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Original article

In silico and In vitroactivityof compounds obtained from Caricapapaya and Ocimum sanctumseeds against Dengue-2 viral envelope and capsid protein

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Abstract

Dengue, arthropod borne disease is present major threat leading to millions of affected people and thousands of deaths around the world. In recent times dengue cases have been increasing since there is no vaccine and proper drug available. The presently available DenVax and yellow fever vaccine is no efficient for India. So, there is increase for need of drug and vaccine development for dengue in India. As there are lots of medicinal properties in commonly occurring medicinal plants in India, we have selected few medicinal plant seeds to study their antiviral properties against Dengue-2 virus.To identify the antiviral activity of compounds obtained from Carica papaya andOcimum sanctum seeds against Dengue-2 viral protein by insilico method. C. papaya and O. sanctum seeds showed less toxicity in Vero cells and proceeded with antiviral activity. The antiviral activity of medicinal plants showed promising results in vero cells. Hence proceeded with phytochemical, antioxidant and other analysis. The phytochemical analysis of Tulsi and papaya seeds showed positive for many bioactive compounds. When the sample extract proceeded with TLC, GC-MS and UV-vis spectrophotometer analysis bioactive 34 and 51 compounds were identified in C. papaya and O. sanctumrespectively. These compounds were further analyzed for inhibiting Dengue viral proteins insilico. Docking of the bioactive compounds were done using Patchdock, Argus lab and autodock software to obtain best fit and the site of activity were identified using Discovery studio. Hence, these compounds identified can be further tested in vitro for future drug design and development.

Keywords–*Dengue-2, Ocimum sanctum, Carica papaya , Flavivirus, Oleic acid, Eugenol*

Introduction

Dengue is an arthropod-borne viral disease in humans caused by the dengue virus (DENV), an RNA virus belonging to the family *Flaviviridae* and genus *Flavivirus*. There are four serologically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. These serotypes differ by 25%–40% at the amino acid level in the viral envelope proteins, contributing to high morbidity and mortality, particularly during secondary infections involving a different serotype than the one encountered initially (Guzman & Harris, 2015). Globally, 50–100 million dengue cases are reported annually, with approximately 40% of the world's population at risk. Severe dengue requires hospitalization in about 500,000 individuals each year, with an estimated mortality rate of 2.5% (World Health Organization [WHO], 2017).The DENV genome follows the gene order: C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5. It comprises a 5′ noncoding region (NCR), a 3′ NCR, a short untranslated region at the 5′ end, and a non-polyadenylated 3′ terminus. Three structural genes encode the capsid (C), membrane precursor (prM), and envelope (E) proteins. The E glycoprotein is the most conserved structural protein among serotypes and, along with prM, forms the viral envelope. The C protein interacts with the viral RNA to form the nucleocapsid, which is enclosed in a lipid bilayer. The non-structural proteins—NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5—are essential for viral replication and polyprotein processing (Halstead et al., 1988).Dengue virus is primarily transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, with major breeding habitats being freshwater storage containers. Transovarial transmission of all four serotypes has been observed in both mosquito species, facilitating viral

persistence during inter-epidemic periods (Gubler et al., 1998).Clinically, dengue manifests as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). DF is characterized by acute fever, retro-orbital pain, headache, rash, myalgia, arthralgia, leukopenia, and hemorrhagic tendencies. DHF presents with fever lasting 2–7 days, thrombocytopenia (≤100,000/mm³), and plasma leakage evidenced by hemoconcentration or pleural effusion. DSS involves hypotension, a weak and rapid pulse, narrow pulse pressure (<20 mmHg), cold clammy skin, and restlessness (Guzman & Harris, 2015).Diagnostic methods include polymerase chain reaction (PCR), MAC-ELISA, IgG ELISA, NS1 antigen ELISA, plaque reduction neutralization test (PRNT), microneutralization assays, and rapid diagnostic tests (WHO, 2017). There is currently no specific antiviral treatment for dengue. Symptomatic management involves paracetamol for fever and pain relief, along with adequate fluid intake to prevent dehydration. With proper medical care, mortality can be significantly reduced (WHO, 2017). In India, traditional Siddha formulations such as **NilavembuKudineer** and **Carica papaya** extract tablets are widely used to support recovery in dengue patients (Nagaraj et al., 2020; Subenthiran et al., 2013). NilavembuKudineer contains *Andrographis paniculata*, *Plectranthusvettiveroides*, *Vetiveriazizanioides*, *Zingiber officinale*, *Piper nigrum*, *Cyperus rotundus*, *Santalum album*, *Trichosanthescucumerina*, and *Mollugocerviana* (Ilango & Chitra, 2011; Kadir et al., 2019). While their mechanisms remain unclear, these herbal constituents are reported to alleviate symptoms and enhance platelet counts.Primary infection with one dengue serotype provides lifelong immunity against that serotype but only transient cross-protection against others. Consequently, secondary infections with heterologous serotypes increase the risk of severe disease, complicating vaccine development. Current vaccine efforts focus on tetravalent formulations to ensure protection against all four serotypes (Katzelnick& Harris, 2017). However, limitations in suitable animal models and a lack of comprehensive understanding of protective immune responses continue to hinder the development of effective antivirals and vaccines (Halstead et al., 1988).No antiviral agents have been approved for dengue, largely due to the virus's complex pathogenesis. Ongoing antiviral research explores nucleoside inhibitors and replication-targeting compounds, guided by *in vitro* assays and structure-based drug design (Guzman & Harris, 2015). Symptomatic agents such as antibiotics, NSAIDs, and corticosteroids are occasionally used but may induce adverse effects, including gastritis, bleeding, and immunosuppression (Guzman & Harris, 2015).Dengue-associated thrombocytopenia is believed to result from impaired megakaryopoiesis, apoptosis of progenitor cells, or immune-mediated platelet destruction. Although thrombopoietin receptor agonists such as eltrombopag and romiplostim have shown promise, there is increasing interest in plant-based therapies. Traditional medical texts describe several herbs with antipyretic, antiviral, and anti-inflammatory properties. *Quercus lusitanica* and *Gastrodiaelata* have demonstrated *in vitro* activity against DENV-2 by inhibiting viral replication (Ilango & Chitra, 2011). Nevertheless, *Carica papaya* leaf extract and NilavembuKudineer remain the most widely recommended plant-based therapies for dengue in India (Subenthiran et al., 2013; Nagaraj et al., 2020).

Methods and methodology

Extraction of plant seeds from *Carica papaya* and *Ocimum sanctum*

Fresh Tulsi and papaya seeds were collected, washed and dried. Then seeds were crushed using motor and pestel and powdered samples were extracted using methanol solvent using Soxhlet apparatus. Then the extracted samples were concentrated using rotatory evaporator. After evaporation processing solvent was dried and samples were collected. The collected samples were stored at 4^{o}C.

Cell culture and virus propagation

Vero cells were procured from Sathyabama cell repository and revived using DMEM (Himedia) with 10%FBS (Lonza) and antibiotic Penicillin and Streptomycin 100units concentration. Cells were then grown in 10% DMEM till appearance of monolayer in 5% CO_2 incubator. After growth cells were splited using Trypsin-EDTA and then disintegrated cells were used for cytotoxicity and antiviral assays. Dengue-2 virus was propagated in Vero cells and incubated in 5% CO_2 incubator till cytopathic effect were observed. After the CPE appearance cells were trypsinized, washed and centrifuged. After centrifugation virus have been collected in supernatant which is further used for antiviral activity while cell deposits as pellets are discarded.

Cytoctoxicity assay of plant extracts in VERO cells

In 96 well microtiter plate the trypsinized and separated cells were seeded and grown overnight and observed for the cell growth. After 24 hours of cell growth the cells were treated with crude extracts with minimal concentration and incubated in 5% CO_2 incubator for 24hours. Then the 10uL of pre prepared MTT reagent was added in each well and incubated for 4 hours. After 4hrs incubation stop solution provided with kit was added and read at 450nm in ELISA reader ELx800. The observed OD nm was measured and calculated for percentage of viability in Vero cells.

Gas Chromatography – Mass Spectrophotometry analysis

The crude extracts of *Ocimumsanctum* and *Caricapapaya* seeds were run in Agilent 7890B GC in column HP_5MS 5% Phenyl Methyl Silox -60^{o}C to 325^{o}C 30mX250µmX0.25µm. In this analysis bioactive compounds were identified which might be the responsible for Dengue-2 virus inhibition. The mass spectrum of compounds present in the extracts were by obtained by electron ionization at 70eV and the detector operates in scan mode 30-500 Da atomic units. The peak table with area and percentage was compared with NIST MS2011 library and identified few compounds.

UV-Vis spectrophotometry

The extract was centrifuged at 3000rpm for 10min and filtered through Whatmann No.1 filter paper. The sample is diluted to 1:10 with the same solvent. The extract was scanned at wave length ranging from 200 to 1100 nm using Shimadzu UV–vis spectrophotometer UV-1800, Japan and Shimadzu-RF5301pc Spectrofluorophotometer Japan, the characteristic peaks were detected. The peak values of the UV-VIS were recorded.

Toxicity profiling using OSIRIS and SWISS-ADME

Osiris property explorer and Swiss ADME were used to predict the toxicity and drug likeness. O. sanctum and *Caricapapaya* plant seed compounds analysed by GC-MS were subjected to toxicity and drug prediction by in silico analysis. GC-MS analysed compounds were selected and screened for evaluation of parameterssuch as mutagenic, irritant, tumorigenic and reproductive effects using Osiris property explorer forinsilico toxicity studies. Totalof 85compounds were selected to analyze their drug score for drug likeness and evaluate their potential to be qualified as drug.SWISS-ADME profiling software was used to carry out evaluation process of drug score and drug likeness based on Lipinski rule.

Molecular docking of GC-MS analysed compounds

Using SWISS ADME sixteen small molecules were selected as best fit compounds based on the Lipinski rule. Insilico method of Patchdock and Arguslab were used forDengue capsid protein 6VG5 from PDB with 16 small molecules was employed to analyze the binding efficiency. Discovery studio software was used for evaluating and visualizing the performed docked results.

Results

Cell culture and virus propagation

The monolayer formed Vero cells in 10% DMEM with FBS and without antibiotics shown in Figure1(c) were inoculated with Dengue-2 virus it showed Cytopathic effect (CPE) in 48 hours as mentioned in figure1(d).

Cell viability assay of the seed extracts by MTT assay

When the 100mM and 10mM concentration of crude extracts are incubated with 24hrs vero cells culture and MTT reagent was added, OD at 450nm was measured after 24hours incubation. In this 100mM and 10mM concentration of C.papaya (L1) seed extract showed 93.5% and 97% viability in vero cells respectively. Then 100mM and 10mM concentration of O.sanctum (L2) seed extract showed 79% and 80% viability respectively as shown in Figure1(e).

Gas Chromatography – Mass spectrophotometry

The crude extracts of *Ocimumsanctum* and *Caricapapaya* seeds were run in Agilent 7890B GC in column HP_5MS 5% Phenyl Methyl Silox -60^{o}C to 325^{o}C 30mX250µmX0.25µm. In thisanalysis bioactive compounds were identified which might be the responsible for Dengue-2 virus inhibition. The mass spectrum of compounds present in the extracts were by obtained by electron ionization at 70eV and the detector operates in scan mode 30-500 Da atomic units. The peak table with area and percentage was compared with NIST MS2011 library and identified few compounds.

GC-MS result of *Carica papaya* seed extract

While analyzing*Carica papaya* 34 compounds were identified 3,5-Dithiahexanol 5,5-dioxide (2.44%), Ethane, 1,1-diethoxy- (2.67%), 2-propyl-tetrahydropyran-3-ol (7.54%), 3,6-Octadecadiynoic acid, methyl ester (8.8%), Benzyl nitrile (9.5%), Benzene, (isocyanomethyl)- (9.99%), Benzeneacetic acid (12%), Tetradecane (12.9%), Methyleugenol (13.2%), Benzeneacetamide (13.8%), Benzeneacetamide N-methyl- (14.6%), Diethyl Phthalate (15.6%), Benzoic acid, 4-hydroxy- (16.9%), Tetradecanoic acid (17.6%), 3,4-Dimethoxy-di-phenylalanine (18.8%), Hexadecanoic acid, methyl ester (19%), Benzenepropanoic acid acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-,methyl ester (19.3%), Palmitoleic acid (19.4%), n-Hexadecanoic acid (20%), 9,12-Octadecadienoic acid, methyl ester (20.7%), trans-13-octadecenoic acid, methyl ester (20.7%), Methyl stearate (20.9%), cis-Vaccenic acid (21.3%), Octadecanoic acid (21.4%), Octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl- (22.14%), Ethanol, 2-(octadecyloxy)- (23.2%), Ethyl iso-allocholate (24.4%), Stigmasterol (25.5%), 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester (26.3%), Tetratriacontane (27.1%), γ-sitosterol (27.89%), Tritriacontane (30.4%), 3-methyl-, Heptadecane, 9-hexyl- (31.8%)

GC-MS result of *Ocimum sanctum* seed extract

While analyzing*Ocimum sanctum*crude extract 51 bioactive compounds were identified in the peak table and compared with library. Identified compounds are Eugenol, ETHANE, 1,1-DIETHOXY-, Glycerin, 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl- , Benzofuran, 2,3-dihydro-, Catechol, 2-Methoxy-4-vinylphenol, alpha-copaene, Cyclohexane, 1-ethenyl-1-methyl-2,4-bis(1-methylethenyl)-, [1S-(1α,2β,4β)]-, Methyleugenol , Caryophyllene, Humulene, 1H-Cycloprop[e]azulene, 1a,2,3,4,4a,5,6,7b-octahydro-1,1,4,7-tetramethyl-, [1aR-(1aα,4α,4aβ,7bα)], Naphthalene, decahydro-4a-methyl-1-methylene-7-(1-methylethenyl)-, [4aR-(4aα,7α,8aβ)]- , Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2-(1-methylethenyl)-, [2R-(2α,4aα,8aβ)]- , Naphthalene, 1,2,3,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-, (1S-cis)-, Caryophyllene oxide, Diethyl Phthalate, Tetracyclo[6.3.2.0(2,5).0(1,8)]tridecan-9-ol, 4,4-dimethyl-, Globulol, Diepicedrene-1-oxide, Ledene oxide-(II), Isoaromadendrene epoxide, 3,4-Dimethoxy-dl-phenylalanine, Benzene, 4-butyl-1,2-dimethoxy-, Hexadecanoic acid, methyl ester, n-Hexadecanoic acid, 9,12-Octadecadienoic acid, methyl ester, 9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-, Phytol, Methyl stearate, 9,12-Octadecadienoic acid (Z,Z)- , 9,12,15-Octadecatrienoic acid, (Z,Z,Z)- , Octadecanoic acid , trans-2-Hexadecenoic acid, Methyl 18-methylnonadecanoate, cis-5,8,11,14,17-Eicosapentaenoic acid, Oxalic acid, isobutyl hexadecyl ester, Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester, Diisooctyl phthalate , Eicosanoic acid, Ethyl iso-allocholate , Eicosane , Squalene, Nonadecane, 2-methyl- , γ-Tocopherol.

Uv-vis spectrophotometer analysis result of *Carica papaya*

The qualitative UV-VIS spectrum profile of ethanolic extract of L1 was selected at wavelength from 200 to 800 nm due to sharpness of the peaks and proper baseline. The profile showed the peaks at 211.5, 250 and 239.5 nm with the absorption of 4, 1.857, and 1.824 respectively.

Uv-vis spectrophotometer analysis result of *Ocimum sanctum*

The profile for ethanolic extract of L2 was selected at wavelength from 200 to 800 nm due to sharpness of the peaks and proper baseline.The profile shows the peaks at 265, 231.5, 224.5, 2.8.5, 263, 230, 216.5 and 203.5 nm with the absorption of 2.511,4,4,4,3.977,3.915,3.817 respectively. The spectrum of 2a extract shows the 3 similar peaks at 231.5, 224.5, 2.8.5 nm if the peaks at the in the region from 200 to 400 nm is a clear indication of the presence of unsaturated groups and heteroatoms such as S, N, O Njokua*et al*.,2013.

These absorption bands are characteristic for flavonoids and its derivatives. The flavonoids spectra typically consist of two absorption maxima in the ranges 230-285 nm (band I) and 300-350 nm (band II). The precise position and relative intensities of these maxima give valuable information on the nature of the flavonoids according to Mamta*et al*.,2012 for the plant extract Acorus calamus.

Toxicity profiling using OSIRIS and SWISS-ADME

Based on the Osiris property explorer and Swiss ADME the toxicity and drug likeness were predicted and 16 compounds out of 33 compounds were found to be low toxic based on the Lipinski rule and eligible for docking with Dengue capsid and envelope protein as mentioned in Fig. 2 and Fig. 3

In Silico activity of compounds obtained from *C. papaya* and *O. sanctum* seeds

When the compounds Methyleugenol, Methoxy_4_vinylphenol and eugenol analysed for docking with Dengue-2 protein capsid protein 6VG5 using different software showed best fit resulting the insilico activity of the compounds to virus. When Methyleugenol docked with protein showed energy scores 3614, -9.39305, 4.12 in Patchdock, Arguslab and Autodock respectively. When Methoxy_4_vinylphenol docked with protein showed energy scores 2864, 9.0162, -4.00 in Patchdock, Arguslab and Autodock respectively. When eugenol was docked with protein showed energy scores 3218, -9.9799, -3.97 in Patchdock, Arguslab and Autodock respectively. The results were analysed using Discovery studio as shown in the figures 4-6.

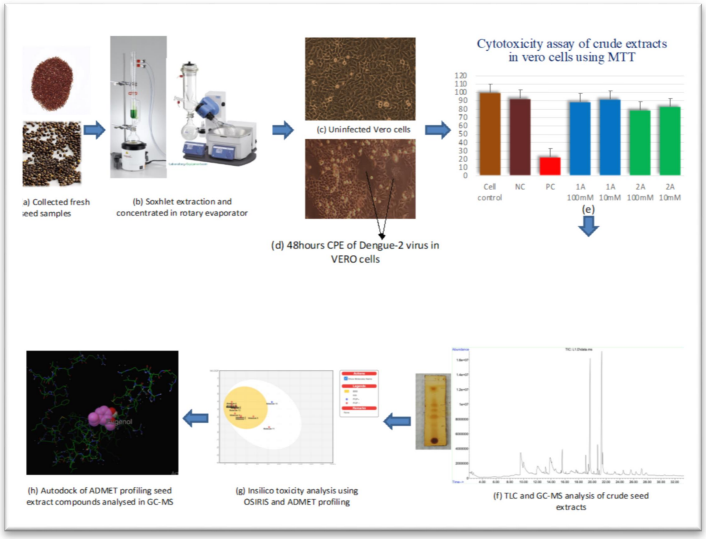


Figure 1: This flow chart represents the (a) sample collection, (b) processing, (c) Vero cells propagation, (d) virus propagation, (e) cytotoxicity assay of in Vero cells, (f) TLC and GC-MS analysis for crude extracts, (g) Boiled egg result of ADMET profiling (h) Autodock results

OSIRIS and ADMET profiling of C.papaya compounds anlayzed by GC-MS

Molecules	Compounds	Canonical SMILES	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	iLOGP
Molecule 1	2-propyl-tetrahydropyran-3-ol	CCCC1OCCCC1O	144.21	2	2	1	40.7	29.46	2.15
Molecule 2	Methyleugenol	C=CCC1CCC(C(C1)OC)OC	178.23	4	2	0	53.53	18.46	2.65
Molecule 3	Benzeneacetamide, N-methyl-	CNC(=O)CC1CCCCC1	149.19	3	1	1	44.02	29.1	1.6
Molecule 4	Diethyl Phthalate	CCOC(=O)C1CCCCC1C(=O)OCC	222.24	6	4	0	58.61	52.6	2.26
Molecule 5	Benzenepropanoic acid acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-,methyl ester	COC(=O)CCC1CC(C(C(C1)C(C)(C)C)O)C(C)(C)C	292.41	6	3	1	87.68	46.53	3.75

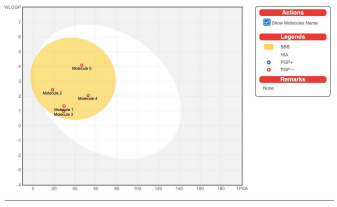


Figure 2. ADMET profiling showing drug likeness of 5 selected compounds of *C. papaya* analysed from GC-MS.

OSIRIS and ADMET profiling of O.sanctum compounds anlayzed by GC-MS

Molecule	Compounds	Canonical SMILES	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	iLOGP
Molecule 1	2-Methoxy-4-vinylphenol	COc1cc(C=C)ccc1O	150.17	2	2	1	45.05	29.46	2.14
Molecule 2	Eugenol	C=CCc1ccc(c(c1)OC)O	164.2	3	2	1	49.06	29.46	2.37
Molecule 3	Methyleugenol	C=CCc1ccc(c(c1)OC)OC	178.23	4	2	0	53.53	18.46	2.65
Molecule 4	Caryophyllene oxide	C=C1CCC2OC2(CCC2C1CC2(C)C)C	220.35	0	1	0	68.27	12.53	3.15
Molecule 5	Diethyl Phthalate	CCOC(=O)c1ccccc1C(=O)OCC	222.24	6	4	0	58.61	52.6	2.26
Molecule 6	Tetracyclo[6.3.2.0(2,5).0(1,8)]trideca n-9-ol, 4,4-dimethyl-	OC1CCC23C1(CCC1C3CC1(C)C)CC2	220.35	0	1	1	66.14	20.23	2.97
Molecule 7	Globulol	CC1CCC2C1C1C(C1(C)C)CCC2(C)O	222.37	0	1	1	68.82	20.23	3.08
Molecule 8	Diepicedrene-1-oxide	CC1C2OC2C23CC1C(C)(C)C2CCC3C	220.35	0	1	0	66.33	12.53	3.11
Molecule 9	Ledene oxide-(II)	CC1CCC23C1C1C(C1(C)C)CCC3(O2)C	220.35	0	1	0	66.66	12.53	3.25
Molecule 10	Isoaromadendrene epoxide	CC1CCC2C1C1C(C1(C)C)CC1C2(C)O1	220.35	0	1	0	66.63	12.53	3.23
Molecule 11	3,4-Dimethoxy-dl-phenylalanine	COc1cc(ccc1OC)CC(C(=O)O)N	225.24	5	5	2	58.49	81.78	1.48
Molecule 12	Benzene, 4-butyl-1,2-dimethoxy-	CCCCc1ccc(c(c1)OC)OC	194.27	5	2	0	58.81	18.46	3.03
Molecule 13	Ethyl iso-allocholate	CCOC(=O)CCC(C1CC2C1(C)C(O)CC1C2C(O)CC2C1(C)CCC(C2)O)C	436.62	6	5	3	122.89	86.99	3.99

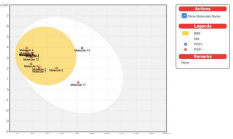
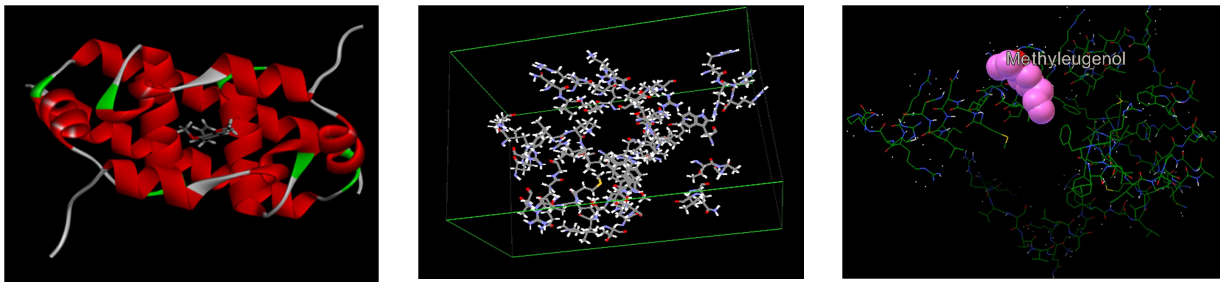
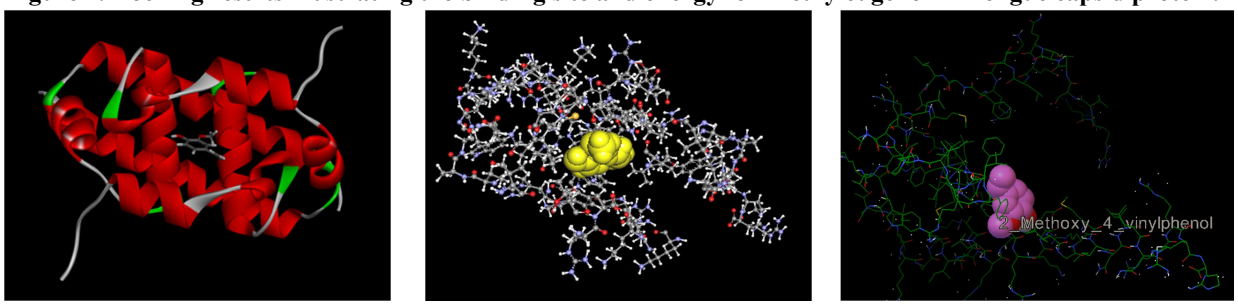


Figure 3. ADMET profiling showing drug likeness of 13 selected compounds of *O. sanctum* analysed from GC-MS.



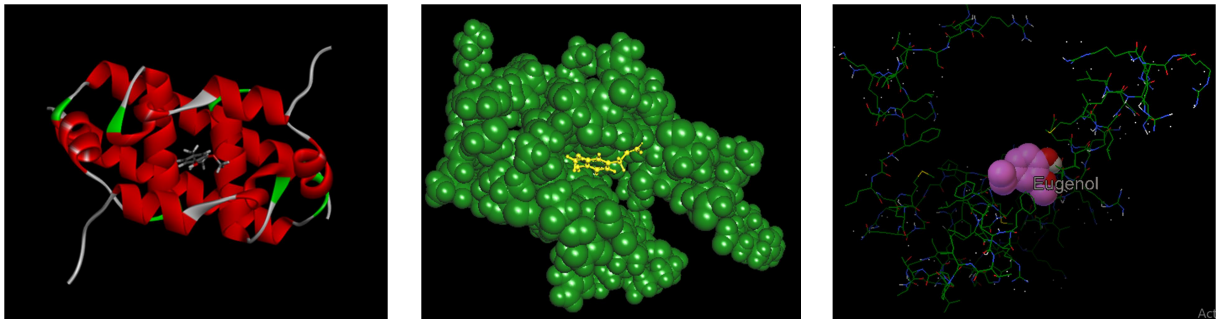
a. Patchdock Score = 3614 **b. Arguslab Energy score = -9.39305** **c. AutodockBinding energy= -4.12**

Figure 4. Docking results illustrating the binding site and energy for Methyleugenol in Dengue capsid protein.



a. Patchdock Score = 2864 **b. Arguslab Energy score = -9.0162** **c. AutodockBinding energy = -4.00**

Figure 5.Docking results illustrating the binding site and energy for Methoxy_4_vinylphenol in Dengue capsid protein.



a. Patchdock Score = 3218 **b. Arguslab Energy score = -9.9799** **c. AutodockBinding energy= -3.97**

Figure 6.Docking results illustrating the binding site and energy for eugenol in Dengue capsid protein.

Discussion

The rising global incidence of dengue fever, especially in India, underscores the urgent need for effective antiviral agents. In the absence of specific vaccines or therapies, medicinal plants offer promising sources of antiviral compounds. This study investigated the antiviral potential of *Carica papaya* and *Ocimum sanctum* seed extracts, both commonly used in Indian traditional medicine. Cytotoxicity tests on Vero cells showed minimal toxicity, supporting their suitability for further study. Phytochemical screening using TLC, GC-MS, and UV–vis spectroscopy identified 34 compounds in papaya seeds and 51 in tulsi seeds, including flavonoids, alkaloids, and phenolics.

In silico docking analysis revealed that several identified compounds could bind effectively to dengue viral proteins, suggesting potential inhibitory activity. These findings align with existing evidence on the antiviral roles of phytochemicals.Though promising, the study's in vitro and in silico nature limits direct applicability. Future research should focus on in vivo validation and isolation of key bioactive molecules to support therapeutic development.In conclusion, *Carica papaya* and *Ocimum sanctum* seeds contain compounds with notable activity against DENV-2, meriting further investigation for dengue treatment.

Conclusion

This study highlights the potential antiviral activity of bioactive compounds derived from *Carica papaya* and*Ocimum sanctum* seeds against Dengue-2 virus, as evidenced by in vitro assessments and in silico docking analyses. The promising toxicity profiles and the presence of numerous phytochemicals underscore the therapeutic potential of these medicinal plants. These findings warrant further *in vivo* validation and could contribute to the development of novel, plant-based antiviral agents for dengue management, especially in regions where effective vaccines and treatments are limited.

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