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Investigation of the Physicochemical and Biological Properties of Carica Papaya Seed Extract via GC-MS Analysis and Integrated Bioinformatics Approaches Unveils Potential Anti-Dengue Type 2 Compounds

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Abstract

Carica papaya Linn. belongs to the family Caricaceae and is well known for its therapeutic and nutritional properties. The study evaluated the seed extract phytocompounds for their potential antiviral properties using integrated computational analysis. Phytocompounds were analyzed using GC-MS analysis. Compounds were classified and annotated using the Classy Fire methodology. Physicochemical characteristics were predicted via the Swiss ADME web service. Antiviral properties were predicted using Pass online. Natural product-likeness was assessed using the NP-Scout system. Kinase targets prediction was determined using the Kin Screen application. Gene expression profiles were extrapolated using the DIGEP Pred web service. The compounds belonged to the organic compound kingdoms. Classy Fire hierarchical revealed compound 1, 4, and 5 as fatty acid methyl esters, compound 2, 6, and 7 as long-chain fatty acids, and compound 3, 8, 9, and 10 as linoleic acids and derivatives, very long-chain fatty acids, phosphatidylethanolamines, and fatty aldehydes. Compounds 1 and 2 showed potential drug properties using ADME analysis and natural product likeness. Compound 2 exhibits the best target in the kinase members. The compounds were active against the dengue virus type 2 genome polyprotein. Compounds 2 and 7 were the most active and had the highest confidence level of 0.6981. Gene expression profiling analysis revealed overlapping genes. IL23A was significantly upregulated while MT1H, ELAVL1, and SMARCC1 were significantly downregulated. The phytocompounds could exhibit antiviral properties against dengue virus type 2 by interfering with mRNA expression of key genes and mediating signaling in coordinating immune defenses against DENV infection.

Key words: *Carica Papaya* Seed, Phytocompounds, Dengue Virus Kinase, Genes

1. Introduction

In 2023, the dengue fever virus (DENV) spread to many parts of the world, including, surprisingly, developed nations where the disease had either no recent occurrence or not. About half of the world's population is at risk for this disease, which is mostly found in urban and semiurban regions in tropical and subtropical climates worldwide. Between 100 and 400 million instances of the disease are reported to occur each year, according to the World Health Organization [1].

According to the Centres for Disease Control and Prevention (CDC) more than 80 nations and territories across the world reported more than five million dengue fever cases, (Centres for Disease Control and Prevention, 2023). Compared to the 2.8 million instances recorded during the entire year of 2022, most cases were reported in the Americas in 2023, with over three million suspected and confirmed cases [2]. With nearly three million suspected and confirmed cases, including 28,203 severe cases and 1823 fatalities, Brazil, Peru, and Bolivia have recorded the largest number of dengue cases in 2023 (Centres for Disease Control and Prevention, 2023). Angola, Burkina Faso, Chad, Côte d'Ivoire, Egypt, Ethiopia, Guinea, Mali, Mauritius, Sao Tome & Principe, Senegal, and Sudan are among the African nations where dengue outbreaks have been documented (Pan American Health Organization, 2023) [63]. A significant public health problem has been created by the continuous transmission and unanticipated increase in dengue cases in 2023, necessitating concerted efforts for efficient prevention and control measures.

Ethnopharmacological study has contributed greatly in advancing phytotherapeutics and enable drug discovery [3]. Medicinal plants and their bioactive ingredients have gained substantial attention as possible sources for the development of effective, efficient, and affordable therapeutic agents to cope with the modern medical challenges [4]. Traditional herbal medicine, derived from indigenous origin has been historically used for the management and treatment of many chronic and communicable diseases. Although synthetic antiviral agents are important in disease management, increasing focus is being given to plant-derived metabolites as potential therapeutic alternatives. Plant bioactive compounds can interfere with viral replication mechanisms without affecting the host physiology causing limited side effects [5,6]. These natural compounds may have the ability to alter the host's immune responses to viral infections in addition to directly interfering with the viral replication process [7]. Numerous antiviral medicinal plants, including *Lindera chunii, Andrographis paniculata, Wistaria floribunda, Dioscorea bulbifera, Aegle marmelos and Xanthoceras sorbifoli*, have been shown to exhibit significant anti-HIV activity, according to research [8]. It has also been shown that certain natural or plant-derived substances from various chemical groups have anti-HBV properties [9,10]. Compared to interferons and/or lamivudine treatment, some plant products have demonstrated comparable or even greater efficiency against this virus [11]. *Carica papaya* (C. papaya) L., is a member of the *Caricaceae* family. Around the world, it is utilized as a food and a medicinal plant to treat a variety of illnesses [12]. There are numerous documented medicinal uses for the various components of the *C. papaya*, including the leaf, bark, roots, flower, fruit, seed, and latex. According to Nguyen et al., *C. papaya* has been demonstrated to possess antiviral, antibacterial, anthelmintic, antifungal, antiprotozoan, anti-inflammatory, antihypertensive, hypoglycemic and hypolipidemic, anticancer, wound healing, free radical scavenging, neuroprotective, antisickling, diuretic, antisickling, abortifacient, and postpartum properties [13]. The leaves of *C. papaya* are used in traditional medicine for their immunomodulatory and antiviral properties, as well as to treat a wide range of ailments, such as malaria, dengue fever, and jaundice [14]. The study evaluated the seed extract phytocompounds of *C. papaya* for its potential antiviral compound against dengue virus using integrated computation analysis.

2. Materials and Methods

2.1. Collection of Plant Material

Carica papaya Linn. fruits were collected from a farmland at Ofuorachi Igalamela-Odolu in Kogi state, Nigeria. Kogi state has a latitude 7◦ 6◦ 24◦ N and longitude 6◦ 48◦ 49◦ E. The fruit seed was authenticated by a botanist at the Department of Plant Sciences, School of Life Sciences, Modibbo Adama University of Technology Yola, Nigeria. The ripe seeds were collected and washed under running tap water. It was shade dried at ambient temperature and then pulverized into a fine powder using laboratory blender.

2.2. Extraction of the Plant Material

Extraction procedure of the plant material was carried out as earlier reported in our previously published manuscript (Agada et al. 2020). The ripe seed powder (200 g) was extracted using SoXhlet apparatus. The powdered sample was sequentially extracted using hexane, ethyl acetate, and methanol solvents. Extracts acquired were filtered using Whatman filter paper and the filtrate was concentrated on a rotary evaporator to recover the solvents used.

2.3. Phyto-Compounds Origin

In the current work, we predicated and investigated in depth some fundamental properties of 10 compounds that were previously determined by our team using GC-MS from the *Carica papaya* seed (Linn.) (Agada et al. 2020). We studied the physicochemical and biological properties of these compounds for possible predication of antiviral properties using the Passonline (http://www.way2drug.com/ge/). These compounds are Pentadecanoic acid (compound 1), n-Hexadecanoic acid (compound 2), 9,12-Octadecadienoic acid (compound 3), 11-Octadecenoic acid (compound 4), Octadecanoic acid (compound 5), Oleic acid (compound 6), n-Octadecanoic acid (compound 7), (E)-13-Docosenoic acid (compound 8), Palmitin (compound 9), 9-Octadecenal (compound 10). The compounds classification was further annotated using the Classy Fire methodology (http://classyfire.wishartlab.com/) [15].

2.4. Computational Analysis

2.4.1. Physicochemical and Natural Product-likeness Characteristics

The intrinsic physical and chemical characteristics of each tested compound has been predicted via Swiss ADME web-service (http://www.swissadme.ch). For this purpose, the pharmacokinetic characteristics were chosen for the studies which includes gastrointestinal (GI) absorption, p-glycoprotein (PGP) substrate, and blood–brain barrier (BBB) permeability. Additionally, the drug-likeness of the phyto-compounds were considered, an orally bioavailable drug candidate is considered by possessing drug-like properties and major pharmaceutical companies constantly make use of filters such as Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) to exclude drug candidates with unfavourable pharmacokinetic profiles [16]. Furthermore, the natural product-likeness of each compound was assessed using an innovative machine learning technique incorporated into the NP-Scout system, developed by the Computational Drug Discovery and Design team at the University of Vienna (https://nerdd.univie.ac.at/npscout/about/).

2.5. Kinase Targets Prediction

Protein kinases play an important role in the regulation of nearly all cellular functions and are therefore of important interest as probable therapeutic targets. Nevertheless, kinases may also contribute to the development of pathological states and disease manifestation at the organismal level [17]. In that vein, KinScreen, a recently developed platform was employed to calculate the probability of our compounds to target various classes of kinases. This application server allows for the visualization of results in the form of a mapped kinome tree (https://www.way2drug.com/KinScreen/).

2.6. Antiviral Properties Prediction

To explore this parameter, Way2Drug antiviral-Pred webserver was used (https://www.way2drug.com/antivir/process.php). The conical smiles of each compound were imported and the antiviral predication was carried out based on the virus, protein target and the confidence score. Additionally, the servers generate information based ChEMBL database.

2.7. Gene Expression Profiles

The probable influence of the compounds to induce changes in gene expression profiles was explored using DIGEP Pred web service (http://www.way2drug.com/ge/) and hence to understand the upregulation or downregulation processes of the selected genes [18]. Overlapping genes of the upregulation or downregulation processes were further analysed for functional role in viral diseases using Comparative Toxicogenomics Database web server (https://ctdbase.org/detail.go).

3. Results and Discussion

3.1. Canonical Format Extraction of Phyto-Compounds

To accurately predict the properties of specific chemicals, it is essential to use a canonicalization algorithm to generate the corresponding canonical SMILES of the compounds. Table 1 outlines details about the chemical structure, molecular formula, Pub Chem identifier, and the respective canonical smiles of each target compound. The compounds were annotated with their corresponding compound classes using Classy Fire hierarchy (Figure 1). All the compounds were classified as belonging to the organic compound kingdoms. In terms of Classy Fire hierarchical classes, compound 1,4 and 5 were classified as fatty acid methyl esters, compound 2, 6 and 7 were classified as long-chain fatty acids, compound 3,8,9 and 10 were classified as lineolic acids and derivatives, very long-chain fatty acids, phosphatidylethanolamines, and Fatty aldehydes respectively.

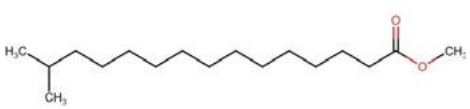
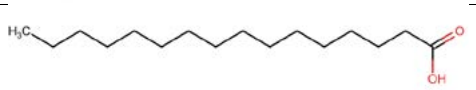
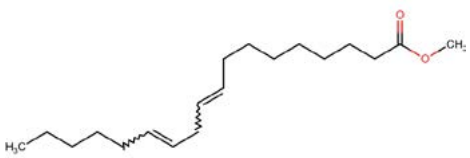
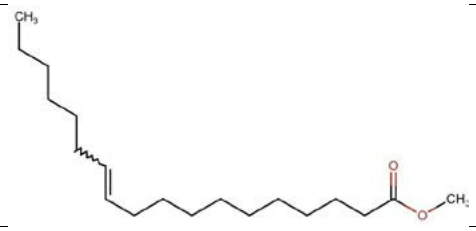
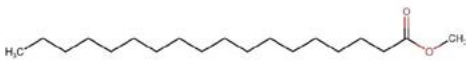
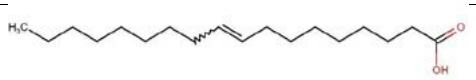
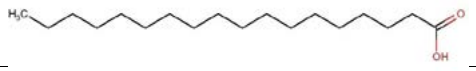
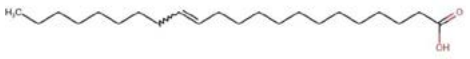
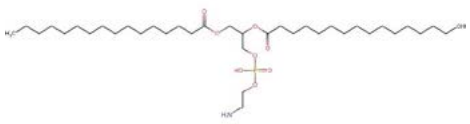
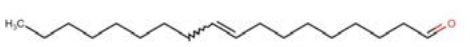
Compound	Formula	3D structure	PubChem identifier	Canonical smiles
C1	C17H34O2		21205	CC (C)CCCCCCCCCCCCC(=O)OC
C2	C16H32O2		985	CCCCCCCCCCCCCCCC(=O)O
C3	C19H34O2		5284421	CCCCCC=CCC=CCCCCCCCC(=O)OC
C4	C19H36O2		5364432	CCCCCCC=CCCCCCCCCCC(=O)OC
C5	C19H38O2		8201	CCCCCCCCCCCCCCCCCC(=O)OC
C6	C18H34O2		445639	CCCCCCCCC=CCCCCCCCC(=O)O
C7	C18H36O2		5281	CCCCCCCCCCCCCCCCCC(=O)O
C8	C22H42O2		5282772	CCCCCCCCC=CCCCCCCCCCCCC(=O)O
C9	C37H74NO8P		445468	CCCCCCCCCCCCCCCC(=O)OCC(COP(=O)(O)OCCN)OC(=O)CCCCCCCCCCCCCCC
C10	C18H34O		17029	CCCCCCCCC=CCCCCCCCC=O

Table 1: Structural Characteristics of Selected Compound

Citation: Thagriki, D. S., Agada, R., Gideon, H. B., Yaduma, W. G., Toma, I. (2026). Investigation of the Physicochemical and Biological Properties of Carica Papaya Seed Extract via GC-MS Analysis and Integrated Bioinformatics Approaches Unveils Potential Anti-Dengue type 2 Compounds. *J Biomed Eng Res, 4*(2), 1-13.

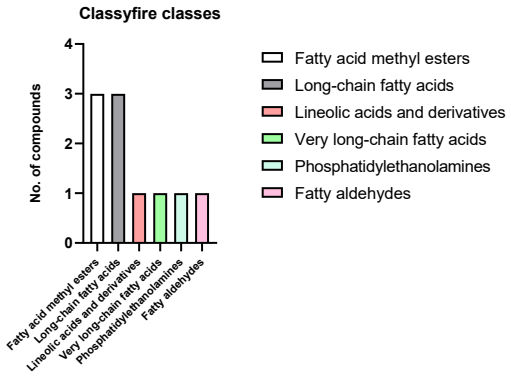


Figure 1: Annotation of Gc-Ms Chemical Compounds Based on Classy Fire Class Taxonomies of the Compounds

3.2. ADME Profile and Drug Likeliness Analysis

The 10 compounds were screened for ADME and drug likeliness analysis by Swiss ADME server (Table 2). The pharmacokinetic characteristics that were chosen for the studies included gastrointestinal (GI) absorption, p-glycoprotein (PGP) substrate, and blood–brain barrier (BBB) permeability. To fully comprehend the idea of drug delivery and distribution, GI absorption is central parameter. A drug with a high GI absorption is said to be appropriate for oral consumption [19]. The permeability of the blood-brain barrier (BBB) is a critical factor for drug candidates. Once a drug crosses the BBB, it has the capability to interact with the central nervous system (CNS), which could result in adverse effects on the brain. Moreover, p-glycoprotein (PGP) serves as an efflux transporter, removing the drug from the BBB if it manages to penetrate this barrier [16]. Our result revealed that apart from compounds 8, 9 and 10, all the other compounds (1-7) exhibited high GI absorption. All the compounds exhibited non-permeable to BBB excluding compounds 1 and 2. The boiled egg analysis conducted by the same server yielded identical results. In this analysis, the yolk of the egg symbolizes the blood-brain barrier (BBB), while the egg white represents gastrointestinal (GI) absorption. (Figure 2). In addition to pharmacokinetics data, another vital parameter is drug-likeness. An orally bioavailable drug candidate is considered by possessing drug-like properties. Major pharmaceutical companies constantly make use of filters such as Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) to exclude drug candidates with unfavourable pharmacokinetic profiles [16].

The most promising result was shown by compound 1 and 2 which only violated Veber (GSK) and Muegge (Bayer) drug likeliness method and had a good bioavailability score. Although other compounds (C3-C7, C8 and C10) exhibited some violations out of the drug likeliness methods but had good bioavailability score. Compound 9 exhibited the most unsatisfactory result by violating all the drug likeliness methods and had a lower bioavailability score of 0.17. Comparable studies on ADME toxicity and drug-likeness were previously documented by [16]. The data further revealed that all the compounds possess natural product-likeness property with the phyto-compounds 1,2, 5-8 and 10 exhibiting a perfect score (Table 3). This potential connection may be directly attributed to the structural and physicochemical characteristics of these compounds [20]. Nakashima et al. demonstrated that these characteristics significantly influence drug-likeness and the anticipated pharmacological effects of a compound [20]. Additionally, NP-likeness is now regarded as a critical criterion in the selection and design of new drugs.

	Pharmacokinetics			Drug likeness					
Compound	**GI absorption**	**BBB permeant**	**PGP substrate**	**Lipinski (Pfizer)**	**Ghose (Amgen)**	**Veber (GSK)**	**Egan (Pharmacia)**	**Muegge (Bayer)**	**Bioavailability score**
1	High	Yes	No	Yes	Yes	No (1)	Yes	No (1)	0.55
2	High	Yes	No	Yes	Yes	No (1)	Yes	No (1)	0.85
3	High	No	No	Yes	No (1)	No (1)	No (1)	No (1)	0.55
4	High	No	No	Yes	No (1)	No (1)	No (1)	No (2)	0.55
5	High	No	No	Yes	No (1)	No (1)	No (1)	No (2)	0.55
6	High	No	No	Yes	No (1)	No (1)	No (1)	No (1)	0.85
7	High	No	No	Yes	No (1)	No (1)	No (1)	No (2)	0.85
8	Low	No	No	Yes	No (1)	No (1)	No (1)	No (2)	0.85
9	Low	No	Yes	No (2)	No (4)	No (2)	No (2)	No (3)	0.17
10	Low	No	No	Yes	No (1)	No (1)	No (1)	No (2)	0.55
Note: GI, gastro intestinal; BBB, blood–brain barrier; PGP, p-glycoprotein									

Table 2: Pharmacokinetics and Drug-Likeness Parameters of The Selected Phytocompounds From Carica Papaya Seed Extract

Compound	NP class probability	Prediction
C1	1	Possible NP-likeness
C2	1	Possible NP-likeness
C3	0.98	Possible NP-likeness
C4	0.98	Possible NP-likeness
C5	1	Possible NP-likeness
C6	1	Possible NP-likeness
C7	1	Possible NP-likeness
C8	1	Possible NP-likeness
C9	0.97	Possible NP-likeness
C10	1	Possible NP-likeness
NP-likeness: Natural product-likeness and 1: Perfect score		

Table 3: Estimation of Natural Product-Likeness Characteristics of Selected Phyto-Compounds

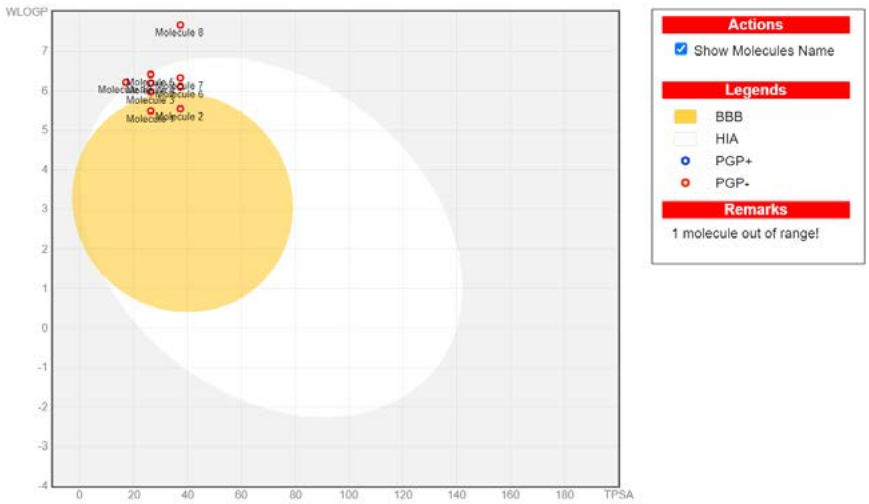


Figure 2: The Boiled-egg Model Illustrates the Absorption of Molecules in the Gastrointestinal Tract and Their Penetration into the Brain. Molecules Located in The Yolk of The Boiled Egg Are Hypothesized to Passively Traverse the Blood-Brain Barrier (BBB). In Contrast, Molecules in The Egg White Are Believed to Be Passively Absorbed by The Digestive Tract. *p* -Glycoproteins (PGPs) are Thought to Expel Blue-Dotted Molecules from the Central Nervous System (CNS)

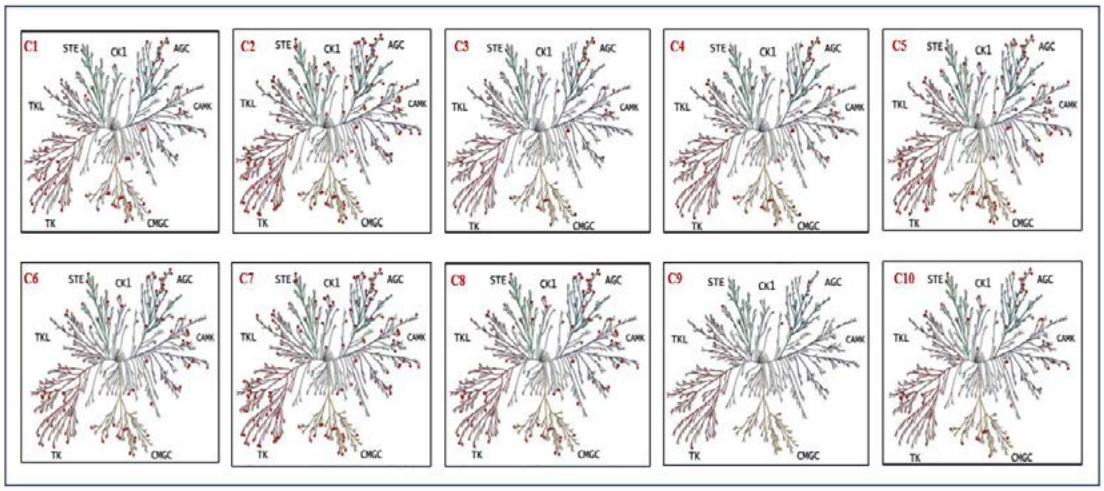


Figure 3: Mapped Kinome Tree Visualization of The Possible Distribution of Identified Compounds (C1-C10) Across the Kinase Families. AGC: Containing PKA, PKG, PKC Families; CAMK: Calcium/Calmodulin-Dependent Protein Kinase; CK1: Casein Kinase 1; CMGC: Containing CDK, MAPK, GSK3, CLK Families; STE: Homologs of Yeast Sterile 7, Sterile 11, Sterile 20 Kinases; TK: Tyrosine Kinase and TKL: Tyrosine Kinase-like

3.4. Kinase Targets Prediction

In this study, the likelihood of our compound interacting with key kinase classes was assessed, as illustrated in Figure 3. The findings show that compounds (C1, C2, C5, C6, C7 & C8) had good distribution profile across kinase families with compound 2 exhibiting the best target in the kinase members including TK (tyrosine kinase), AGC (containing PKA, PKG and PKC families) and CMGC (containing CDK, MAPK, GSK3 and CLK families). Compounds 3, 4, 9 and 10 did not show a good distribution profile across kinase families. The results align with previous analyses of the ADME profile and assessments of drug-likeness. The study further revealed that compound 2, 6, 7 and 8 could potentially target and regulate the MAP kinase-activated protein kinase 5 with a significant confidence score of p = 0.71, 0.63, 0.71 and 0.63. Compounds 3 and 4 could potentially target and regulate Protein kinase C alpha with a significant confidence score of p = 0.46 and 0.41. Compound 9 could potentially target and regulate Tyrosine-protein kinase SRC and did not show any significant confidence score. Compound 10 could potentially target and regulate MAP kinase ERK1 with a significant confidence score of p = 0.36 as presented in Table 4. The confidence score denotes the differential possibility betwixt a compound's likelihood to inhibit a particular kinase and its possibility not to inhibit the same kinase [21]. Table 4 summarises the main classes of kinases targeted by identified compounds. Mitogen-activated protein kinases (MAPKs) play a crucial role in mediating inflammatory responses and cellular stress during viral infections. MAPK signalling in dengue virus (DENV) infection reveals that this pathway contributes to the regulation of inflammatory responses and hepatocyte apoptosis in both *in vitro* and *in vivo* models. Reports revealed that modulation of MAPK signalling can mitigate the inflammatory response and reduce hepatic cell apoptosis associated with DENV infection [22,23,24].

3.5. Protein Kinase Calpha

Protein kinases (PKs) catalyse the phosphorylation of proteins, primarily targeting serine, threonine, and tyrosine residues. These enzymes play a pivotal role in cellular signaling pathways, regulating essential cellular processes such as growth, differentiation, and metabolism [25]. Phosphorylated proteins can trigger a downstream cascade of molecular events, leading to diverse cellular responses such as modulation of enzyme activities through activation or inhibition, alterations in biological function, regulation of intracellular trafficking, and the facilitation or disruption of protein-protein interactions [26,27]. It was reported that PKC may function as a regulatory mechanism that modulates dengue virus (DENV) replication and suppresses viral proliferation within host cells. The *in-silico* studies revealed that the non-structural protein 5 (NS5), predominantly within the RNA-dependent RNA polymerase (RdRp) domain, harbors conserved phosphorylation sites for protein kinase C (PKC). This phosphorylation of NS5 RdRp was confirmed using an in vitro kinase assay with PKC. Inhibition of PKC through a specific chemical inhibitor or siRNA reduced NS5 phosphorylation *in vivo*, leading to enhanced viral replication and decreased viability of DENV-infected cells. Conversely, activation of PKC significantly suppressed the intracellular viral load [28].

3.6. MAP Kinase ERK1

The MAPK family, a class of serine/threonine kinases, encompasses three principal subclasses: p38 MAPK, JNK, and ERK1/2, which mediate crucial signaling cascades [29]. DENV infection has been shown to activate ERK1/2 in hepatocytes, endothelial cells, and macrophages [30,31,32]. Nonetheless, ERK1/2 activation is remarkably attenuated in DENV-infected A549 human alveolar epithelial carcinoma cells, highlighting cell-type specific differences in ERK1/2 signaling responses to DENV infection [33]. Sreekanth et al. demonstrated that Dengue Virus (DENV) infection triggers the phosphorylation and activation of Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2) *in vivo*. Notably, pharmacological inhibition of ERK1/2 using FR180204 significantly attenuated immune cell-mediated liver injury during DENV infection, suggesting a critical role for ERK1/2 signaling in the pathogenesis of DENV-induced liver damage [34].

Compound	Name	UniProt ID	ChEMBL ID	Confidence score
1	MAP kinase ERK1	P27361	CHEMBL3385	0.45
	Protein kinase C alpha	P17252	CHEMBL299	0.44
	Dual-specificity tyrosine-phosphorylation regulated kinase 2	Q92630	CHEMBL4376	0.41
2	MAP kinase-activated protein kinase 5	Q8IW41	CHEMBL3094	0.71
	MAP kinase ERK1	P27361	CHEMBL3385	0.7
	Serine/threonine-protein kinase 11	Q15831	CHEMBL5606	0.62
3	Protein kinase C alpha	P17252	CHEMBL299	0.46
	cGMP-dependent protein kinase 1 beta	Q13976	CHEMBL4273	0.37
	Protein kinase C epsilon	Q02156	CHEMBL3582	0.36
4	Protein kinase C alpha	P17252	CHEMBL299	0.44
	cGMP-dependent protein kinase 1 beta	Q13976	CHEMBL4273	0.42
	Dual-specificity tyrosine-phosphorylation regulated kinase 2	Q92630	CHEMBL4376	0.38

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5	MAP kinase ERK1	P27361	CHEMBL3385	0.5
	cGMP-dependent protein kinase 1 beta	Q13976	CHEMBL4273	0.48
	Serine/threonine-protein kinase 11	Q15831	CHEMBL5606	0.44
	Dual-specificity tyrosine-phosphorylation regulated kinase 2	Q92630	CHEMBL4376	0.44
6	MAP kinase-activated protein kinase 5	Q8IW41	CHEMBL3094	0.63
	Serine/threonine-protein kinase 11	Q15831	CHEMBL5606	0.55
	MAP kinase ERK1	P27361	CHEMBL3385	0.54
7	MAP kinase-activated protein kinase 5	Q8IW41	CHEMBL3094	0.71
	MAP kinase ERK1	P27361	CHEMBL3385	0.7
	Serine/threonine-protein kinase 11	Q15831	CHEMBL5606	0.62
8	MAP kinase-activated protein kinase 5	Q8IW41	CHEMBL3094	0.63
	Serine/threonine-protein kinase 11	Q15831	CHEMBL5606	0.55
	MAP kinase ERK1	P27361	CHEMBL3385	0.54
9	Tyrosine-protein kinase SRC	P12931	CHEMBL267	
	Protein kinase C alpha	P17252	CHEMBL299	
	3-phosphoinositide dependent protein kinase-1	O15530	CHEMBL2534	
10	MAP kinase ERK1	P27361	CHEMBL3385	0.36
	Dual-specificity tyrosine-phosphorylation regulated kinase 2	Q92630	CHEMBL4376	0.34
	cGMP-dependent protein kinase 1 beta	Q13976	CHEMBL4273	0.33

Table 4: Main Classes of Kinases Targeted by Identified Compounds

3.7. Antiviral Properties Prediction

Initially *Carica papaya* juice has been used traditionally for the treatment and management of dengue fever [35,36]. *Carica papaya* juice extract has been studied for its anti-dengue effect *in vitro, in vivo* and in clinical trials [14,37-47]. In this context, this work investigated the antiviral properties of the studied compounds for its anti-dengue effect Table 5. Interestingly, the compounds (C1-C8, C10) were potentially active against dengue virus type 2 except for compound 9. The compounds were active against dengue virus genome polyprotein based on the confidence score. Compounds 2 and 7 has the highest confidence level of 0.6981 and the most active against dengue virus type 2 followed by compounds 6 and 8 with confidence level of 0.63 having a potency slightly more pronounced. This is followed by compounds 5: 0.5404 confidence level, compounds 4: 0.4544 confidence level, compounds 1: 0.442 confidence level, compounds 3: 0.4069 confidence level, and compounds 10: 0.34 confidence level were slightly active against dengue virus type 2. Compound 9 has no predicted antiviral property against dengue virus type 2 but against Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3) with a very low confidence score: 0.1244. The predicted anti-dengue properties of the compounds agree with previously studied effects of *Carica papaya* extract and juice against dengue virus *in vitro, in vivo* and in clinical trials. The compounds were also potentially active against severe acute respiratory syndrome coronavirus 2 targeting the replicase polyprotein 1ab based on the on the confidence score. All the compounds (C1-C8) were potentially active against severe acute respiratory syndrome coronavirus 2 except for compound 9 and 10 Table 5. Dengue is a serious public health problem around the world [48]. Dengue is responsible for a wide spectrum of clinical illnesses, ranging from mild, self-limiting forms of the disease associated with fever, condition, and other non-specific symptoms to more serious, potentially fatal cases, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [49]. Despite years of study, specific treatment approaches for dengue fever are still in their early stages. Several antiviral medications and other host immune modulators are still in clinical testing and will not be available anytime soon [50]. There are various dengue vaccines in development, and a few have already been approved for use, but there is no clear evidence of efficacy across all age groups, and they do not confer immunity to all serotypes [51].

Compound	Virus	Protein target	Confidence
C1	Dengue virus type 2	Genome polyprotein	0.442
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.2626
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.2252
	Middle East respiratory syndrome-related coronavirus (isolate United Kingdom/H123990006/2012) (Beta-coronavirus England 1) (Human coronavirus EMC)	Replicase polyprotein 1ab	0.138
	SARS coronavirus	Replicase polyprotein 1ab	0.1085
C2	Dengue virus type 2	Genome polyprotein	0.6981
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.488
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.2556
	Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3)	DNA polymerase	0.2166
	Herpes simplex virus (type 1 / strain 17)	Human herpesvirus 1 DNA polymerase	0.2166
	Middle East respiratory syndrome-related coronavirus (isolate United Kingdom/H123990006/2012) (Beta-coronavirus England 1) (Human coronavirus EMC)	Replicase polyprotein 1ab	0.1371
	Macacine herpesvirus 1	Thymidine kinase	0.1156
	SARS coronavirus	Replicase polyprotein 1ab	0.1152
	Human immunodeficiency virus 2	Human immunodeficiency virus type 2 pol protein	0.1147
C3	Dengue virus type 2	Genome polyprotein	0.4069
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.2726
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.1881
C4	Dengue virus type 2	Genome polyprotein	0.4544
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.3314
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.2294
C5	Dengue virus type 2	Genome polyprotein	0.5404
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.456
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.3239
	Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3)	DNA polymerase	0.1424
	Herpes simplex virus (type 1 / strain 17)	Human herpesvirus 1 DNA polymerase	0.1424
	Middle East respiratory syndrome-related coronavirus (isolate United Kingdom/H123990006/2012) (Beta coronavirus England 1) (Human coronavirus EMC)	Replicase polyprotein 1ab	0.1218
	Dengue virus type 2 (strain Thailand/16681/1984) (DENV-2)	Dengue virus type 2 NS3 protein	0.1033
C6	Dengue virus type 2	Genome polyprotein	0.63
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.3581
	Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3)	DNA polymerase	0.1417
	Herpes simplex virus (type 1 / strain 17)	Human herpesvirus 1 DNA polymerase	0.1417
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.1304
	Middle East respiratory syndrome-related coronavirus (isolate United Kingdom/H123990006/2012) (Beta-coronavirus England 1) (Human coronavirus EMC)	Replicase polyprotein 1ab	0.1126

C7	Dengue virus type 2	Genome polyprotein	0.6981
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.488
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.2556
	Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3)	DNA polymerase	0.2166
	Herpes simplex virus (type 1 / strain 17)	Human herpesvirus 1 DNA polymerase	0.2166
	Middle East respiratory syndrome-related coronavirus (isolate United Kingdom/H123990006/2012) (Beta-coronavirus England 1) (Human coronavirus EMC)	Replicase polyprotein 1ab	0.1371
	Macacine herpesvirus 1	Thymidine kinase	0.1156
	SARS coronavirus	Replicase polyprotein 1ab	0.1152
	Human immunodeficiency virus 2	Human immunodeficiency virus type 2 pol protein	0.1147
C8	Dengue virus type 2	Genome polyprotein	0.63
	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab	0.3581
	Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3)	DNA polymerase	0.1417
	Herpes simplex virus (type 1 / strain 17)	Human herpesvirus 1 DNA polymerase	0.1417
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.1304
	Middle East respiratory syndrome-related coronavirus (isolate United Kingdom/H123990006/2012) (Beta-coronavirus England 1) (Human coronavirus EMC)	Replicase polyprotein 1ab	0.1126
C9	Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3)	DNA polymerase	0.1244
	Herpes simplex virus (type 1 / strain 17)	Human herpesvirus 1 DNA polymerase	0.1244
C10	Dengue virus type 2	Genome polyprotein	0.34
	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase	0.1805
	Middle East respiratory syndrome-related coronavirus (isolate United Kingdom/H123990006/2012) (Beta coronavirus England 1) (Human coronavirus EMC)	Replicase polyprotein 1ab	0.1516
	Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3)	DNA polymerase	0.1379
	Herpes simplex virus (type 1 / strain 17)	Human herpesvirus 1 DNA polymerase	0.1379
	Dengue virus type 2 (strain Thailand/16681/1984) (DENV-2)	Dengue virus type 2 NS3 protein	0.1359
	West Nile virus	Genome polyprotein	0.1055

Table 5: Antiviral Properties of the Test Compounds

3.8. Gene Expression Profiles

Gene expression profiles of the compounds were analysed. Table 5 (supplementary) showed a significant upregulation and downregulation processes has been exerted by the phyto-compounds on the mRNA expression of key genes. The genes were further analysed for identification of overlapping genes among the different compounds. Interestingly, Interleukin 23 Subunit Alpha (IL23A) gene was upregulated and common among the compounds (C1-10). Compound 5, 4 and 1-3 could significantly increase the mRNA expression of IL23A genes with a respective value of Pa=0.732, Pa=0.722 and Pa=0.716. Combines with IL12B to generate the pro-inflammatory cytokine IL-23, functions in both adaptive and innate immunity in distinct ways [52]. Produced by antigen-presenting cells like macrophages or dendritic cells. It binds to a heterodimeric receptor complex made up of IL12RB1 and IL23R, activating JAK2 and TYK2, which phosphorylate the receptor and create a docking site where STAT3 and STAT4 are phosphorylated [53,54,55]. Upon DENV infection, macrophages produce IL-23, a key cytokine that drives the activation of Th17 cells, a subset of CD4+ T cells characterized by the production of interleukin-17 (IL-17). The ensuing Th17-associated responses contribute to the initiation of antiviral mechanisms, highlighting the importance of IL-23-mediated signaling in coordinating immune defenses against DENV infection [56].

Conversely, analyses of the unique downregulated genes revealed Metallothionein 1H (MT1H), ELAV Like RNA Binding Protein 1 (ELAVL1) and SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin Subfamily C Member 1 (SMARCC1) as the overlapping genes. The compounds could effectively decrease the mRNA expression of MT1H with the following values; C1-C3 = 0.504, C4 = 0.657, C5 = 0.752, C6 & C8 = 0.857, C7 = 0.897, C10 = 0.58. Compound 7 significantly decrease MT1H mRNA expression compared other compounds. MT1H (Metallothionein 1H) is a gene that codes for a protein involved in several biological pathways, including metal ion SLC transporters and cellular responses to stimuli. A significant paralog of this gene is MT1HL1. MT1H is predicted to facilitate zinc ion binding activity and plays a role in the cellular response to cadmium and zinc ions. The protein is expected to be active in the cytoplasm and nucleus. This gene has been linked to multiple viral illnesses and is involved in several biological processes. The MT1H gene is associated with dengue disease, with connections established either through curated associations or inferred via curated chemical interactions [57]. Compounds 6 and 8 could efficiently decrease the mRNA expression of ELAVL1 and SMARCC1 with a respective value of Pa=0.857 and Pa=0.809.

The ELAVL1 gene encodes a member of the ELAV-like family of RNA-binding proteins, distinguished by multiple RNA recognition motifs (RRMs). These proteins selectively interact with adenine- and uridine-rich elements (AREs) situated in the 3' untranslated regions (3' UTRs) of messenger RNAs (mRNAs), thereby regulating mRNA stability and turnover. By binding to AREs, ELAVL proteins exert a stabilizing effect on ARE-containing mRNAs, modulating gene expression. ELAVL1 has been implicated in various biological processes and has been linked to several viral diseases. Although its direct involvement in dengue pathogenesis remains unclear, ELAVL1/HuR has been identified as a crucial regulator of microRNA-122 (miR-122) and Hepatitis C virus (HCV) replication, suggesting a potential role in HCV-associated diseases [58]. HCV, a member of the Hepacivirus genus within the *Flaviviridae* family, possesses a single-stranded positive-sense RNA genome [59]. Our findings revealed that the compounds could effectively decrease the mRNA expression of MT1H with the following values; C1-C3 = 0.626, C4 = 0.616, C5 = 0.668, C6 & C8 = 0.822, C7 = 0.847, C10 = 0.826. Significant decrease in the mRNA expression of ELAVL1 was observed in compound 7.

SMARCC1 (SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin Subfamily C Member 1) is a gene that encodes a protein associated with several critical biological processes, including gene expression (transcription) and chromatin organization. Pathogenic variants in SMARCC1 have been connected to congenital hydrocephalus types 5 and general congenital hydrocephalus. Additionally, SMARCC1 has been implicated in various viral diseases, most notably COVID-19 [60]. Additionally, SMARCC1 plays a role in the transcriptional activation and repression of definite genes through chromatin remodelling. It is a constituent of the SWI/SNF chromatin remodelling complexes, which perform crucial enzymatic activities by altering chromatin structure through alterations of DNA-histone contacts within nucleosomes in an ATP-dependent manner. SMARCC1 is also thought to increase the ATPase action of the complex's catalytic subunit [61,62]. The compounds could effectively decrease the mRNA expression of SMARCC1 with the following values; C1-C3 = 0.776, C4 = 0.641, C5 = 0.698, C6 & C8 = 0.809, C7 = 0.845, C10 = 0.656. Similarly, compound 7 Significant decrease in the mRNA expression of SMARCC1.

The Overlapping genes of the upregulation (IL23A) and downregulation (MT1H, ELAVL1 and SMARCC1) processes were also analysed for its functional role in viral diseases. Data obtained from Comparative Toxicogenomics Database revealed that IL23A is upregulated in dengue virus and COVID-19 diseases with an inference score of 8.2 and 13.2 respectively. Similarly, mRNA expression of MT1H genes was downregulated in dengue virus diseases only with an inference score of 3.58. The mRNA expression of MT1H, ELAVL1 and SMARCC1 downregulated genes were implicated in COVID-19 disease with inference score of 15.43, 7.38 and 5.7 respectively.

4. Conclusion

The data revealed that biologically active compounds from *Carica papaya* seeds extract could serve as potent antiviral agents against DENV-2. Computational analysis unveiled that, compounds 2 and 7 exhibited the optimum antiviral potency, whereas other compounds also exhibited promising drug-like properties, kinase specificity, and natural product-likeness. Gene expression profiling analysis showed overlapping differentially expressed genes. IL23A was upregulated while MT1H, ELAVL1, and SMARCC1 were downregulated. The findings suggest that the compounds could exert antiviral activity through modulation of important genes of the immune system, hence making them potential candidates for antiviral development [64,65].

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