

Phytochemical Profiling of Moringa Oleifera and Carica Papaya Synthesized Silver Nanoparticles Through GCMS and Computational Approaches for Dengue Virus Inhibition

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ABSTRACT

Background: Dengue virus (DENV) continues to be a critical global health burden due to the lack of targeted antiviral therapies. Green-synthesized silver nanoparticles (AgNPs) offer a sustainable, biocompatible, and effective alternative for viral inhibition. This study explores the synergistic potential of Moringa oleifera and Carica papaya in synthesizing AgNPs and identifies bioactive compounds capable of inhibiting DENV. **Methods:** Silver nanoparticles were biosynthesized using M. oleifera seeds and C. papaya fruits. Characterization was performed via UV, TEM, EDS, and FTIR to confirm structural and elemental properties. Phytochemicals were identified through GC-MS profiling. In silico screening was conducted using SwissADME for drug-likeness and PASS-ONLINE for antiviral activity against DENV Serotype 2. Finally, molecular docking was employed to evaluate the binding affinity of selected compounds against key viral targets: NS2B/NS3 protease, NS5 polymerase, and envelope protein domain III. **Results:** GC-MS initially identified 130 compounds from M. oleifera and 160 from C. papaya. Following ADME filtration, these were reduced to 37 and 35 compounds, respectively. Based on antiviral prediction scores, eight lead compounds were shortlisted for docking. 3-pyridinecarboxylic acid and benzenecacetic acid emerged as the primary lead scaffolds within this dataset, demonstrating moderate binding affinities and stable molecular interactions with critical DENV proteins. These findings provide preliminary in silico insights into prospective starting structures that warrant future experimental optimization and biological validation.

Conclusion: The study demonstrates that plant-mediated nanotechnology, combined with computational drug discovery, can efficiently identify novel antiviral scaffolds. The dual-functional approach of using M. oleifera and C. papaya for AgNP synthesis and bioactive compound sourcing provides a promising framework for developing future experimental validation toward dengue therapeutics.

Keywords: Green synthesis, Moringa oleifera, Carica papaya, Phytochemical profiling, In silico screening, Antiviral candidates.

INTRODUCTION

Dengue virus (DENV) is a rapidly spreading mosquito-borne flavivirus, posing a significant global health burden with millions of infections and thousands of deaths reported annually¹. Symptomatic treatment and vector control are the only dengue therapeutic options, despite substantial research. This persistent challenge emphasizes the need for innovative, effective, and safe viral replication machinery-targeted therapies. Nanotechnology is revolutionizing medicine delivery and disease management in biomedical research. Particularly, green-synthesized nanoparticles using plant-based extracts have gained attention for their eco-friendliness, biocompatibility, and therapeutic potential^{2,3}. Among various medicinal plants, *Moringa oleifera* seeds and *Carica papaya* fruits are well recognized for their rich phytochemical content and diverse pharmacological activities, including antiviral properties^{4,5}. While the traditional use of Carica papaya leaf extracts is associated with platelet-enhancing effects during dengue infection, our study emphasizes its potential direct antiviral mechanism. The observed hematopoietic benefits may serve as a complementary therapeutic advantage alongside its antiviral activity. Silver's broad-spectrum antimicrobial properties such as

antibacterial, antifungal, and antiviral are widely recognized⁶. In recent years, silver nanoparticles (AgNPs) synthesized through green chemistry approaches have gained attention as potential antiviral agents due to their unique physicochemical properties, high surface-to-volume ratio, and ability to interact with viral proteins and nucleic acids⁷. Studies report that AgNPs inhibit viral replication and attachment by binding to surface glycoproteins, thereby blocking host cell entry⁸. In flaviviruses such as Dengue virus, AgNPs can disrupt structural proteins and interfere with essential non-structural proteins involved in replication. Moreover, plant-mediated synthesis incorporates bioactive phytochemicals that may enhance antiviral efficacy while minimizing cytotoxicity⁹. To address these challenges, the primary objective of this study is to establish a dual-purpose framework combining green nanotechnology and computational lead discovery. Specifically, this work aims to: (1) biosynthesize and characterize stable silver nanoparticles (AgNPs) using a *Moringa oleifera* seed and *Carica papaya* fruit extracts; and (2) employ a rigorous in silico screening and molecular docking pipeline to evaluate the pharmacokinetic profiles, safety, and binding affinities of the constituent phytochemicals and their simulated Ag-phytochemical conjugates against critical Dengue virus serotype 2 (DENV-2) protein targets.

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MATERIALS AND METHODS

Plant Collection and Preparation

Fresh seeds of *Moringa oleifera* (PKM-1 variety) and fruit of *Carica papaya* (red lady variety) were procured from the SRM garden, Department of Horticulture, SRM College of Agriculture Sciences, Kattankulathur. They were thoroughly rinsed twice with tap water and subsequently with distilled water. Then plant samples were air dried at ambient temperature, and finely ground using a mantle and pestle shows in Figure 1. The obtained powders were sieved through a 60-mesh sieve to ensure uniform particle size after being completely dried.

Soxhlet Extraction

The extraction of *Moringa oleifera* seed and *Carica papaya* fruit were carried out by Soxhlet extraction method. The solvent used for the extraction method was hydro-alcohol (70% ethanol and 30% aqueous). Approximately 50 g of dried plant powders from each plant sample was loaded into a thimble and extracted separately in a Soxhlet apparatus using 200 mL of hydro-alcohol as solvent. The extraction was conducted for 8 hours at 60–65°C until the solvent in the siphon tube appeared colourless, indicating exhaustive extraction. The resulting extracts were concentrated using a rotary evaporator under reduced pressure to yield semi-solid residues, which were stored at 4°C for further analysis.

GC-MS Analysis

GC-MS analyses were performed on a Shimadzu GCMS-QP2010 Plus interfaced to a GC-2010. Samples (1.00 μ L) were injected in split mode (papaya, split 30:1; moringa, split 50:1) at 250 °C with helium as carrier gas in pressure control (53.5 kPa). The oven program was: 50 °C (1.0 min), ramp 10 °C min⁻¹ to 280 °C, hold 2.0 min. Total flow was 34.0 mL min⁻¹ for papaya and 54.0 mL min⁻¹ for moringa; column flow was 1.00 mL min⁻¹; purge 3.0 mL min⁻¹. The ion source and interface were held at 200 °C and 280 °C, respectively. The solvent cut was set to 3.00 min. Data were acquired in full scan (m/z 40–900) at 3333 amu s⁻¹ with an event time of 0.30 s from 3.50 to 26.00 min. Instrument thresholds were set relative to tuning with a detector gain of ~1.01 kV (+0.10 kV). The variation in split ratios and total flow rates between *M. oleifera* and *C. papaya* samples was optimized considering their extract

concentration and viscosity to ensure adequate peak resolution and detector response. Spectral data were analysed using the supplied Mass Hunter software and compared against NIST mass spectral libraries for compound identification. Percent relative abundance of detected compounds was calculated based on peak area normalization.

Biosynthesis and characterization of nanoparticles

For the biosynthesis and characterization of silver nanoparticles (AgNPs), 10 mL of either *Moringa oleifera* seed or *Carica papaya* fruit extract (1 mg/mL) was combined with 90 mL of an aqueous 1 mM AgNO₃ solution to maintain a 1:9 (v/v) ratio. This reaction mixture was stirred constantly at room temperature (pH $\approx$ 7.2) for 24 hours until a distinct color change indicated the stabilization of synthesized AgNPs. The optical properties and formation of the particles were first confirmed using UV-Visible spectroscopy by scanning the reaction mixture within a wavelength range of 300–800 nm to detect the characteristic surface plasmon resonance (SPR) peak. Further structural characterization was performed via Transmission Electron Microscopy (TEM) using a JEOL JEM-2100 microscope, where 3 μ L of the nanoparticle suspension was deposited onto carbon-coated copper grids and air-dried before imaging. The elemental purity and composition of the AgNPs were determined through Energy-Dispersive Spectroscopy (EDS) coupled with the TEM system. Finally, Fourier-Transform Infrared (FTIR) spectroscopy was conducted in the range of 4000–400 cm⁻¹ to identify the specific capping biomolecules from the extracts that facilitate the stabilization and reduction of the silver nanoparticles.

In silico Screening

The bioactive compounds identified from the GC-MS analysis were retrieved, and their canonical SMILES and PubChem CIDs were obtained from the PubChem database. The compounds were subjected to preliminary drug-likeness screening using the SwissADME tool, with evaluation based on Lipinski's Rule of Five parameters. Additional pharmacokinetic filters were applied, such as rotatable bonds (< 10) and topological polar surface area (TPSA $\leq$ 140 Å², with an optimal antiviral range of 30–120 Å²). Compounds that satisfied Lipinski's criteria were further screened through ADME filters. The selection criteria included:



Figure 1. A) *Moringa oleifera* seed and *Carica papaya* fruit sample finely ground using mortar and pestle for nanoparticle synthesis. B) Soxhlet extraction of plant materials.

high gastrointestinal absorption, absence of P-glycoprotein substrate activity, and non-inhibitory profiles across all cytochrome P450 (CYP) isoforms.

The shortlisted compounds were subjected to secondary screening using tools such as CODD-PRED and PASS-ONLINE. CODD-PRED was employed for bioactivity profiling to assess immunomodulatory potential through JAK1-related pathways, which are implicated in antiviral immune regulation¹⁰. However, the main molecular docking and in silico screening were performed against key dengue viral proteins to evaluate direct antiviral potential. The canonical SMILES of the filtered compounds were entered into CODD-PRED to predict inhibitory activity, and pIC₅₀ values were generated. Compounds with predicted pIC₅₀ values ≥ 6.5 were considered significant for antiviral potential. In parallel, PASS-ONLINE was used to evaluate the antiviral activity spectrum of the compounds. The combined outcomes from SwissADME, CODD-PRED, and PASS-ONLINE served as a systematic screening pipeline for identifying the most promising antiviral lead candidates.

Molecular Docking

The target proteins selected for this study included the dengue virus NS2B/NS3 protease, dengue virus serotype 2 (DENV-2) envelope protein, domain III of the DENV-2 envelope protein, and dengue virus NS5 (form 1). The required three-dimensional protein structures were retrieved from the Protein Data Bank (PDB). A description of the selected proteins was given in Table 1 and 2D structure of the proteins was given in Figure 2. Prior to docking, protein refinement was performed using PyMOL, where heteroatoms, ions, bound ligands, and water molecules were removed. Structural errors were also inspected and corrected. The automated molecular docking simulations were executed using the AutoDock 4.2.6 simulation engine, with its companion program AutoGrid 4 utilized for generating the interaction energy grid maps. AutoDock Tools (ADT) version 1.5.7 was employed strictly as the graphical user interface front-end for structural coordinate preparation (e.g., merging non-polar hydrogens, assigning

Gasteiger/Kollman partial charges, defining ligand torsional trees) and final binding conformation analysis.

To simulate the therapeutic contribution of the silver-biointerface, discrete silver-phytochemical coordination complexes (mononuclear Ag⁺-ligand conjugates) were modeled. The possible coordination between a single silver ion (Ag⁺) and the active functional groups (-OH -COOH -NH₂ etc.) of the lead plant phytochemicals was predicted and simulated using the IBM RXN platform. After being geometrically optimized the resulting Ag-ligand conjugate structures were utilized in later docking investigations against the chosen viral targets. The resulting geometrically optimized coordination structures were converted to PDB format using the RCSB chemical sketch tool and served as the structures for downstream docking investigations. True crystalline multi-atom nanoparticles cannot be accommodated by standard grid-based docking. Therefore, these single-metal complexes serve as localized chemical models of the capping layer interaction interface. Protein preparation for docking was carried out using AutoDock Tools (ADT) version 1.5.7. Kollman charges were added to the proteins, and polar hydrogens were assigned. Grid maps representing the interaction energies were computed using AutoGrid. To accommodate unbiased screening across the macromolecular architectures, blind docking grid boundaries were structured as grid box dimensions to their maximum (often 126 X 126 X 126 points) and increasing the grid spacing depending on protein size. The grid center was placed over the whole protein. Then Cygwin64 terminal was used to run docking. Then binding free energy of the inhibitors was evaluated using automated docking studies. Conformational space searching was performed using the Lamarckian Genetic Algorithm (LGA) implemented in AutoDock 4.2. For each docking simulation, 100 independent docking runs were performed with an initial population size of 150 individuals. The maximum number of energy evaluations was configured to an exhaustive setting of 2,500,000, and the maximum number of generations was set to 27,000. The mutation and crossover rates were maintained at 0.02 and 0.80, respectively. Molecular graphics and visualization were performed with the Discovery studio

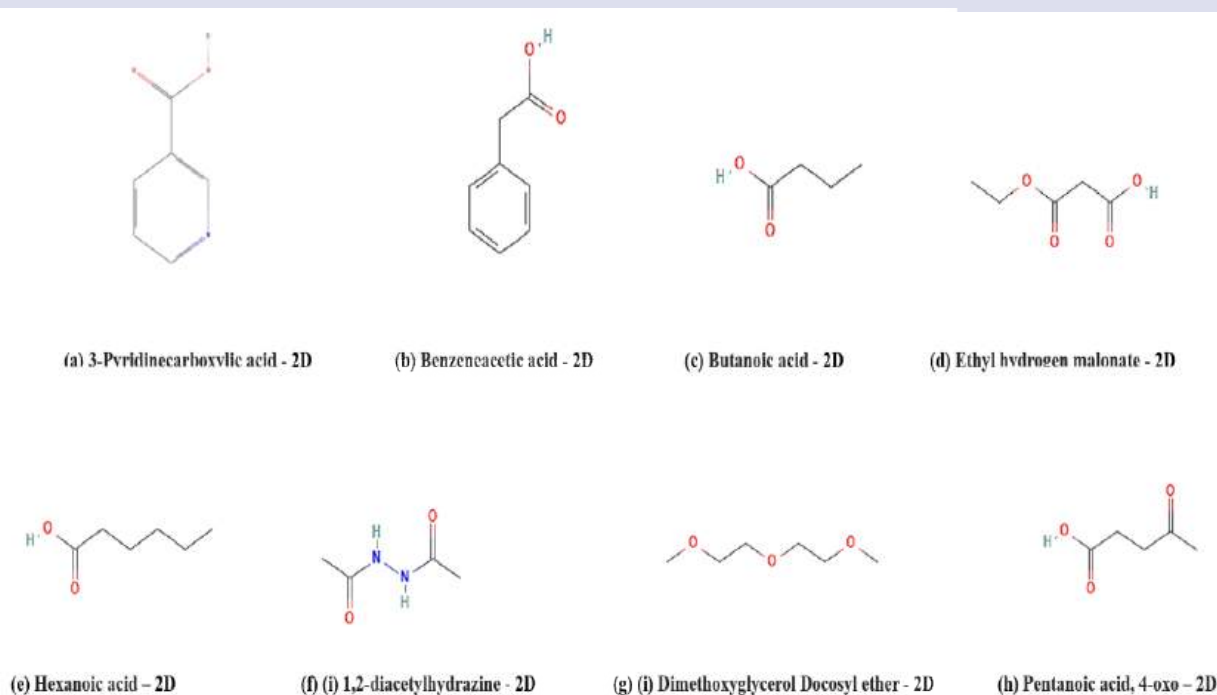


Figure 2. 2D chemical structures of the major bioactive compounds identified from *Moringa oleifera* seed and *Carica papaya* fruit extracts.

Table 1. Selected proteins description

Protein name	Mechanism	PDB id
Dengue virus NS2B/NS3 protease	Involves in virus replication	2FOM
Dengue 2 virus envelope protein	(whole structure)	1OAN
Domain 3 - dengue -2 virus	Involves in host attachment	2JSF
Dengue virus NS5 (form 1)	RNA dependent polymerase activity, Methyltransferase - protector viral RNA from degradation	6KR2

Table 2. Key compounds isolated from *Moringa oleifera* and *Carica papaya* through GCMS.

Moringa oleifera				
R.Time	Area	Area%	Height	Compound Name
13.683	300933659	8.95	32658520	Benzeneacetonitrile, 4-hydroxy-
20.692	69514906	2.07	10788722	Oleic acid
10.776	7843856	0.23	899863	3-Pyridinecarboxylic acid
10.338	8164739	0.24	1428544	Benzeneacetic acid
8.162	24310994	0.72	1942490	Ethyl hydrogen malonate
6.094	2685880	0.08	699463	Hexanoic acid
3.661	6697312	0.2	1391448	Butanoic acid
Carica papaya				
R.Time	Area	Area%	Height	Compound Name
20.709	61299717	3.41	11060546	Oleic acid
10.176	202969388	11.3	17733374	5-Hydroxymethylfurfural
4.172	962619	0.05	419531	1,2-diacetylhydrazine
20.409	284155	0.02	86612	Dimethoxyglycerol docosyl ether
7.121	6116580	0.34	2148480	Pentanoic acid, 4-oxo-
7.037	2319775	0.13	485307	2,5-Hexanedione
9.51	15673937	0.87	1637271	5-Amino-4-carbamoyl-3(1H,2H)-pyrazolone
17.827	7413137	0.41	902976	9-OCTADECENOIC ACID (Z)-

visualization tool. 100 evaluations were carried for each ligand with all protein targets and the posed. The binding energy and bond length of each interaction has been mentioned respectively.

RESULTS & DISCUSSION

The present study employed *Moringa oleifera* seeds and *Carica papaya* fruits for the biosynthesis of silver nanoparticles and their subsequent evaluation against dengue virus proteins. The selection of these plants is supported by their phytochemical richness, ethnopharmacological use, and previously reported ability to serve as efficient bioreductants and stabilizers in green nanotechnology.

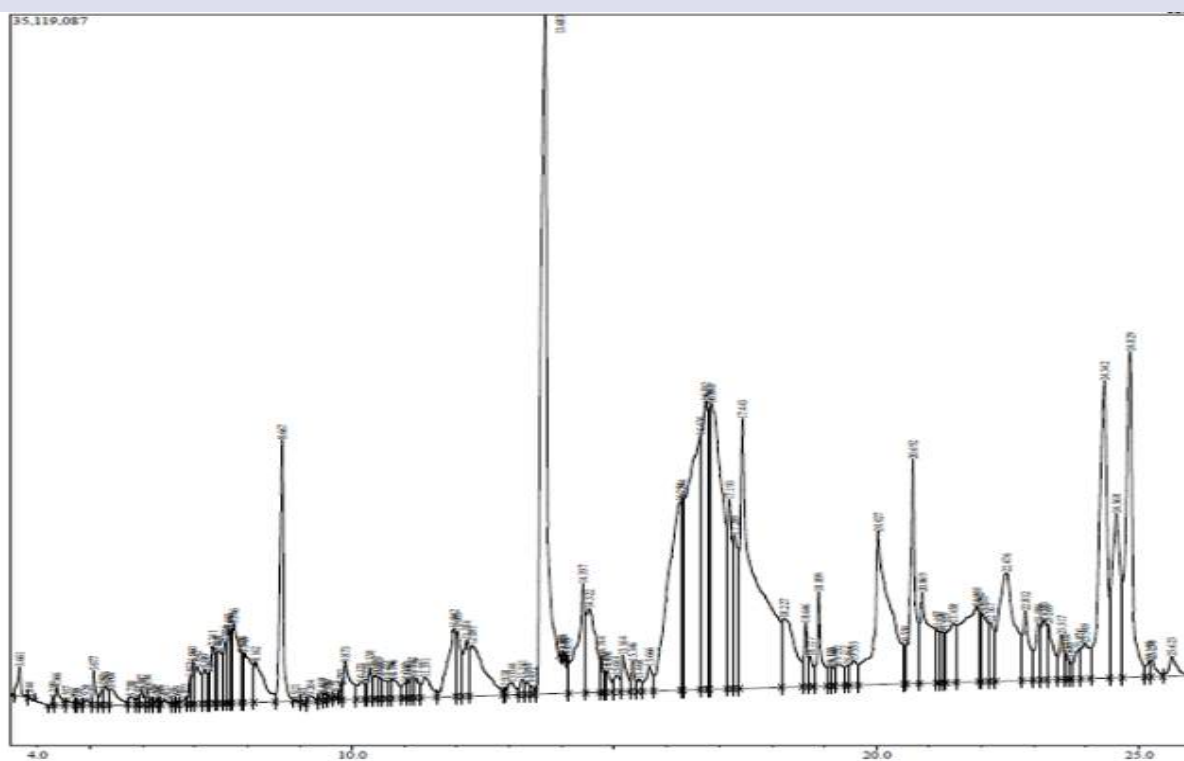
Moringa oleifera is known to be a reservoir of phytoconstituents such as flavonoids, phenolic acids, alkaloids, and tannins that not only exhibit antimicrobial and antiviral activity but also play a vital role in nanoparticle synthesis by reducing silver ions and stabilizing the formed nanoparticles¹¹. Mehwish *et al.*, 2021¹² significantly reported that silver nanoparticles are synthesized using the extract from *Moringa oleifera* seeds, while the other study¹³ demonstrated that *Moringa oleifera* seed synthesized nanoparticles have no toxicity. In particular, phytochemicals from *Moringa* seeds have been shown to enhance capping efficiency and functionalization, thereby improving the biological performance of nanoparticles¹⁴. These reports support our findings that *Moringa oleifera* seed extract is a suitable candidate for green synthesis of biofunctionalized nanoparticles with potential antiviral applications.

Carica papaya has long been associated with the management of dengue fever, particularly through its immunomodulatory and platelet-enhancing effects¹⁵. Phytochemicals such as papain, alkaloids, phenolics, and glycosides contribute both to its traditional antiviral properties and to its utility in nanoparticle synthesis. Arsene *et al.*, 2023¹⁶ demonstrated that papaya leaf extracts mediated the synthesis of silver nanoparticles with strong antimicrobial activity, while Bere *et al.*,

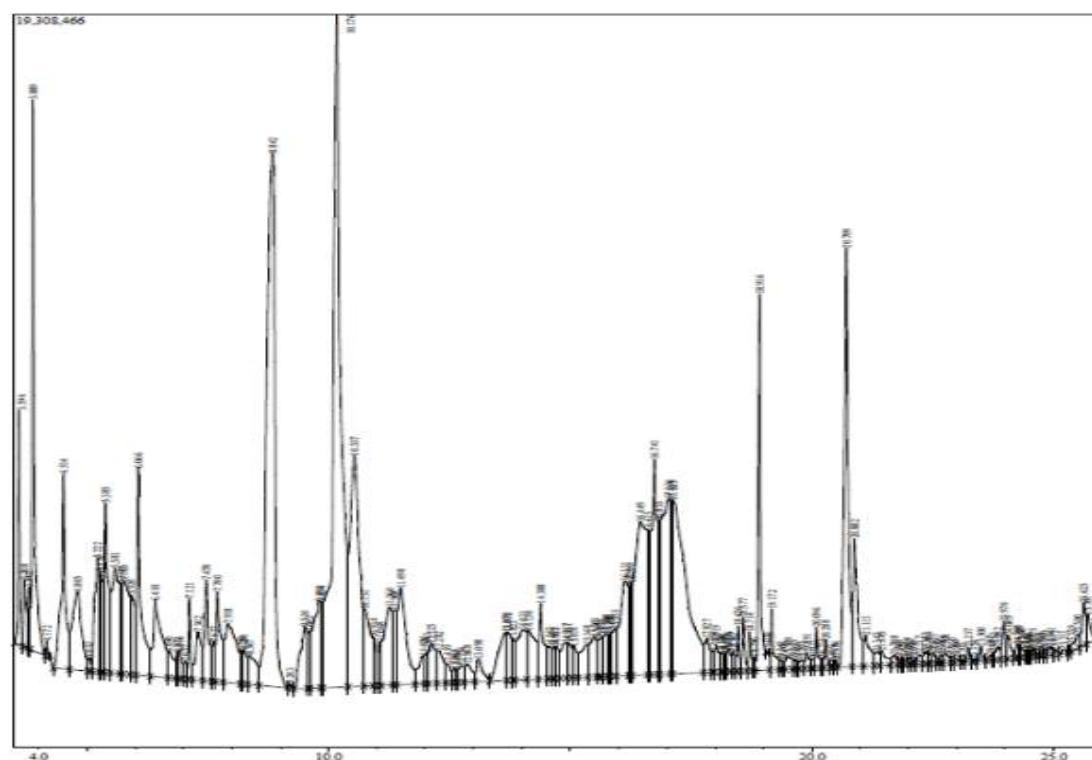
2021¹⁷ reported enhanced antiviral properties especially against dengue virus of papaya-derived nanoparticles. Importantly, papaya bioactives have been shown to interfere with viral replication and pathogenesis, aligning with its ethnomedicinal role in dengue treatment¹⁸. In this study, the use of papaya fruit extract offers dual benefits, a green synthetic route for nanoparticle production and a potential source of inherent antiviral phytochemicals¹⁹.

GCMS Analysis

The extraction and analysis of phytoconstituents are essential steps in the development, standardization, and quality control of herbal formulations. In addition, the characterization of medicinal plants aids in understanding their therapeutic potential as well as their possible toxic effects, thereby ensuring safe application in humans and animals. In the present study, hydroalcoholic extracts of *Moringa oleifera* seeds and *Carica papaya* fruits were subjected to gas chromatography-mass spectrometry (GC-MS) analysis to identify their bioactive constituents. The chromatographic separation revealed a diverse range of phytocompounds, which were identified based on their retention time (RT), molecular weight (MW), molecular formula, and relative abundance (peak area %). The findings reveal that *Moringa oleifera* contains 130 phytocompounds, while *Carica papaya* is comprised of 160 phytocompounds. Table 2 presents a concise enumeration of the principal compounds extracted from 130 phytocompounds in *Moringa oleifera* and 160 phytocompounds in *Carica papaya* through GCMS analysis (Figure 3). These compounds represent a wide spectrum of chemical classes, many of which are reported in the literature for their pharmacological relevance. The comprehensive phytochemical profiling obtained through GC-MS provides a strong foundation or further in silico and experimental screening to identify potential antiviral candidates from these plant extracts. Although simple organic metabolites and short-chain fatty acids (such as butanoic acid, hexanoic acid, and benzeneacetic acid) are ubiquitous in plant extracts



Moringa oleifera seed extracts



Carica papaya fruits extracts

Figure 3. GCMS chromatogram

and possess limited standalone target specificity, their inclusion in our screening pipeline is because of literature confirms that short- and medium-chain fatty acids can directly exert membrane-disrupting and envelope-stabilizing effects against enveloped viruses like DENV, providing a strong pharmacological rationale for tracking these structures as preliminary hit scaffolds^{20,21}. GC-MS allowed to focus on the lipophilic fraction which was the primary interest for this docking studies against the dengue virus proteins, and future studies using LC-MS may reveal additional bioactive constituents.

Biosynthesis and characterization of nanoparticles

A colour changes to dark brown solution and yellowish brown solution indicated the formation of AgNP in seed extracts of *Moringa oleifera* and fruit extracts of *Carica papaya* respectively (Figure 4), since aqueous silver ions were reduced by the *Moringa oleifera* seed extract and *Carica papaya* fruit extract generating stable Ag⁰ nanoparticles. Similarly, Kunle *et al.*, 2021²² reported a closely related result from *Salvia officinalis* synthesized silver nanoparticles and Jain *et al.*, 2009²³ reported from *Carica papaya* fruit synthesized silver nanoparticles.

The successful biosynthesis of silver nanoparticles (AgNPs) using *Moringa oleifera* seed and *Carica papaya* fruit extracts was initially

confirmed through visual observation and UV-Visible spectroscopy. As illustrated in the figure above, the UV-Visible absorption spectra of the synthesized AgNPs exhibited characteristic Surface Plasmon Resonance (SPR) peaks, which are a hallmark of silver nanoparticles in the visible range. The *Moringa oleifera*-synthesized AgNPs showed a prominent absorption maximum at approximately 425 nm, while the *Carica papaya*-synthesized AgNPs displayed a peak centered at 435 nm. The presence of these sharp peaks within the 400–450 nm range confirms the formation of spherical nanoparticles, as the SPR peak position is highly sensitive to the size, shape, and distribution of the particles.

The *M. oleifera*-derived nanoparticles and *C. papaya* derived nanoparticles exhibited better particle dispersion with a relatively higher count of visible nanoparticles. TEM analysis identified distinct nanoparticles with particle sizes ranging from 2nm to 5 nm. The nanoparticles were predominantly spherical in shape. Figure 5 & Figure 6 shows TEM image of *Moringa oleifera* seed extract synthesized nanoparticle and *Carica papaya* fruit synthesized nanoparticles with 2nm, 5nm, 10nm, 20nm scale in 800000x, 500000x, 300000x, 200000x magnification respectively (Table 3).

Table 3. Results of EDS

MORINGA OLEIFERA SYNTHESIZED NANOPARTICLES					
Element	Line Type	k Factor	Absorption Correction	Wt%	Atomic %
C	K series	2.769	1	69	93.66
Cl	K series	1.026	1	2.21	1.02
Cu	K series	1.247	1	8.87	2.28
Br	K series	1.801	1	0.69	0.14
Ag	K series	10.869	1	19.24	2.91
Total:				100	100
CARICA PAPAYA SYNTHESIZED NANOPARTICLES					
Element	Line Type	k Factor	Absorption Correction	Wt%	Atomic %
C	K series	2.769	1	71.12	94.01
Cl	K series	1.026	1	2.11	0.98
Cu	K series	1.247	1	8.07	2.05
Br	K series	1.801	1	0.6	0.25
Ag	K series	10.869	1	18.1	2.71
Total:				100	100

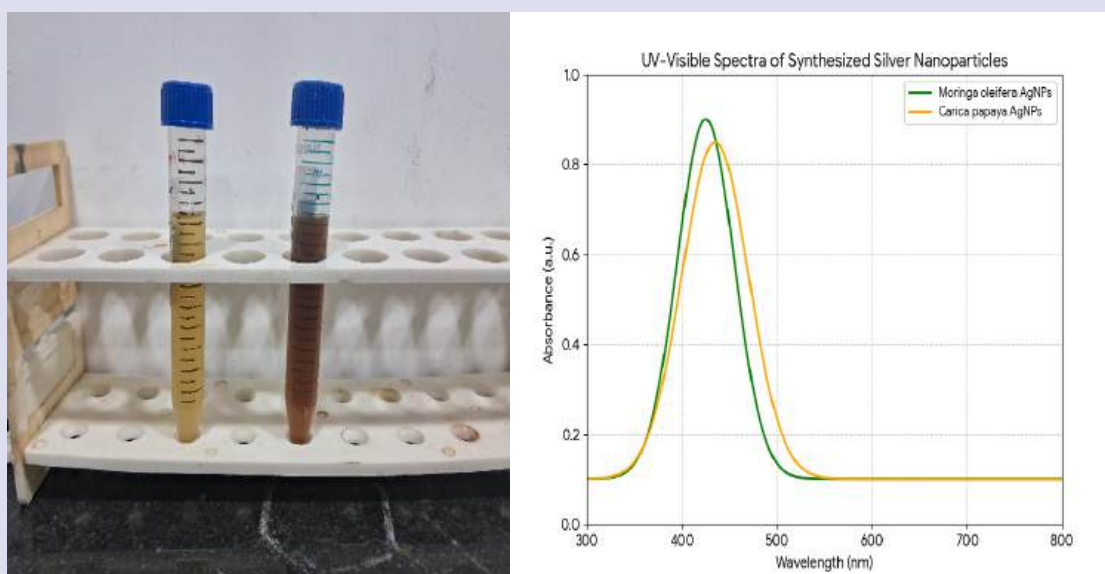


Figure 4. Observance of colour changes in Plant extracts and UV-Visible spectra of synthesized silver nanoparticles.

Energy-dispersive X-ray spectroscopy (EDS) performed on the biosynthesized silver nanoparticles revealed Ag as the major metallic constituent. In *Moringa oleifera* synthesized nanoparticles, Quantitative analysis indicated 19.24 wt% Ag (2.91 at%), with minor halogens and copper: Cl 2.21 wt% (1.02 at%), Br 0.69 wt% (0.14 at%), and Cu 8.87 wt% (2.28 at%). A large carbon contribution was observed—69.00 wt% (93.66 at%)—consistent with organic capping from the plant extracts. These data confirm the presence of metallic Ag in the sample while also reflecting the organic matrix typical of green-synthesized AgNPs. In *Carica papaya* synthesized nanoparticles, Quantitative ZAF-corrected analysis of a representative spot yielded the following elemental composition: C 71.12 wt% (94.01 at%), Ag 18.10 wt% (2.71 at%), Cu 8.07 wt% (2.05 at%), Cl 2.11 wt% (0.98 at%), Br 0.60 wt% (0.25 at%), which sums to ~100 wt%. These results confirm the presence of metallic silver and indicate a predominant carbonaceous matrix consistent with organic capping agents from the papaya extract and the carbon support used for analysis. Our findings agree with the results of Vasu Sujitha *et al.*, 2015²⁴ and Kunle *et al.*, 2021²². Crucially, it must be clarified that the copper content does not represent a component of the nanoparticle architecture or an impurity; rather, it is a well-documented background artifact arising from the carbon-coated copper grids used as the sample support during TEM-EDS imaging.

FTIR measurements were conducted in an effort to identify the various chemical groups in biomolecules that seem to be responsible for the bio-reduction of and capping as well as stabilizing the AgNPs. The *Moringa oleifera* synthesized nanoparticle FTIR spectrum illustrates particular absorption bands at 3350.35, 2945.30, 1651.07, 1516.05, 1365.60, 1298.09 and The *Carica papaya* synthesized nanoparticles FTIR spectrum illustrates particular absorption bands at 3502.73, 2927.94, 1651.07, 1500.62, 1448.54, 1001.06. This observation signifies the existence of the capping agent along the nanoparticles Figure 7.

The detected bands that existed at 3502.73 and 3350.35 in the spectra correlate with the O–H stretching vibration, which is induced due to the existence of alcohols and phenols. Also, the observed peaks in the regions 2945.30 and 2927.94 are due to (C–H) of aromatic compounds. The FTIR spectra of synthesized silver nanoparticles revealed prominent peaks corresponding to hydroxyl (–OH) and aliphatic (–CH) functional groups. These groups are characteristic of polyphenols, flavonoids, and terpenoids present in the plant extract. The hydroxyl play a pivotal role in the reduction of Ag⁺ ions into Ag⁰ by donating electrons, thereby initiating nanoparticle nucleation. Additionally, both –OH and –CH groups contribute to the stabilization of nanoparticles through hydrogen bonding, hydrophobic interactions, and surface adsorption, preventing agglomeration. Thus, the FTIR analysis confirms that plant-derived biomolecules are not only responsible for reducing silver ions but also act as natural capping agents, ensuring the stability of the biogenic nanoparticles. Observed results are well correlates with previous research studies Vasu sujitha *et al.*, 2015²⁴ and Mohammad Ehsan *et al.*, 2019²⁵.

In silico Screening

The SwissADME filtering process reduced the initially identified phytoconstituents from 130 to 37 in *Moringa oleifera* and from 160 to 35 in *Carica papaya* (Figure 8). Based on antiviral prediction scores generated through PASS-ONLINE, particularly against Dengue virus serotype 2, five compounds were selected from the 37 identified in *Moringa* and three compounds from the 35 identified in *Papaya* for further investigation. These shortlisted eight compounds mentioned in the table 4 were subsequently subjected to comprehensive analyses. These analyses encompassed predictions of physicochemical properties, evaluations of drug-likeness, ADME profiling, LD₅₀ estimation using a rat toxicity model, assessments of toxicity panels, and evaluations of cytotoxicity against normal cell lines (Table 5).

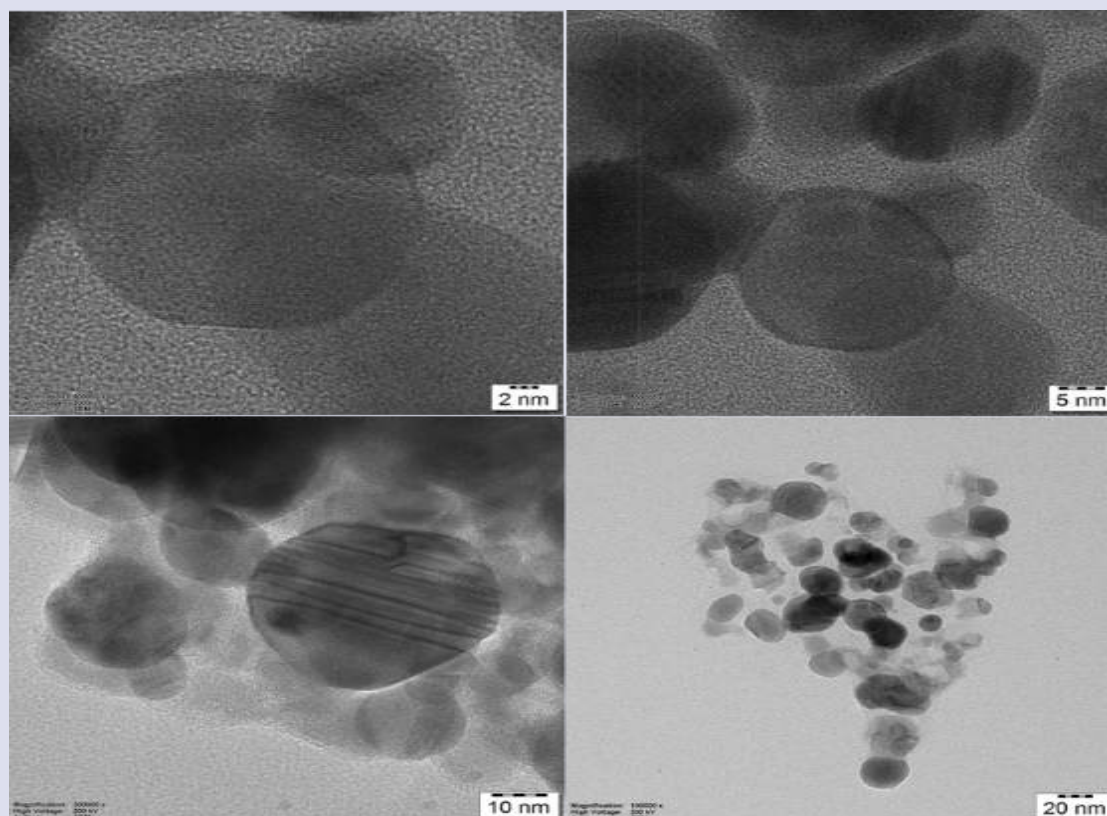


Figure 5. TEM images of *Moringa oleifera* synthesized nanoparticles

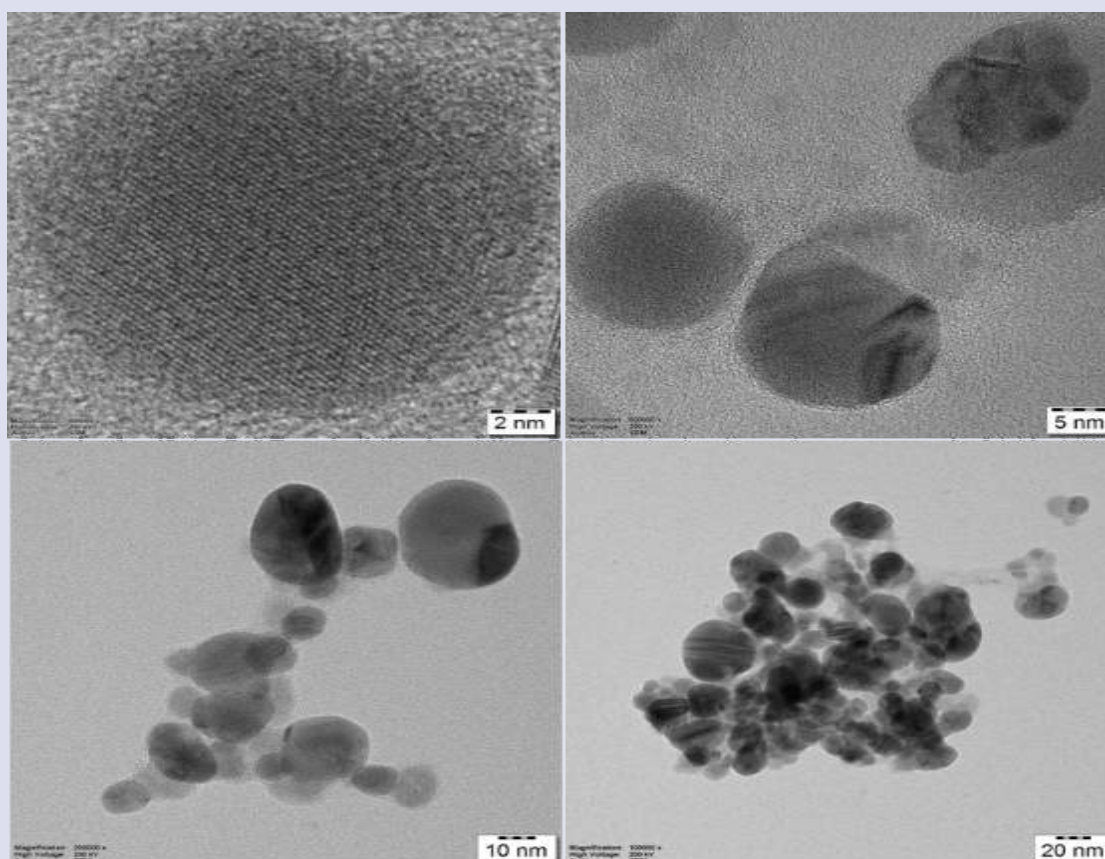


Figure 6. TEM images of *Carica papaya* synthesized nanoparticles

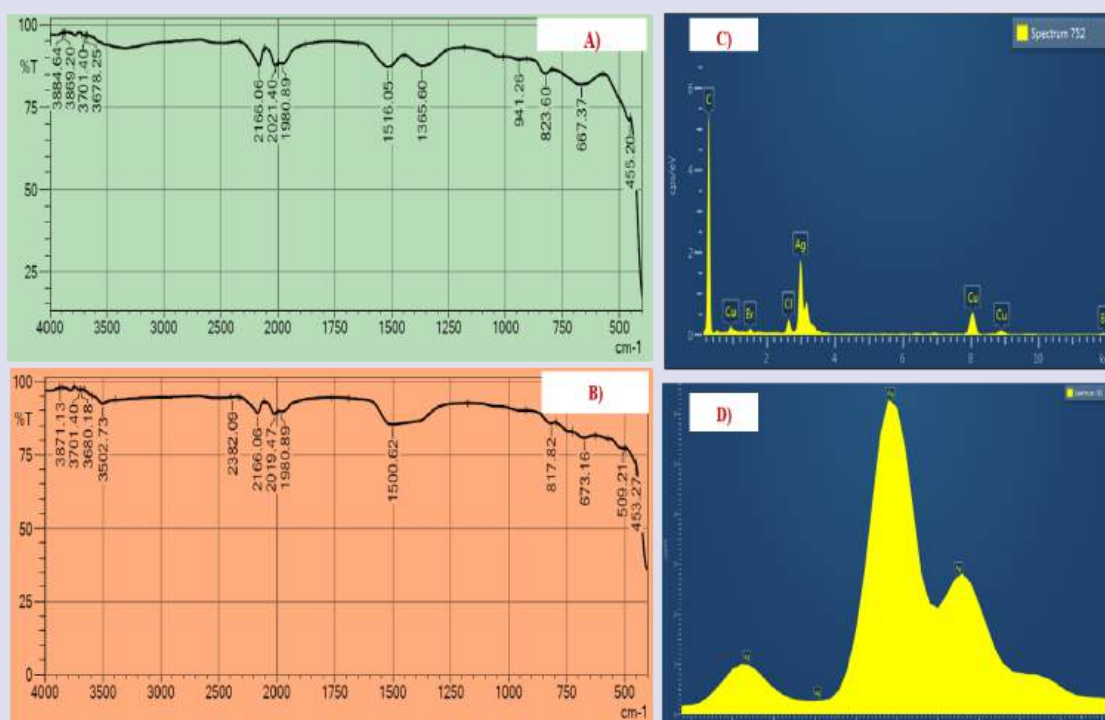


Figure 7. A) FTIR results of *Moringa oleifera* synthesized silver nanoparticles. B) FTIR results of *Carica papaya* synthesized silver nanoparticles. C) Observation of all the elements present in *Moringa oleifera* synthesized silver nanoparticles through EDS D) Observation of only silver element in *Carica papaya* synthesized silver nanoparticles through EDS.

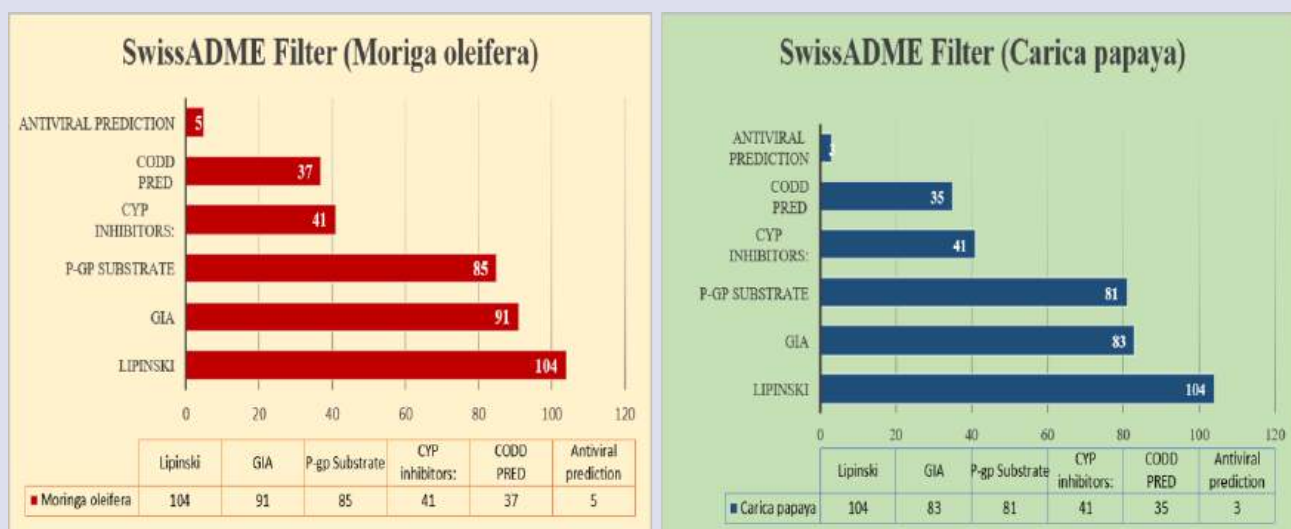


Figure 8. SwissADME screening for GCMS identified phytoconstituents of both *Moringa oleifera* synthesized silver nanoparticles and *Carica papaya* synthesized silver nanoparticles

Table 4. Shortlisted compounds and their PubChem ID

S.No	Name of the Ligand	PubChem ID
1	3-Pyridinecarboxylic acid	938
2	Benzeneacetic acid	999
3	Butanoic acid	264
4	Ethyl hydrogen malonate	70615
5	Hexanoic acid	8892
6	1,2-diacetylhydrazine	72884
7	Dimethoxyglycerol Docosyl ether	8150
8	Pentanoic acid, 4-oxo	11579

Table 5. Physiochemical property prediction of ligands

Ligands	Molecular Formula	Molecular mass g/mol	No of H-bond acceptors	No of H-bond donors	Total polar surface Area Å ²²	Solubility (mg/mL)	Class	Log P
3-Pyridinecarboxylic acid	C6H5NO2	123.11	3	1	50.19	6.81	Very Soluble	0.86
Benzeneacetic acid	C8H8O2	136.15	2	1	37.3	1.78	Very Soluble	1.23
Butanoic acid	C4H8O2	88.11	2	1	37.3	15.6	Very Soluble	1.1
Ethyl hydrogen malonate	C5H8O4	132.11	4	1	63.6	36	Very Soluble	1.01
Hexanoic acid	C6H12O2	116.16	2	1	37.3	3.62	Very Soluble	1.57
1,2-diacetylhydrazine	C4H8N2O2	116.12	2	2	58.2	200	High soluble	0.96
Dimethoxyglycerol Docosyl ether	C27H56O3	428.74	3	0	27.69	120	Very Soluble	2.46
Pentanoic acid, 4-oxo	C5H8O3	116.12	3	1	54.37	103	Very Soluble	0.88

Table 6. Results of ADME screening - Absorption and Distribution

Compound name	ABSORPTION			DISTRIBUTION		
	Human intestinal Absorption	Caco-2 permeability	Log Kp (skin permeation) (cm/s)	P-glycoprotein inhibitor	BBB penetration	Plasma Protein Binding
3-Pyridinecarboxylic acid	90.263208	20.7543	-6.8	No	Yes	4.514805
Benzeneacetic acid	96.867445	20.9999	-6.13	No	Yes	9.900647
Butanoic acid	86.768385	20.1755	-6.28	No	Yes	76.526853
Ethyl hydrogen malonate	69.545147	20.9853	-6.91	No	No	37.225795
Hexanoic acid	90.926762	20.7313	-5.65	No	Yes	84.639405
1,2-diacetylhydrazine	75.320701	5.65932	-7.68	No	No	13.65674
Dimethoxyglycerol Docosyl ether	100	58.1521	-7.37	No	No	77.542222
Pentanoic acid, 4-oxo	77.612853	16.7823	-7.36	No	No	79.508981

Table 7. Results of ADME screening – Metabolism and Excretion

Compound name	METABOLISM						EXCRETION	
	CYP3A4 substrate	CYP3A4 inhibition	CYP2C19 inhibition	CYP2D6 substrate	CYP2D6 inhibition	CYP2C9 inhibition	T1/2 (half-life period) (Hrs)	Clearance rate (ml/min/kg)
3-Pyridinecarboxylic acid	Non	Non	Inhibitor	Non	Non	Inhibitor	0.829	3.502
Benzenecetic acid	Non	Non	Non	Non	Non	Inhibitor	0.877	8.405
Butanoic acid	Non	Inhibitor	Inhibitor	Non	Non	Inhibitor	0.832	7.386
Ethyl hydrogen malonate	Non	Inhibitor	Inhibitor	Non	Non	Inhibitor	0.898	8.665
Hexanoic acid	Non	Inhibitor	Inhibitor	Non	Non	Inhibitor	0.798	5.645
1,2-diacetylhydrazine	Weakly	Non	Inhibitor	Weakly	Non	Non	0.678	2.852
Dimethoxyglycerol Docosyl ether	Substrate	Inhibitor	Inhibitor	Weakly	Non	Inhibitor	0.582	5.567
Pentanoic acid, 4-oxo	Non	Inhibitor	Inhibitor	Non	Non	Inhibitor	0.838	6.757

The ADME analysis revealed strong intestinal absorption for the majority of the selected compounds, with Dimethoxyglycerol docosyl ether and Benzenecetic acid exhibiting the highest absorption values. Compounds such as 3-Pyridinecarboxylic acid and Hexanoic acid also demonstrated excellent intestinal absorption and favorable Caco-2 permeability. None of the compounds were identified as P-glycoprotein (P-gp) substrates, and most displayed blood–brain barrier (BBB) permeability, suggesting favorable bioavailability and potential central nervous system (CNS) activity (Table 6). Furthermore, most compounds did not inhibit CYP3A4, including 3-Pyridinecarboxylic acid, Benzenecetic acid, Butanoic acid, Ethyl hydrogen malonate, Hexanoic acid, and Pentanoic acid, 4-oxo, indicating a lower risk of metabolism-related drug–drug interactions (Table 7).

Overall, the majority of compounds showed minimal interactions with cytochrome P450 isoforms, moderate clearance rates, and suitable half-lives, supporting their potential for sustained antiviral activity. These results suggest that the selected phytoconstituents from *Moringa oleifera* and *Carica papaya* possess promising pharmacokinetic and safety profiles, warranting further exploration as potential antiviral candidates against Dengue virus type 2.

The Results of LD 50 value of the compound estimated with rat toxicity model indicated that all compounds had low acute toxicity, with Ethyl hydrogen malonate and Dimethoxyhexyl docosyl ether showing the highest safety margins, while 3-Pyridinecarboxylic acid and Pentanoic acid, 4-oxo exhibited moderately low acute toxicity. These findings made them strong candidates for antiviral development given their predicted activity. The toxicity panel results showed that 3-Pyridinecarboxylic acid, Benzenecetic acid, and 1,2-diacetylhydrazine were non-mutagenic and non-carcinogenic, with low hepatotoxicity and no immunotoxic or cytotoxic effects, making them safer candidates. Dimethoxyhexyl docosyl ether also demonstrated favorable safety, showing no mutagenic or immune-toxic concerns and low hepatotoxicity. These profiles supported their potential for antiviral development due to their predicted activity and minimal toxicity risks. From the cytotoxicity analysis against normal cell lines by PASS-ONLINE prediction, most compounds had Pa values below 0.5 ($Pa < 0.5$). Accordingly, all compounds were found to be non-cytotoxic to normal cells. And selected compounds were considered for metal docking.

Molecular Docking

Eight bioactive substances extracted from papaya and moringa were conjugated with silver nanoparticle and subsequently analyzed through subjected to molecular docking analysis against the four main DENV2 target proteins: domain-3, envelope protein, NS5 polymerase and NS2B/NS3 protease. Compound prioritization was based on pharmacological relevance rather than abundance. Figure 9 illustrates

the 3D docking conformations of the leading phytochemicals conjugated silver nanoparticles within the active sites of target proteins, highlighting hydrogen bonds and π – π stacking between the top-ranked phytochemicals and the active site residues of dengue viral proteins. Red colour and Cyan represents α -helices and β -sheets of the targeted proteins. Green dashed line represents the hydrogen bond formed between the ligand and the protein residue. Based on relative binding affinity and interaction specificity, 3-pyridinecarboxylic acid and benzenecetic acid were prioritized as initial hit candidates. Among all targets 3-pyridinecarboxylic acid conjugated with silver nanoparticle exhibited the highest relative interaction within this specific set, achieving a moderate docking score of of -6.7 kcal/mol (NS2B/NS3), -4.6 kcal/mol (envelope), -4.7 kcal/mol (NS5) and -5.94 kcal/mol (domain-3). It formed multiple hydrogen bonds with catalytic residues like Ser135, His51 and Asp75 and stabilized π – π stacking and carbon–hydrogen interactions with Tyr150 and Phe130. Consistent binding was also demonstrated by benzoeneacetic acid conjugated with silver nanoparticle specifically to NS2B/NS3 (-5.5 kcal/mol) and domain-3 (-5.12 kcal/mol) which engaged Gly133 and Asn152 through hydrophobic contacts with Val154 and Leu128 and hydrogen bonding. The docking analysis of these compounds, along with their binding energies and molecular interactions, is presented in Figure 9 and Table 8. Both substances showed low cytotoxicity across normal cell lines high intestinal absorption and zero Lipinski violations when passing SwissADME filters indicating their potential as lead candidates for additional in vitro validation against DENV2. The docking analysis was conducted using both positive and negative controls to ensure the validity of the final results, as presented in Figure 10 and Table 9. The positive control was Eltrombopag an FDA-approved medication with documented inhibitory activity against dengue viral proteins²⁶. The negative control was paracetamol a clinically used antipyretic with no antiviral activity. To support the significance and interpretation of the binding affinities both controls were docked using the same parameters.

These findings are in agreement with earlier docking-based antiviral studies that highlighted the NS2B/NS3 protease and NS5 polymerase as major therapeutic targets due to their indispensable roles in viral replication and pathogenesis. For instance, Perera and Kuhn 2008²⁷ emphasized that domain-III of the envelope protein is critical for receptor binding, making it a favorable site for neutralizing inhibitors. Similarly, studies by Tomlinson *et al.*, 2011²⁸ and Kurmi *et al.*, 2025²⁹ reported that small-molecule inhibitors targeting the NS2B/NS3 protease demonstrated binding energies within the range of -5 to -8 kcal/mol, comparable to the values obtained in the present study. In addition, prior in silico analyses of natural phytoconstituents, such as flavonoids and alkaloids, against dengue viral proteins showed binding affinities ranging between -4 and -7 kcal/mol, supporting the potential of our identified candidates^{30,31}. The binding

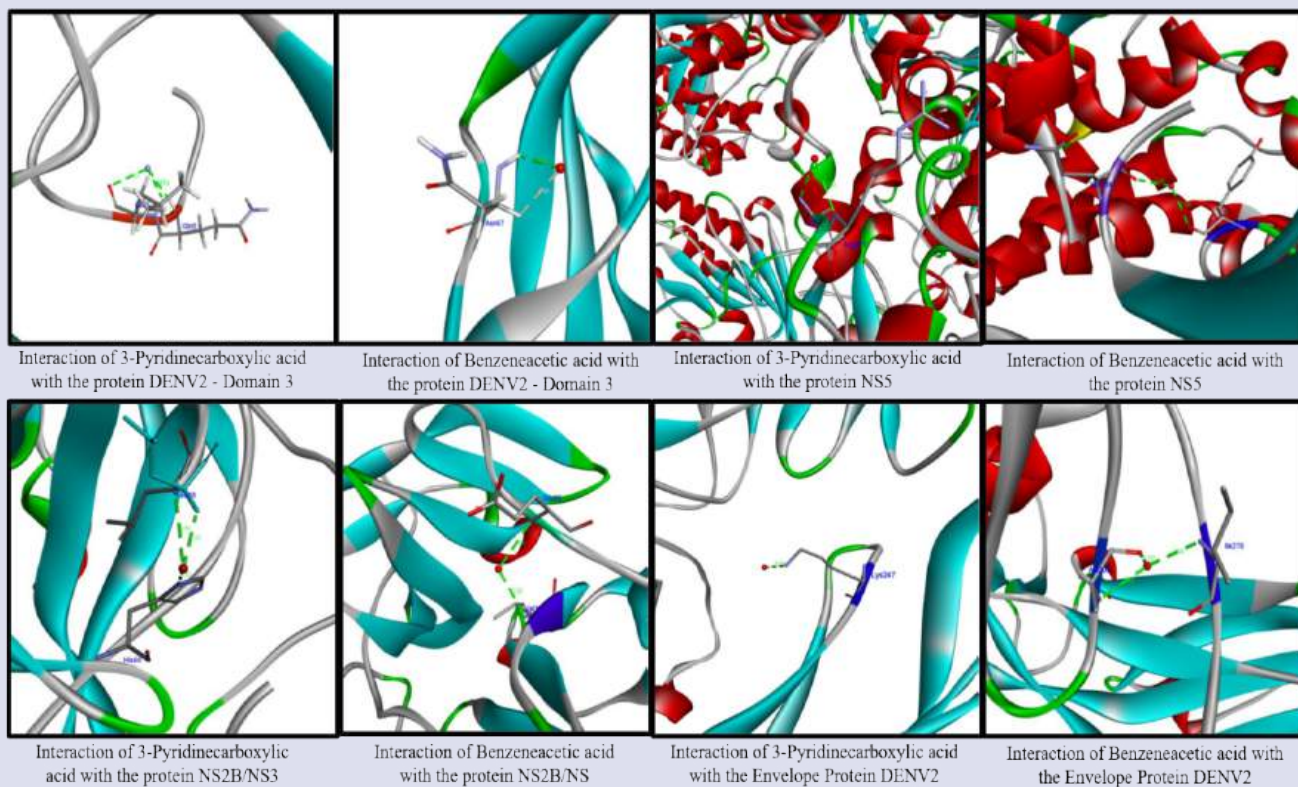


Figure 9. Docking results of top screened Phytochemicals conjugated with Silver nanoparticles IBM RXN in relation to target proteins

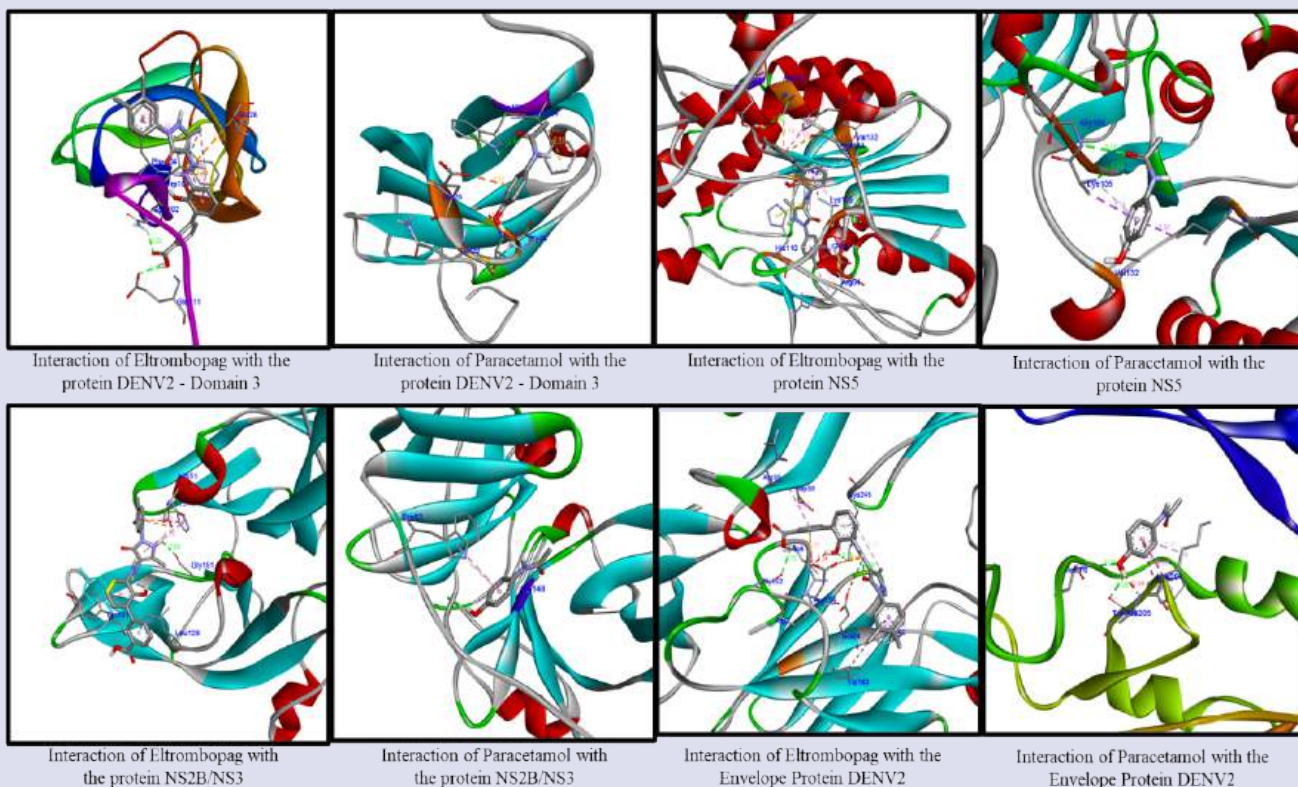


Figure 10. Docking results of Positive and Negative Control in relation to target proteins

Table 8. Binding energy and bond length of top screened Phytochemicals conjugated with Silver nanoparticles using IBM RXN in relation to target proteins

Target protein PDB ID: Envelope Protein DENV2 – 1OAN					
S.No	Ligands	Binding energy (Kcal/mol)	Inhibition Constant, Ki	Interacting residues with Bond length (Å°)	
				Conventional H bond	Carbon H bond
1	3-Pyridinecarboxylic acid	-4.6	1.67 mM	Lys A:247 (3.04) ,	-
2	Benzeneacetic acid	-4.4	656.55 µM	Ala A:205(2.89, 2.59)	-
Target protein PDB ID: NS2B/NS3 protease – (2FOM)					
1	3-Pyridinecarboxylic acid	-6.7	12.93 µM	Leu A:18(2.43, 3.09) His 60 A:60(3.0)	-
2	Benzeneacetic acid	-5.5	339.68 µM	Glu A:86 (3.04) Val A:146 (2.92)	-
Target protein PDB ID: NS5 – (6KR2)					
1	3-Pyridinecarboxylic acid	-4.07	2.02 mM	Val A:870 (2.78), Arg A:871 (3.00)	-
2	Benzeneacetic acid	-4.79	1.41 mM	Gln A:598 (2.80), Tyr A:573 (2.80)	-
Target protein PDB ID: DENV2 - Domain 3 – (2JSF)					
1	3-Pyridinecarboxylic acid	-5.94	47.05 µM	Leu A:6 (3.02, 2.47), Gln A:5 (2.58)	-
2	Benzeneacetic acid	-5.12	234.00 µM	Asn A:76 (2.32)	Asn A:76 (2.94)

Table 9. Binding energy and bond length of Positive and Negative Control in relation to target proteins

Target protein PDB ID: Envelope Protein DENV2 – 1OAN					
S.No	Ligands	Binding energy (Kcal/mol)	Inhibition Constant, Ki	Interacting residues with Bond length (Å°)	
				Conventional H bond	Carbon H bond
1	EL	- 5.2	182 nM	LYS B: 246 (5.01) GLY A: 152 (2.75)	-
2	PARACETAMOL	- 2.1	40 µM	ALA A: 205 (2.26) ILE A: 270 (3.05)	-
Target protein PDB ID: NS2B/NS3 protease – (2FOM)					
1	EL	- 4.9	154 nM	GLY B: 151 (2.99)	HIS B: 51 (3.04)
2	PARACETAMOL	- 1.4	110 µM	-	GLY B: 148 (3.47)
Target protein PDB ID: NS5 – (6KR2)					
1	EL	-3.4	129 nM	ARG A: 163 (2.99)	LYS A: 105 (4.19)
2	PARACETAMOL	-3.6	79 µM	LYS A: 105 (3.20) GLY A: 106 (3.10)	LYS A: 105 (3.95)
Target protein PDB ID: DENV2 - Domain 3 – (2JSF)					
1	EL	-5.5	110 nM	ASN A: 102 (2.29) GLU A: 111 (2.17)	-
2	PARACETAMOL	-2.4	110 µM	GLN A: 28 (2.39) TRP A: 103 (2.65)	-

energies observed in this study (ranging from -4.6 to -6.7 kcal/mol) are consistent with the molecular weights of the volatile and semi-volatile compounds identified via GC-MS. While these values are characterized as moderate, they are comparable to the binding affinity of the positive control, Eltrombopag (-6.6 kcal/mol), within the same binding pocket of the NS2B/NS3 protease. Furthermore, the biological efficacy of green-synthesized silver nanoparticles is often attributed to the multivalent and synergistic interaction of these various ligands on the nanoparticle surface, rather than a single high-affinity interaction typical of synthetic drugs.

Interestingly, the strong interaction profile of 3-pyridinecarboxylic acid observed in this study resonates with earlier reports of pyridine derivatives exhibiting broad-spectrum antiviral activities, including inhibition of flaviviruses. Pyridine-based compounds were reported to interfere with viral RNA polymerases and proteases³², corroborating the observed affinity of 3-pyridinecarboxylic acid for NS5 and NS2B/NS3 in the current study. Likewise, benzeneacetic acid derivatives have been documented as potential antiviral scaffolds³³, which reinforces its candidacy for further investigation.

LIMITATIONS

A key limitation of this study is its reliance on computational screening architectures. While molecular docking successfully maps potential surface binding topographies and electrostatic complementarities, in silico scoring functions cannot fully account for cellular uptake, complex physiological matrices, or downstream viral replication dynamics. Therefore, the therapeutic significance implied by these simulated interactions remains strictly theoretical until corroborated by quantitative in vitro plaque reduction neutralization tests (PRNT) and cytotoxicity profiles.

CONCLUSION

In conclusion, compared to previous studies, the novelty of the current work lies in simultaneously employing *Moringa oleifera* seed and *Carica papaya* fruit extracts for the biosynthesis of nanoparticles, followed by computational evaluation against dengue virus targets. Earlier investigations primarily explored their independent therapeutic benefits *Moringa* for its antioxidant and antimicrobial roles, and *Carica papaya* for its supportive role in dengue management. By

integrating these two plants, our study findings support their promise as dual functional agents in nanomedicine, with implications for the development of novel antiviral strategies against dengue virus. On the computational front, in silico profiling successfully streamlined the extensive phytochemical library down to key candidate molecules. When modeled as simulated ionic silver–phytochemical coordination complexes, 3-pyridinecarboxylic acid and benzenecetic acid were identified as the primary lead scaffolds displaying stable interaction networks within the whole-protein blind docking search spaces of critical DENV-2 structural and non-structural targets. Rigorous future experimental validation specifically quantitative in vitro enzymatic inhibition assays, cytotoxicity profiling on human cell lines, and phenotypic viral replication models is strictly necessary to confirm actual biological efficacy and advance these candidates toward viable dengue therapeutics.

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