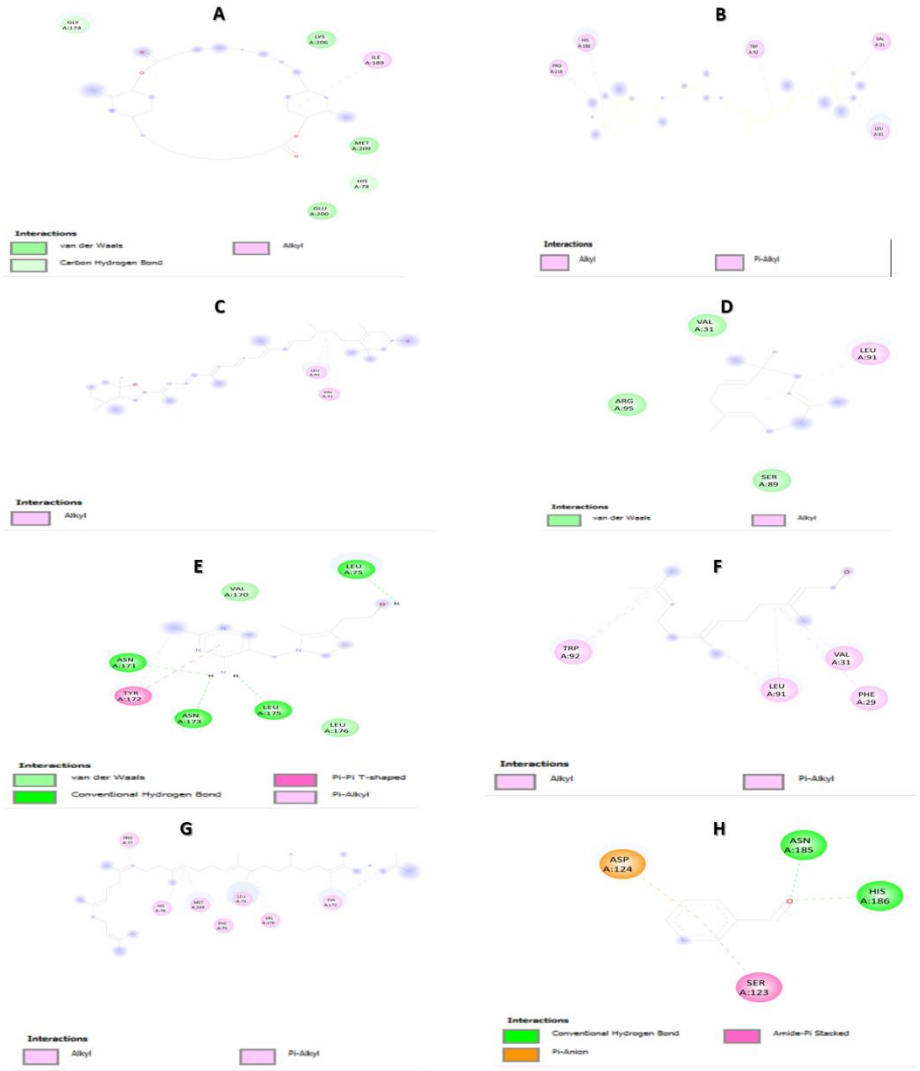

Figure 5. 2D structure of the selected ligands. A. Carpaine, B. Citroxanthin, C. Cryptoflavin, D. Humulene, E. Thiamine, F. Farnesol, G. Phytofluene, H. Benzaldehyde.

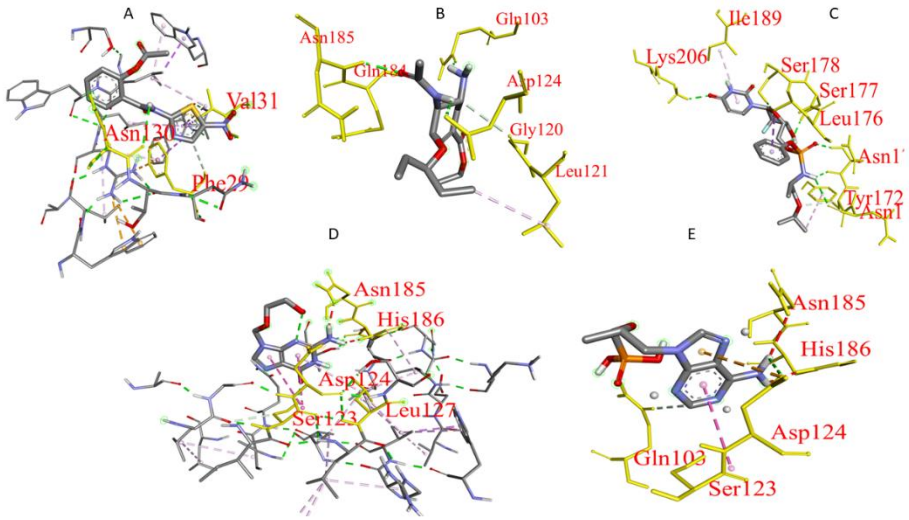

Figure 6. 3D structures of the Antivirals. A. Nitazoxanide, B. Oseltamivir, C. Sofosbuvir, D. Acyclovir, E. Tenofovir.

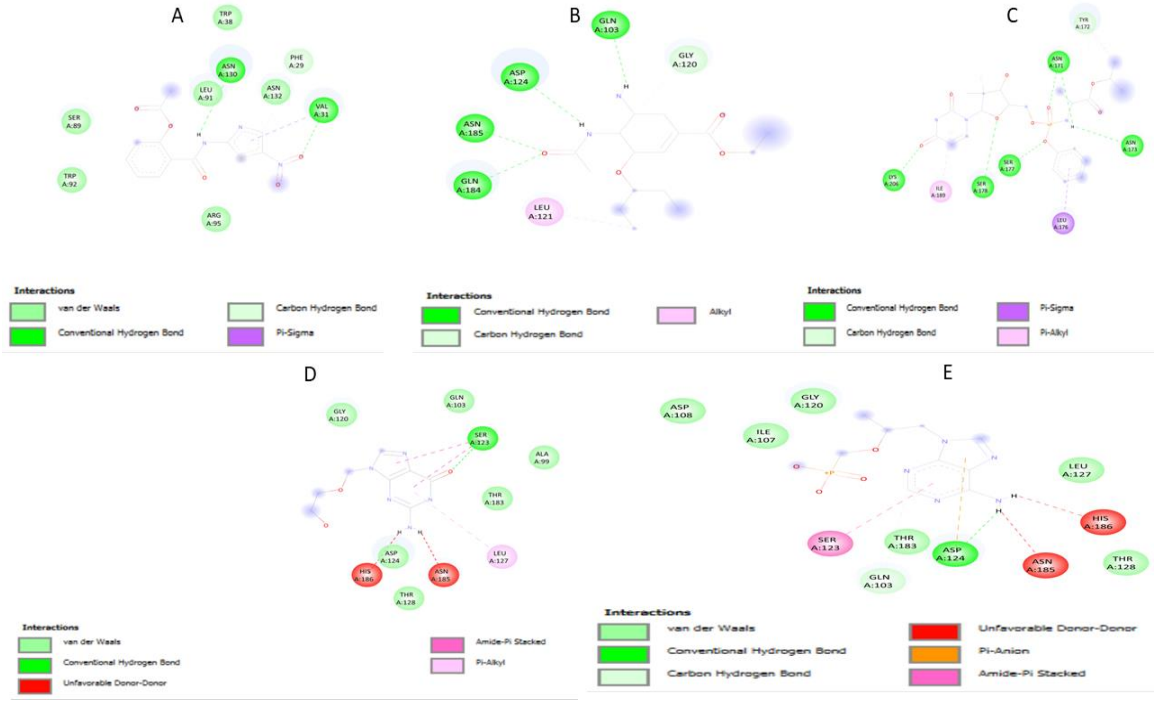

Figure 7. 2D structures of the Antivirals. A. Nitazoxanide, B. Oseltamivir, C. Sofosbuvir, D. Acyclovir, E. Tenofovir.

Table 3. Physicochemical properties of CPP and antiviral drugs.

PubChem CID	LogS	MW	nHA	nHD	TPSA	nRot	nRing	nHet	nRig	Flex
CPP										
442630	-4.424	478.38	6	2	76.66	0	6	6	34	0
5281246	-7.491	552.43	1	0	9.23	9	3	1	24	0.375
5376350	-7.073	568.43	2	1	29.46	9	3	2	24	0.375
5281520	-5.873	204.19	0	0	0	0	1	0	11	0
1130	-1.172	265.11	5	3	76.64	4	2	6	12	0.333
445070	-4.091	222.2	1	1	20.23	7	0	1	3	2.333
6436722	-7.432	542.49	0	0	0	19	0	0	10	1.9
240	-1.574	106.04	1	0	17.07	1	1	1	7	0.143
Antiviral drugs										
41684	-3.214	307.03	8	1	114.66	5	2	9	15	0.333
65028	-1.75	312.2	6	3	90.65	9	1	6	8	1.125
45375808	-2.392	529.16	12	3	158.18	11	3	14	21	0.524
135398513	-2.042	225.09	8	4	119.78	4	2	8	12	0.333
464205	-1.406	287.08	9	3	133.95	5	2	10	13	0.385

MW: Molecular weight; nHA: Number of hydrogen bond acceptors; nHD: Number of hydrogen bond donors; nRot: Number of rotatable bonds; nRing: Number of rings; nHet: Number of heteroatoms; nRig: Number of rigid bonds: Flex: Flexibility; TPSA: Topological polar surface area; logS: The logarithm of aqueous solubility value

Medicinal Chemistry Properties

Determining the medicinal properties of phytocompounds is essential for identifying potential drug candidates for the treatment of various diseases. Phytocompounds are naturally occurring compounds found in plants and possess diverse chemical structures and biological activities [41, 42]. The medicinal properties of phytocompounds can be attributed to their interaction with various biological targets, such as enzymes, receptors, and ion channels. These interactions can modulate various cellular pathways, leading to therapeutic effects. Furthermore, phytocompounds are known to exhibit synergistic and multi-targeted effects, which can enhance their efficacy and reduce the risk of resistance development. Therefore, identifying the medicinal properties of phytocompounds is crucial for drug discovery and can lead to the development of novel and effective drugs for the treatment of various diseases.

The CPP including 5281246, 5376350, 6436722 and the antiviral drug 45375808 did not fulfil the Lipinski screening. Both the CPP and antiviral did not exhibit any probability to cause off target binding.

Table 4. Medicinal chemistry properties of CPP and Antiviral drugs.

PubChem CID	QED	Synth	Fsp3	PAINS	Lipinski
CPP					
442630	0.444	5.842	0.929	0	Accepted
5281246	0.204	4.803	0.5	0	Rejected
5376350	0.221	5.069	0.5	0	Rejected
5281520	0.485	3.693	0.6	0	Accepted
1130	0.702	3.797	0.417	0	Accepted
445070	0.633	2.812	0.6	0	Accepted
6436722	0.112	3.411	0.5	0	Rejected
240	0.496	1.439	0	0	Accepted
Antiviral drugs					
41684	0.401	3.016	0.083	0	Accepted
65028	0.691	3.758	0.75	0	Accepted
45375808	0.305	4.375	0.5	0	Rejected
135398513	0.473	3.195	0.375	0	Accepted
464205	0.66	4.868	0.444	0	Accepted

QED: A measure of drug-likeness based on the concept of desirability; PAINS: Pan Assay Interference Compounds; Lipinski Rule of 5: Molecular weight less than 500 daltons, nHD<5, nHA<10, and lipohilicity<4.15; Fsp3: the number of sp3 hybridized carbons/total carbon count; SAScore: Synthetic accessibility score were accounted

Absorption Properties

The determination of absorption properties of phytocompounds is paramount for the successful development of potential drug candidates. The absorption of phytocompounds is a complex process that is influenced by numerous factors, such as their physicochemical properties, formulation, and administration route. Absorption properties play a critical role in determining the pharmacokinetic behavior of phytocompounds, including their bioavailability, distribution, and elimination. For instance, compounds that exhibit poor absorption may have limited bioavailability and require higher doses, while highly permeable compounds may rapidly distribute to various tissues, leading to toxicity. Thus, evaluating the absorption properties of phytocompounds is critical for understanding their pharmacokinetics and optimizing their drug-like properties. Moreover, the determination of absorption properties of phytocompounds can aid in the design of drug delivery systems that can enhance their bioavailability and therapeutic efficacy. Therefore, an accurate assessment of the absorption properties of phytocompounds is crucial for their successful development into safe and effective drugs.

In the present research it was observed that CPP exhibited better Caco-2 scores than antivirals. Among the CPP 5281246 and 5376350 were inhibitors for Pgp while all the other compounds in the study were found to be substrate for the Pgp.

Table 5. Absorption properties of CPP and Antiviral drugs.

PubChem CID	Pgp-inh	Pgp-sub	HIA	F(20%)	Caco-2	MDCK
442630	0.366	0.939	0.538	0.232	-4.985	4.62E-05
5281246	1	0.193	0.051	0.016	-5.458	7.72E-06
5376350	1	0.68	0.025	0.014	-5.331	1.49E-05
5281520	0.107	0	0.003	0.835	-4.425	1.58E-05
1130	0	0.999	0.409	1	-5.172	1.82E-05
445070	0.67	0.005	0.004	0.989	-4.408	1.20E-05
6436722	0.843	0.373	0.007	0.845	-5.104	7.78E-06
240	0	0.002	0.014	0.091	-4.306	2.16E-05
Antiviral drugs						
41684	0.002	0.002	0.006	0.003	-4.731	8.10E-05
65028	0.001	0.176	0.005	0.004	-4.871	6.72E-05
45375808	0.03	0.002	0.024	0.027	-6.006	1.54E-05
135398513	0	0.842	0.971	0.998	-6.176	3.48E-05
464205	0.001	0.854	0.998	0.939	-5.791	7.77E-06

Caco-2: Caco-2 Permeability; MDCK: Madin−Darby Canine Kidney cells (MDCK) Permeability; Pgp-inh/ Pgp-sub: the inhibitor and substrate of P-glycoprotein; HIA: Human intestinal absorption; F(20%): the human oral bioavailability 20%

Distribution Properties

The determination of distribution properties of phytocompounds is a crucial aspect of drug development. Distribution properties refer to the process by which phytocompounds are transported throughout the body, including their movement across biological membranes and their distribution into various tissues and organs. Understanding the distribution properties of phytocompounds is essential for predicting their pharmacokinetics, toxicity, and efficacy. The distribution of phytocompounds is influenced by several factors, such as their physicochemical properties, binding to plasma proteins, and interactions with efflux transporters. Furthermore, the distribution properties of phytocompounds can have a significant impact on their therapeutic efficacy and toxicity. For example, compounds that exhibit high binding affinity to plasma proteins may have limited distribution to target tissues, reducing their therapeutic potential. On the other hand, compounds that are highly distributed to non-target tissues may lead to off-target effects and toxicity. Thus, an accurate assessment of the distribution properties of phytocompounds is crucial for predicting their pharmacokinetics and optimizing their drug-like properties. Additionally, understanding the distribution properties of phytocompounds can aid in the development of effective drug delivery strategies, including the design of prodrugs and targeted drug delivery systems.

Both CPP and antivirals did not exhibit BBB permeation and the CPP had significantly higher volume distribution than the antivirals. The plasma protein binding was better among antivirals, while the phytocompounds including 5281246, 5376350, 5281520, and 6436722 exhibited PPB greater than 90% which could eventually result in low therapeutic index.

Table 6. Distribution properties of CPP and Antiviral drugs.

PubChem CID	BBB	PPB	VDss	Fu
CPP				
442630	0.01	71.52%	0.728	8.64%
5281246	0.001	99.51%	6.139	2.68%
5376350	0.006	98.79%	4.876	3.17%
5281520	0.111	93.02%	5.367	6.06%
1130	0.831	27.40%	1.082	66.00%
445070	0.387	89.07%	5.625	6.53%
6436722	0.002	93.99%	11.568	3.35%
240	0.974	75.02%	1.332	20.42%
Antiviral drugs				
41684	0.678	80.28%	0.541	33.01%
65028	0.634	17.63%	0.643	72.51%
45375808	0.27	37.16%	0.567	50.86%
135398513	0.84	12.53%	0.797	83.59%
464205	0.519	8.73%	0.829	86.40%

BBB: Blood–brain barrier; PPB: Plasma protein binding; VDss: Volume Distribution; Fu: fraction unbound in plasma.

Metabolism and Excretion Properties

Determining the metabolism and excretion properties of phytocompounds is critical for the successful development of potential drug candidates. Metabolism and excretion refer to the biotransformation and elimination of phytocompounds from the body. Metabolism is a complex process that involves various enzymes and metabolic pathways that modify the chemical structure of phytocompounds. The metabolism of phytocompounds can have a significant impact on their pharmacokinetics, bioavailability, and toxicity. For example, compounds that are extensively metabolized may have limited bioavailability and require higher doses to achieve therapeutic effects. On the other hand, compounds that are poorly metabolized may have a prolonged half-life, leading to toxicity. Excretion, on the other hand, refers to the removal of phytocompounds from the body, primarily through the kidney and liver. The excretion of phytocompounds is influenced by various factors, such as their physicochemical properties, metabolic stability, and clearance rates. The accurate determination of the metabolism and excretion properties of phytocompounds is crucial for predicting their pharmacokinetics, efficacy, and toxicity. Additionally, understanding the metabolism and excretion

properties of phytocompounds can aid in the design of drug delivery systems that can enhance their pharmacokinetics and therapeutic efficacy. Thus, the assessment of the metabolism and excretion properties of phytocompounds is a critical step in their successful development as safe and effective drugs.

Both CPP and antivirals were found to be substrates for cytochromes. The compounds 5281520, 1130, 445070, 240 had better clearance index and the compounds exhibited relatively lower half-life.

Table 7. Metabolism and excretion properties of CPP and Antiviral drugs.

PubChem CID	CYP1A2-inh	CYP1A2-sub	CYP3A4-inh	CYP3A4-sub	CL	T12
CPP						
442630	0.042	0.127	0.87	0.431	2.198	0.126
5281246	0.036	0.955	0.153	0.924	0.348	0.024
5376350	0.022	0.936	0.077	0.928	0.563	0.041
5281520	0.912	0.173	0.393	0.189	8.432	0.095
1130	0.072	0.218	0.001	0.168	6.681	0.904
445070	0.849	0.147	0.113	0.188	14.237	0.33
6436722	0.214	0.163	0.232	0.32	1.079	0.01
240	0.918	0.131	0.007	0.219	5.971	0.777
Antiviral drugs						
41684	0.958	0.082	0.155	0.215	2.148	0.465
65028	0.037	0.094	0.358	0.402	6.991	0.68
45375808	0.014	0.102	0.038	0.381	7.209	0.473
135398513	0.008	0.923	0.007	0.09	4.17	0.945
464205	0.005	0.401	0.006	0.05	1.821	0.898

Table 8. Toxicity properties of CPP and Antiviral drugs.

PubChem CID	hERG	DILI	Ames	Carcinogenicity	IGC50	LC50
CPP						
442630	0.844	0.229	0.012	0.035	5.242	3.66
5281246	0.44	0.028	0.136	0.026	5.77	8.056
5376350	0.417	0.012	0.17	0.031	5.641	7.844
5281520	0.005	0.034	0.002	0.938	3.323	4.45
1130	0.039	0.109	0.008	0.772	1.439	2.246
445070	0.016	0.033	0.002	0.526	2.376	4.343
6436722	0.924	0.003	0.128	0.101	5.273	6.976
240	0.052	0.038	0.049	0.058	3.051	4.009
Antiviral drugs						
41684	0.009	0.974	0.995	0.843	4.59	4.609
65028	0.097	0.035	0.082	0.112	2.037	3.316
45375808	0.039	0.988	0.371	0.148	3.042	4.036
135398513	0.032	0.991	0.866	0.985	1.255	2.452
464205	0.021	0.98	0.895	0.439	2.277	3.361

hERG: The human ether-a-go-go related gene; DILI: Drug-induced liver injury; AMES: The Ames test for mutagenicity; LC50 FM: 96-hour fathead minnow LC_{50} were examined.

Toxicity Properties

Determining the toxicity properties of phytocompounds is an essential aspect of drug development, which aims to produce safe and effective therapeutic agents. Toxicity refers to the adverse effects of phytocompounds on living organisms, including their potential to cause harm or damage to cells, tissues, organs, or organ systems. Toxicity can arise from various mechanisms, such as metabolic activation, oxidative stress, inflammation, and interference with cellular signaling pathways. The assessment of toxicity properties of phytocompounds is a critical step in the development of new drugs, as it enables the identification of compounds with undesirable toxic effects that can limit their therapeutic potential. Furthermore, an understanding of the toxicity properties of phytocompounds can provide insights into the mechanisms underlying their adverse effects, facilitating the design of strategies to mitigate their toxicity. Toxicity assessment involves the use of various in vitro and in vivo

experimental models, which evaluate the potential of phytocompounds to induce toxicity in different tissues and organs. The determination of the toxicity properties of phytocompounds is essential for ensuring their safety and efficacy in clinical trials and eventual approval for human use. Therefore, toxicity assessment is an essential component of drug development, enabling the production of safe and effective drugs with a favorable risk-benefit profile.

Both CPP and antivirals were found to be inactive towards hERG, DILI, AMES and carcinogencity. These compounds did not exhibit any potential to induce any organ toxicity.

DISCUSSION

The Ebola virus is a highly infectious and deadly disease that has been responsible for several outbreaks in Africa and other parts of the world. The disease is transmitted through contact with the bodily fluids of infected animals or people, leading to severe hemorrhagic fever with high mortality rates. The 2014 outbreak of the Ebola virus in West Africa was the largest in history, leading to over 11,000 deaths and a global public health crisis. The lack of effective treatments for Ebola virus infection posed a significant challenge in managing the outbreak. Due to the high mortality rates and the rapid spread of the disease, there was a pressing need to find effective treatments to combat Ebola. Researchers turned to repurposing drugs such as ZMapp and remdesivir for the management of Ebola virus infection. Additionally, phytotherapy and herbal therapy were also employed in managing the disease, particularly in areas with limited access to conventional medicine. While these drugs showed some efficacy in managing the disease, their effectiveness was limited, and there was still a significant need for the development of new therapies.

Phytotherapy and herbal therapy were also employed in managing the disease, particularly in areas with limited access to conventional medicine. The use of medicinal plants has been a traditional practice for treating various ailments and diseases, and the potential of medicinal plants in the management of viral infections has been a subject of several studies. Carica papaya, commonly known as papaya, is a tropical fruit that has been extensively studied for its medicinal properties. Previous research has indicated that Carica papaya possesses antiviral properties, with several studies demonstrating the inhibitory effects of Carica papaya extract on various viral infections, including the dengue virus, HIV, and the herpes simplex virus. The antiviral activity of Carica papaya has been attributed to its ability to stimulate the immune system and inhibit viral replication. The fruit contains several bioactive compounds, including alkaloids, flavonoids, and phenolic acids, which have been shown to possess antiviral properties.

In our study, we aimed to target the VP24 protein of Ebola virus using Carica papaya phytocompounds (CPP). VP24 plays a critical role in the pathogenesis of the Ebola virus by suppressing the host immune response, allowing the virus to evade the host immune system and replicate efficiently.

The Ebola virus is an enveloped virus with a single-stranded RNA genome that belongs to the family Filoviridae. Ebola virus is composed of seven structural proteins, including the nucleoprotein (NP), the glycoprotein (GP), the matrix protein (VP40), the RNA-dependent RNA polymerase (L), and three others, one of which is VP24. VP24 is a small protein of about 30 amino acids that is highly conserved among filoviruses. It is encoded by the fifth gene of the viral genome and is expressed late in the viral life cycle. VP24 is involved in several processes in the pathogenesis of Ebola virus infection.

One of the primary functions of VP24 is to inhibit the host immune response. VP24 interacts with the host protein karyopherin alpha 5 (KPNA5), which is required for the transport of STAT1 to the nucleus, a key transcription factor for the production of interferon (IFN). Interferons are important cytokines that activate the host immune response against viral infections. By inhibiting the transport of STAT1 to the nucleus, VP24 prevents the activation of interferon-stimulated genes (ISGs) that play a crucial role in controlling viral replication. VP24 also interacts with the host protein dynein, a molecular

motor that moves along microtubules and is involved in the transport of cargo within the cell. By interacting with dynein, VP24 is thought to interfere with the transport of viral particles to the site of replication, thereby reducing the number of virions that are produced. In addition, VP24 is involved in the regulation of viral transcription and replication. VP24 has been shown to interact with the viral protein L, which is responsible for viral replication and transcription. This interaction may facilitate the assembly of the viral RNA polymerase complex and enhance viral replication.

Furthermore, recent studies have suggested that VP24 may play a role in the regulation of viral assembly and budding. VP24 has been shown to interact with the matrix protein VP40, which is involved in viral assembly and budding. This interaction may facilitate the formation of the viral matrix and enhance viral assembly and budding. Therefore, targeting VP24 could be an effective strategy for managing Ebola virus infection.

In the current analysis, phytocompounds such as Carpaine, Citroxanthin, and Cryptoflavin were discovered to have substantially higher binding affinity against the VP24 protein than the five other FDA-approved antiviral drugs.

We selected CPPs based on their docking scores, which indicated their potential to interact with VP24. The CPPs were screened for toxicity using ADMET analysis, which predicted their absorption, distribution, metabolism, excretion, and toxicity properties. The results of the ADMET analysis indicated that the selected CPPs were safe and had favorable pharmacokinetic properties, suggesting their potential as lead compounds for drug development.

In the current research, it was discovered that CPP has better physicochemical properties than FDA-approved antivirals. These top three ligands, in particular, demonstrated superior physicochemical qualities as compared to the remaining Carpine, Cryptoflavin, and Humelene. Because these ligands have more stiff bonds, less flexibility, and more hydrogen acceptors than hydrogen donors. Furthermore, the TPSA value for these three ligands is larger than for the other ligands.

The findings of this study highlight the potential of Carica papaya phytocompounds as a promising source of antiviral agents for managing Ebola virus infection. By targeting VP24, the study provides a new approach for developing effective therapies for Ebola virus infection.

CONCLUSION

The multifunctional VP24 protein plays a critical role in the pathogenesis of Ebola virus by inhibiting the host immune response, interfering with the transport of viral particles, regulating viral replication and transcription, and facilitating viral assembly and budding. Targeting VP24 could be an effective strategy for managing Ebola virus infection. By targeting VP24, the study provides a new approach for developing effective therapies for Ebola virus infection. The docking analysis revealed that the CPP Carpine, Cryptoflavin, and Humelene had better docking scores and pharmacological properties than the standard drugs. Further studies are necessary to validate the efficacy of CPPs against Ebola virus infection in vitro and in vivo. However, the study offers new insights into the potential of phytotherapy as a viable approach for developing novel therapies for viral infections.

Abbreviations

CPP- Carica papaya phytocompounds
VP24- Viral protein 24
FDA- Food and drug administration
BBB- Blood brain barrier

REFERENCES

1. Baseler, L., Chertow, D. S., Johnson, K. M., Feldmann, H., & Morens, D. M. (2017). The Pathogenesis of Ebola Virus Disease. *Annual review of pathology*, *12*, 387–418. https://doi.org/10.1146/annurev-pathol-052016-100506

2. Zawilińska, B., & Kosz-Vnenchak, M. (2014). General introduction into the Ebola virus biology and disease. *Folia medica Cracoviensia*, *54*(3), 57–65.
3. Goeijenbier, M., van Kampen, J. J., Reusken, C. B., Koopmans, M. P., & van Gorp, E. C. (2014). Ebola virus disease: a review on epidemiology, symptoms, treatment and pathogenesis. *The Netherlands journal of medicine*, *72*(9), 442–448.
4. Sakurai Y. (2015). *Uirusu*, *65*(1), 71–82. https://doi.org/10.2222/jsv.65.71
5. Tomori, O., & Kolawole, M. O. (2021). Ebola virus disease: current vaccine solutions. *Current opinion in immunology*, *71*, 27–33. https://doi.org/10.1016/j.coi.2021.03.008
6. Nugroho, A., Heryani, H., Choi, J. S., & Park, H. J. (2017). Identification and quantification of flavonoids in Carica papaya leaf and peroxynitrite-scavenging activity. *Asian Pacific Journal of Tropical Biomedicine*, *7*(3), 208-213.
7. Singh, S. P., Kumar, S., Mathan, S. V., Tomar, M. S., Singh, R. K., Verma, P. K., Kumar, A., Kumar, S., Singh, R. P., & Acharya, A. (2020). Therapeutic application of Carica papaya leaf extract in the management of human diseases. *Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences*, *28*(2), 735–744. https://doi.org/10.1007/s40199-020-00348-7
8. Hussain, S. Z., Razvi, N., Ali, S. I., & Hasan, S. (2018). Development of quality standard and phytochemical analysis of Carica papaya Linn leaves. *Pakistan journal of pharmaceutical sciences*, *31*(5(Supplementary)), 2169–2177.
9. Khadam, S., Afzal, U., Gul, H., Hira, S., Satti, M., Yaqub, A., Ajab, H., & Gulfraz, M. (2019). Phytochemical screening and bioactivity assessment of leaves and fruits extract of Carica papaya. *Pakistan journal of pharmaceutical sciences*, *32*(5), 1941–1948.
10. Santana, L. F., Inada, A. C., Espirito Santo, B., Filiú, W., Pott, A., Alves, F. M., Guimarães, R., Freitas, K. C., & Hiane, P. A. (2019). Nutraceutical Potential of *Carica papaya* in Metabolic Syndrome. *Nutrients*, *11*(7), 1608. https://doi.org/10.3390/nu11071608
11. Doughari, J. H., Elmahmood, A. M., & Manzara, S. (2007). Studies on the antibacterial activity of root extracts of Carica papaya L. *African Journal of Microbiology Research*, *1*(3), 037-041.
12. Asghar, N., Naqvi, S. A. R., Hussain, Z., Rasool, N., Khan, Z. A., Shahzad, S. A., ... & Jaafar, H. Z. (2016). Compositional difference in antioxidant and antibacterial activity of all parts of the Carica papaya using different solvents. *Chemistry Central Journal*, *10*(1), 1-11.
13. Nirosha, N., & Mangalanayaki, R. (2013). Antibacterial activity of leaves and stem extract of Carica papaya L. *IJAPBC*, *2*(3), 473.
14. Singh, O., & Ali, M. (2011). Phytochemical and antifungal profiles of the seeds of Carica papaya L. *Indian Journal of Pharmaceutical Sciences*, *73*(4), 447.
15. Chávez-Quintal, P., González-Flores, T., Rodríguez-Buenfil, I., & Gallegos-Tintoré, S. (2011). Antifungal activity in ethanolic extracts of Carica papaya L. cv. Maradol leaves and seeds. *Indian journal of microbiology*, *51*(1), 54-60.
16. Bi, S., & Goyal, P. K. (2012). Anthelmintic effect of Natural Plant (Carica papaya) extract against the gastrointestinal nematode, Ancylostoma caninum in Mice. *ISCA J. Biological Sci*, *1*(1), 2-6.
17. Adu, O. A., Akingboye, K. A., & Akinfemi, A. (2009). Potency of pawpaw (Carica papaya) latex as an anthelmintic in poultry production. *Bot. Res. Int*, *2*(3), 139-142.
18. Ameen, S. A., Adedeji, O. S., Ojedapo, L. O., Salihu, T., & Fakorede, O. L. (2012). Anthelmintic efficacy of pawpaw (Carica papaya) seeds in commercial layers. *African journal of Biotechnology*, *11*(1), 126-130.
19. Nayak, B. S., Pereira, L. P., & Maharaj, D. (2007). Wound healing activity of Carica papaya L. in experimentally induced diabetic rats.
20. Nayak, B. S., Ramdeen, R., Adogwa, A., Ramsubhag, A., & Marshall, J. R. (2012). Wound-healing potential of an ethanol extract of Carica papaya (Caricaceae) seeds. *International Wound Journal*, *9*(6), 650-655.
21. Pandey, S., Cabot, P. J., Shaw, P. N., & Hewavitharana, A. K. (2016). Anti-inflammatory and immunomodulatory properties of Carica papaya. *Journal of immunotoxicology*, *13*(4), 590-602.
22. Owoyele, B. V., Adebukola, O. M., Funmilayo, A. A., & Soladoye, A. O. (2008). Anti-inflammatory activities of ethanolic extract of Carica papaya leaves. *Inflammopharmacology*, *16*(4), 168-173.

23. Rahmani, A. H., & Aldebasi, Y. H. (2016). Potential role of carica papaya and their active constituents in the prevention and treatment of diseases. *Int J Pharm Pharm Sci*, *8*(1), 11-15.
24. Kovendan, K., Murugan, K., Panneerselvam, C., Aarthi, N., Kumar, P. M., Subramaniam, J., ... & Vincent, S. (2012). Antimalarial activity of Carica papaya (Family: Caricaceae) leaf extract against Plasmodium falciparum. *Asian Pacific Journal of Tropical Disease*, *2*, S306-S311.
25. Ahmad, N., Fazal, H., Ayaz, M., Abbasi, B. H., Mohammad, I., & Fazal, L. (2011). Dengue fever treatment with Carica papaya leaves extracts. *Asian Pacific journal of tropical biomedicine*, *1*(4), 330-333.
26. Sarker, M. M. R., Khan, F., & Mohamed, I. N. (2021). Dengue fever: therapeutic potential of Carica papaya L. Leaves. *Frontiers in Pharmacology*, *12*.
27. Fauziya, S., & Krishnamurthy, R. (2013). Papaya (Carica papaya): source material for anticancer. *CIBTech J Pharm Sci*, *2*(1), 25-34.
28. Heung, T. Y., Huong, J. Y. S., Chen, W. Y., Loh, Y. W., Khaw, K. Y., Goh, B. H., & Ong, Y. S. (2021). Anticancer Potential of Carica papaya through Modulation of Cancer Hallmarks. *Food Reviews International*, 1-19.
29. Unaeze, B. C., Ilo, C. E., Egwuatu, C., Orabueze, I., & Obi, E. (2017). Anti-diarrhoeal effects of three Nigerian medicinal plant extracts on E. coli-induced diarrhea. *International Journal of Biological and Chemical Sciences*, *11*(1), 414-419.
30. Ali, A., Devarajan, S., Waly, M., Essa, M. M., & Rahman, M. S. (2011). Nutritional and medicinal value of papaya (Carica papaya L.). *Natural products and bioactive compounds in disease prevention*, 34-42.
31. Krishna, K. L., Paridhavi, M., & Patel, J. A. (2008). Review on nutritional, medicinal and pharmacological properties of Papaya (Carica papaya Linn.).
32. Pandit, A., Sachdeva, T., & Bafna, P. (2013). Ameliorative effect of leaves of Carica papaya in ethanol and antitubercular drug induced hepatotoxicity. *Br J Pharm Res*, *3*, 648-61.
33. Adeneye, A. A., Olagunju, J. A., Banjo, A. A. F., Abdul, S. F., Sanusi, O. A., Sanni, O. O., ... & Shonoiki, O. E. (2009). The aqueous seed extract of Carica papaya Linn. Prevents carbon tetrachloride induced hepatotoxicity in rats. *International Journal of Applied Research in Natural Products*, *2*(2), 19-32.
34. Hewitt, H., Whittle, S., Lopez, S., Bailey, E., & Weaver, S. (2000). Topical use of papaya in chronic skin ulcer therapy in Jamaica. *The west Indian medical journal*, *49*(1), 32-33.
35. Lohiya, N. K., Pathak, N., Mishra, P. K., & Manivannan, B. (2000). Contraceptive evaluation and toxicological study of aqueous extract of the seeds of Carica papaya in male rabbits. *Journal of ethnopharmacology*, *70*(1), 17-27.
36. Lohiya, N. K., Manivannan, B., & Garg, S. (2006). Toxicological investigations on the methanol sub-fraction of the seeds of Carica papaya as a male contraceptive in albino rats. *Reproductive toxicology*, *22*(3), 461-468.
37. Pandey, S., Cabot, P. J., Shaw, P. N., & Hewavitharana, A. K. (2016). Anti-inflammatory and immunomodulatory properties of Carica papaya. *Journal of immunotoxicology*, *13*(4), 590-602.
38. Mojica-Henshaw, M. P., Francisco, A. D., De Guzman, F., & Tigno, X. T. (2003). Possible immunomodulatory actions of Carica papaya seed extract. *Clinical hemorheology and microcirculation*, *29*(3-4), 219-229.
39. Chen, C. F., Chen, S. M., Chow, S. Y., & Han, P. W. (1981). Protective effects of Carica papaya Linn on the exogenous gastric ulcer in rats. *The American journal of Chinese medicine*, *9*(03), 205-212.
40. Maisarah, A. M., Nurul Amira, B., Asmah, R., & Fauziah, O. (2013). Antioxidant analysis of different parts of Carica papaya. *International Food Research Journal*, *20*(3).
41. Maisarah, A. M., Asmah, R., & Fauziah, O. (2014). Proximate analysis, antioxidant and anti proliferative activities of different parts of Carica papaya. *Journal of Tissue Science & Engineering*, *5*(1), 1.
42. Kothari, V., & Seshadri, S. (2010). Antioxidant activity of seed extracts of Annona squamosa and Carica papaya. *Nutrition & Food Science*.

43. Mohanraj, K., Karthikeyan, B. S., Vivek-Ananth, R. P., Chand, R. P., Aparna, S. R., Mangalapandi, P., & Samal, A. (2018). IMPPAT: a curated database of Indian medicinal plants, phytochemistry and therapeutics. Scientific reports, 8(1), 1-17.
44. Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., ... & Bolton, E. E. (2019). PubChem 2019 update: improved access to chemical data. Nucleic acids research, 47(D1), D1102-D1109.
45. Online SMILES Translator and Structure File Generator https://cactus.nci.nih.gov/translate/
46. Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports, 7(1), 1-13.
47. Xiong, G., Wu, Z., Yi, J., Fu, L., Yang, Z., Hsieh, C., ... & Cao, D. (2021). ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. *Nucleic Acids Research*, *49*(W1), W5-W14.
48. Kemmish, H., Fasnacht, M., & Yan, L. (2017). Fully automated antibody structure prediction using BIOVIA tools: Validation study. *PloS one*, *12*(5), e0177923.
49. Dallakyan, S., & Olson, A. J. (2015). Small-molecule library screening by docking with PyRx. In *Chemical biology* (pp. 243-250). Humana Press, New York, NY.

