Aspects of Molecular Medicine 4 (2024) 100050

Contents lists available at ScienceDirect

Aspects of Molecular Medicine

journal homepage: www.journals.elsevier.com/aspects-of-molecular-medicine

Current insights and future perspectives of *In silico* molecular docking in dengue virus proteins inhibition: A review

K. Dass [a,*], N. Prakash [b], P. Manogar [c], R. Murugesan [a]

[a] Department of Zoology, Annai Vailankanni Arts and Science College, Thanjavur (Affiliated to Bharathidasan University, Tiruchirappalli), Tamil Nadu, India
[b] Department of Chemistry, Annai Vailankanni Arts and Science College, Thanjavur (Affiliated to Bharathidasan University, Tiruchirappalli), Tamil Nadu, India
[c] Department of Botany, Annai Vailankanni Arts and Science College, Thanjavur (Affiliated to Bharathidasan University, Tiruchirappalli), Tamil Nadu, India

ARTICLE INFO

Handling Editor: A Angelo Azzi

Keywords:
Mosquito diseases
Aedes
Molecular docking
Drug discovery
Dengue proteins

ABSTRACT

Mosquito-borne diseases such as dengue, yellow fever, chikungunya, Zika, malaria, Japanese encephalitis, West Nile fever, and elephantiasis pose significant public health threats globally. Dengue virus (DENV), transmitted primarily by *Aedes* mosquitoes, infects millions annually, particularly in tropical and subtropical regions. The virus, belonging to the Flaviviridae family, comprises four serotypes (DENV-I to DENV-IV) with distinct structural and non-structural proteins. Transmission occurs through mosquito bites, predominantly by *Aedes aegypti* and *Aedes albopictus*. In 2022, India reported 223,251 dengue cases with 308 fatalities, underscoring the urgent need for effective control strategies beyond synthetic drugs due to their costs and adverse effects. Plant-derived compounds have emerged as promising alternatives due to their biological origin, safety profile, and diverse pharmacological activities, including antiviral properties. This review focuses on the application of molecular docking techniques to evaluate the interaction between plant-derived phytochemicals and key dengue viral proteins, particularly NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. Phytochemicals such as apigenin, hesperidin, kaempferol, and myricetin demonstrated significant binding affinity and potential inhibition of crucial viral enzymes, highlighting their therapeutic promise. Studies on compounds from medicinal plants like *Tanacetum parthenium, Silybum marianum, Cyamopsis tetragonoloba*, and Astragalus spp. further support the efficacy of plant-based therapies against dengue. The findings underscore the potential of phytochemicals to inhibit viral replication and protein activity, offering a novel avenue for developing antiviral treatments. Molecular docking simulations provided insights into the molecular interactions between phytochemicals and viral proteins, guiding future research and drug development efforts. This comprehensive review consolidates current knowledge on plant-based antivirals against dengue, emphasizing their role in integrated vector management and public health strategies.

1. Introduction

Mosquito species such as *Aedes*, *Anopheles*, and *Culex* spread many infectious diseases to humans, including dengue, yellow fever, chikungunya, Zika, malaria, Japanese encephalitis, West Nile fever, and elephantiasis (diseases and causative agents are illustrated graphically in Fig. 1) (Dass and Mariappan, 1998; Tolle, 2009). Among *Aedes* species spread dengue, yellow fever, chikungunya, and Zika viruses. Dengue is a neglected tropical infection (Malavige et al., 2004; Murugesan and Manoharan, 2020). Dengue virus (DENV) disease is a viral infection caused by the *Aedes* mosquito, with an annual incidence of 100–400 million cases, particularly in tropical and subtropical regions (Jagtap et al., 2023).

The dengue virus is of the Flaviviridae family and includes four serotypes: DENV-I, DENV-II, DENV-III, and DENV-IV (Nasar et al., 2020). The DENV genome consists of up to 11 kb of single-stranded positive-sense RNA and is classified into structural proteins such as membrane (M), envelope (E), and capsid (C), and non-structural proteins such as non-structural protein 1 (NS1), non-structural protein 2A (NS2A), non-structural protein 2B (NS2B), non-structural protein 3 (NS3), non-structural protein 4A (NS4A), non-structural protein 4B (NS4B), and non-structural protein 5 (NS5) (Modis et al., 2004; Benfrid et al., 2022; Lee et al., 2023). Fig. 2 exhibits the classified dengue proteins.

* Corresponding author.
E-mail address: kdassrsgc1987@gmail.com (K. Dass).

https://doi.org/10.1016/j.amolm.2024.100050
Received 19 April 2024; Received in revised form 9 July 2024; Accepted 16 July 2024
Available online 18 July 2024

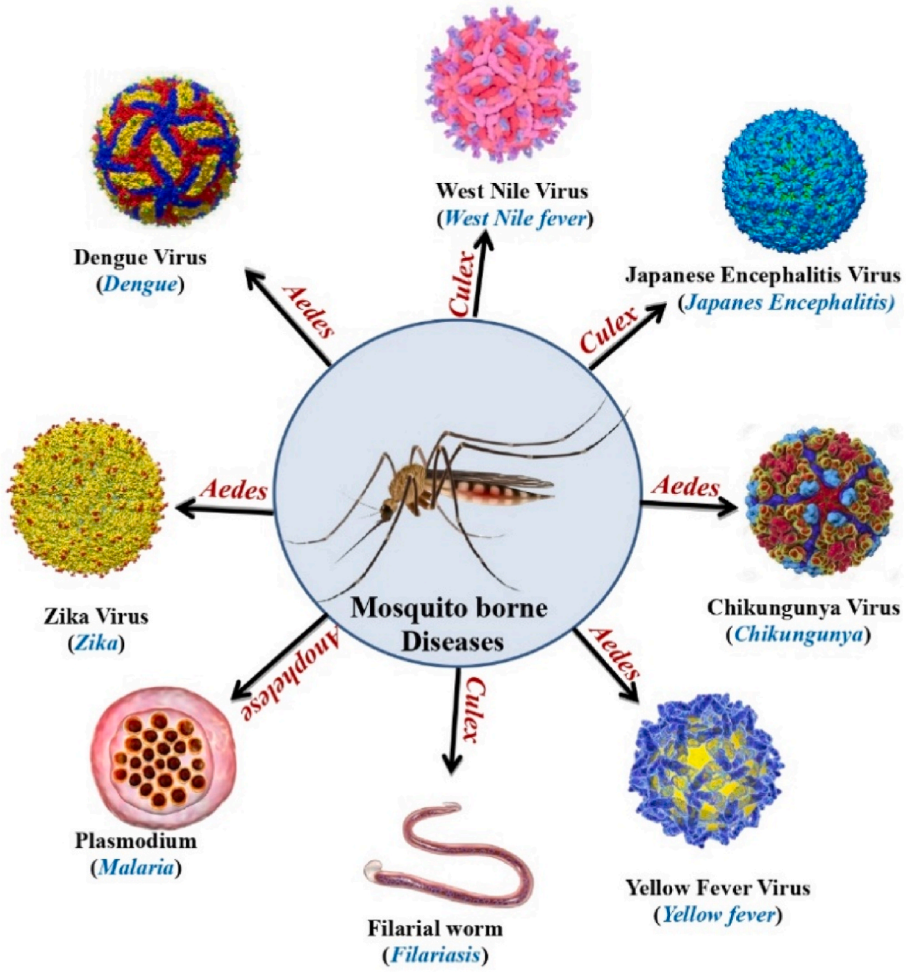

Fig. 1. Mosquito borne diseases.

Dengue fever is caused by four immune-related strains of a single-stranded RNA flavivirus (DENV-1- 4), with the infection pathway of dengue virus proteins shown in Fig. 3. *Aedes* mosquitoes are more common in tropical and subtropical locations and breed in stagnant water in urban and suburban settings such as vases, buckets, tires, and other household water containers (Dass and Mariappan, 1998). People become infected with the virus through the bites of infected female mosquitoes; the principal vectors of dengue fever are *Aedes aegypti, Aedes albopictus*, *Aedes japonicus*, and *Aedes vittatus*. In India, 28,9235 cases of dengue fever were reported in 2023, with 483 fatalities. As of February 2024, 19,447 people have been infected, with 61 confirmed deaths (Fig. 4).

Eradicating dengue fever and its vector using synthetic drugs involves significant costs and side effects on humans. As a result, studying alternative methods and tactics for controlling dengue fever and its vector using plant resources has emerged as a significant area of research (Mgbemena, 2010; Dass et al., 2022). Plant-derived compounds have spurred interest in pharmacological and antiviral research due to their biological source, lack of side effects, and availability. Plant phytochemicals have a wide range of biological and pharmacological effects, including antiallergenic, anti-inflammatory, antioxidant, antimicrobial, anti-larvicidal, pesticidal (antibacterial, antifungal, and antiviral), anticancer, and antidiarrheal properties. Numerous bioflavonoid compounds, including quercetin, hesperidin, naringin, and daidzein, have been experimentally shown to have antiviral properties against various viruses (Dass and Mariappan, 2014a,b; Dass and Mariappan, 2016; Dass et al., 2018; Dass, 2020; Nwozo et al., 2023).

Molecular docking is a popular bioinformatics tool for CADD (Bharatam, 2021; Patel et al., 2022). One important application of bioinformatics in drug development is the use of molecular docking to anticipate drug interactions with target proteins (Agnihotry et al., 2020; Anwar et al., 2021). The purpose of this review was to evaluate the in-silico prediction of antiviral potential against dengue-associated viral proteins.

2. Methods

A literature review on plant phytocompounds and other sources docking with dengue viral protein action in various parts of the world was compiled using internet databases, WHO, and indexed scientific publications such as Web of Science, Taylor and Francis, PubMed, ResearchGate, Springer, Wiley, JSTOR, Google Scholar, and the National Centre for Vector Borne Disease Control (NCVBDC) database of the Ministry of Health and Family Welfare, Government of India. Key topics include molecular docking, phytochemicals with therapeutic potential, and dengue virus proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. Although the study focused on plant phytochemicals docking with dengue viral proteins to derive drugs from plant resources, the search engine results were utilized to clarify the purpose of this review.

3. Main text

Molecular docking revealed that the main phytocomponents, such as apigenin, hesperidin, and kaempferol, have the ability to inhibit RdRp, as indicated by their interaction with the desired protein's vital active

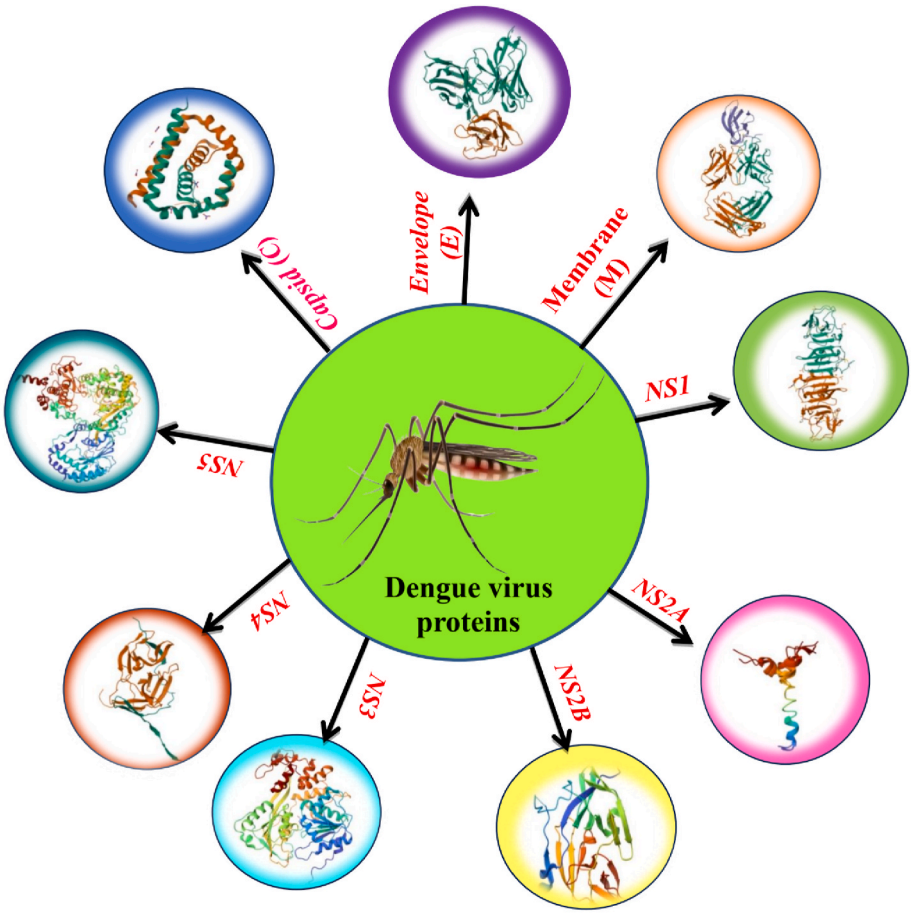

Fig. 2. Various dengue virus proteins.

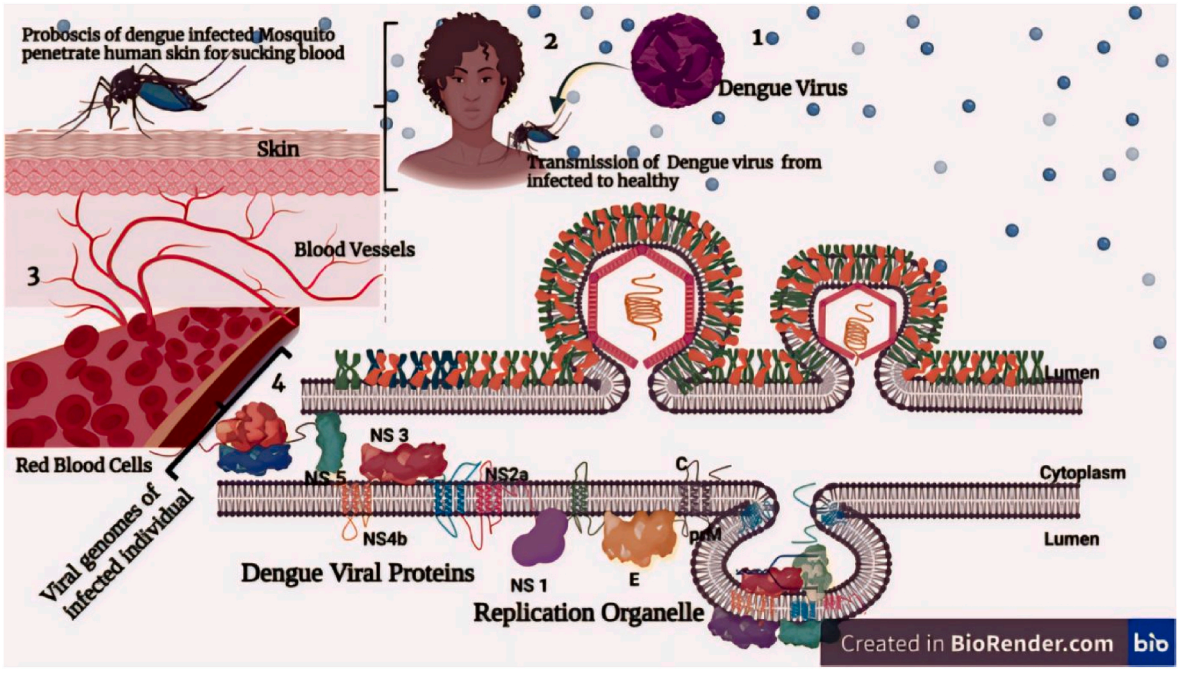

Fig. 3. Infection pathway of dengue virus proteins in human.

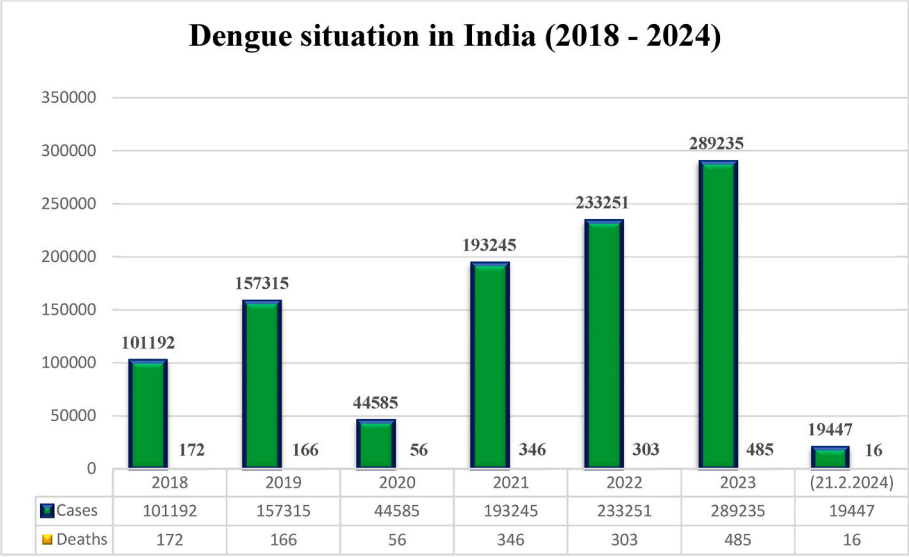

Fig. 4. Dengue situation in India (2018–2024) (NVBDCP).

amino acid residues (710 SER, 729 ARG, and 737 ARG). Apigenin showed the greatest binding affinity for RdRp (−8.28 kcal/mol), followed by kaempferol (−7.00 kcal/mol), myricetin (−4.37 kcal/mol), naringenin (−4.35 kcal/mol), and hesperidin (−3.20 kcal/mol). Among these, apigenin exhibited the highest binding affinity (−8.28 kcal/mol). This work clearly demonstrates that plant-derived bioflavonoids are antiviral against the RNA-dependent RNA polymerase (Sivaraman and Pradeep, 2020).

Qaddir et al. (2020) assessed the inhibitory effects of 18 phytochemicals from two medicinal plants, *Tanacetum parthenium* and *Silybum marianum*, on DENV4-NS1. The proposed results highlight the unique inhibitory activity of jaceidin (−7.0 kcal/mol), centaureidin (−6.4 kcal/mol), artecanin (−7.4 kcal/mol), secotanaparthenolide (−7.4 kcal/mol), artematin (−6.4 kcal/mol) for *Tanacetum parthenium*, likewise schizolaenone B (−7.7 kcal/mol), isopomiferin (−8.7 kcal/mol), 6, 8-diprenyleriodictyol (−7.8 kcal/mol), and anthraxin for *Silybum marianum*. Most phytochemicals have been shown to be utilized in humans to cure a variety of disorders.

Molecular docking studies revealed that phytocompounds from *Cyamopsis tetragonoloba* inhibit the dengue-2 virus. Molecular docking revealed that dengue-2 virus binds with 1,2-benzene dicarboxylic acid, bis(2-methylpropyl) ester (−4.1 kcal/mol), and 9,12-octadecadienoyl chloride (z,z) (−4.0 kcal/mol). *C. tetragonoloba* has been shown to have an important role in inhibiting the dengue-2 virus (Kaushik et al., 2020).

Three phytocompounds, astragaloside I, astragaloside III, and astragaloside IV, were selected based on their maximum binding energy values of dengue protein targets. Astragaloside III had the highest interaction energy values of −8.718 kcal/mol and −8.447 kcal/mol against the envelope protein and NS2b/NS3 protein respectively. Astragaloside IV showed −7.244 kcal/mol against the SAM site and −9.179 kcal/mol against the RNA cap site of NS5 targets. According to the findings of this study, astragaloside II, III, and IV molecules have the ability to inhibit the dengue virus (Indu et al., 2021).

Rahman et al. (2021) studied antiviral phytochemicals such as safficinolide, sageone, thymohydroquinone, thymol, thymoquinone, zingerone, cyanidin 3-glucoside, dithymoquinone, gingerol, glabridin, hibiscus acid, carvacrol, and lopinavir. Among these phytocompounds, cyanidin 3-glucoside (−8.0 kcal/mol), glabridin (−7.4 kcal/mol), lopinavir (−7.4 kcal/mol), and dithymoquinone (−7.3 kcal/mol) are effective inhibitors of the dengue virus NS3 protease.

Polyphenols docking against the dengue protein NS2B47-NS3, the polyphenol (R)-(+)-rosmarinic acid had a docking score of −8.451 kcal/mol and an energy value of −59,860. Curcumin has the second-best docking score of −8.221, followed by D-(+)-catechin (−7.042 kcal/mol) and epicatechin (−7.069). Furthermore, molecular dynamic simulations show that the complex of (R)-(+)-rosmarinic acid and dengue protein provides an in-depth understanding of their specific interactions (Rani et al., 2022).

Mangiferin, a phytocompound derived from *Mangifera indica* L, has been shown in various studies to have potential pharmacological properties including analgesic, anti-aging, anti-cancer, anti-diabetic, antioxidant, anti-proliferative, antiviral, cardiotonic, diuretic, hepatoprotective, and immunomodulatory effects. Kalaimathi et al. (2022) investigated mangiferin's potential via molecular docking with selected dengue enzymes. The docking studies indicate that mangiferin may be against dengue virus (1UZG at −9.729 kcal/mol), dengue virus 3 (NS2B/NS3 at −8.066 kcal/mol), and non-structural protein 5 (NS5 at −9.868 kcal/mol). The data demonstrate that mangiferin has high docking scores and strong binding affinities to all docked proteins.

The NS5 RNA-dependent RNA polymerase (RdRp) docked against various phytochemicals such as curcumin, apigenin, andrographolide, berberine, and (+)-1-alliin. The docking results revealed that all phytocomponents, with the exception of berberine and (+)-1-alliin, had good docking scores of −8.577 kcal/mol (azadirachtin), −8.112 kcal/mol (curcumin), −7.348 kcal/mol (apigenin), and −6.028 kcal/mol (andrographolide). However, berberine and (+)-1-alliin had excellent hydrogen-bonding interactions with RdRp. In conclusion, the data suggest that not only azadirachtin but also curcumin, apigenin, andrographolide, and berberine have strong therapeutic potential against the dengue virus (Rani et al., 2022).

According to Shimu et al. (2022), the dengue viral protease NS2B/NS3 docks with 27 phytocompounds. The top three active compounds identified based on binding results were phellodendroside (−63 kcal/mol), quercimeritrin (−59.5 kcal/mol), and quercetin-7-*O*-rutinoside (−54.1 kcal/mol). The pharmaceutical compounds induced numerous interactions at Lys74, Asn152, and Gln167 residues in the active areas of NS2B/NS3, which are required for the protein's inhibition.

Phytocompounds from *Azadirachta indica, Andrographis paniculata, Tinospora cordifolia*, and *Carica papaya* were screened against Dengue 4 envelope protein domain II ED3 (3WE1), envelope protein domain III (5BIC), Dengue 3 NS5 Methyltransferase (5EC8), and Dengue virus 1 NS5 Methyltransferase (5IKM). As a result, nimbocinol and meliacinanhydride from *A. indica* were the most effective phytocompounds against dengue viral proteins, with the highest binding affinity.

Table 1
Docking interactions between ligand and the various dengue viral proteins.

S. no	*Source of ligands*	Protein (Target)	Phytocompounds (Ligands)	Docking score	References
1.	*Capsicum frutescens*	2J7U (NS5 RNA Dependent RNA polymerase (RdRp))	Apigenin	−8.2	Sivaraman and Pradeep, 2020
	Citrus aurantium, Citrus sinensis, Citrus unshiu, and Citrus mitis		Hesperidin	−3.0	
	Euphorbia pekinensis, Ginkgo biloba L, *and Rosmarinus officinalis*		Kaempferol	−7.0	
	Myrica rubra		Myricetin	−4.3	
	Vitis vinifera		Naringenin	−4.3	
2.	*Tanacetum parthenium*	4O6B (Non-structural protein 1)	Centaureidin	−6.4	Qaddir et al. (2020)
			Parthenolide	−8.6	
			Jaceidin	−7.0	
			Santin	−7.4	
			Secotanaparthenolide B	−7.4	
			Quercetin	−8.0	
			Artecanin	−7.4	
			Artematin	−6.4	
	Silybum marianum	4O6B (Non-structural protein 1)	2,3-dehydrosilybin	−7.8	
			Silybin A	−7.7	
			Silymarin	−7.6	
			Flavobion	−7.7	
			6,8-diprenyleriodictyol	−7.8	
			Anthraxin	−7.7	
			Silydianin A	−8.6	
			Schizolaenone B	−7.7	
			Isopomiferin	−8.7	
3.	*Andrographis paniculata*	1PZ4 (Sterol carrying protein-2)	Paniculide A	−8.6	Paul et al. (2020)
			Panicolin	−9.8	
			3 O beta D glucosyl 14 deoxyandrographolide	−8.9	
			6 acetylneoandrographolide	−9.1	
			Andrographolactone	−9.3	
			3 oxo 14 deoxyandrographolide	−8.8	
	Tinospora cordifolia	1PZ4 (Sterol carrying protein-2)	Beta sitosterol	−9.1	
			Berberine	−10.3	
			Chasmanthin	−6.5	
			Palmatine	−6.9	
			Tetrahydropalmatine	−6.4	
			Tinocordifolin	−6.3	
4.	*Cyamopsis tetragonoloba*	4O6B (Non-structural protein 1)	1,2-benzenedicarboxylic acid, bis (2-methylpropyl) ester	−4.1	Kaushik et al. (2020)
			9,12- Octadecadienoyl chloride (z,z)	−4.0	
			Dodecanoic acid	−3.9	
			Tridecanoic acid, 12-methyl-, methyl-ester	−3.8	
			3,7,11,15-tetramethyl-2 hexadecen-1-ol	−3.8	
			Methyl dodecanoic acid	−3.6	
			Methyl stearate	−3.0	
			Hexadecanoic acid, 15-methyl-, methyl ester	−3.0	
			Tetracontane, 3,5,24-trimethyl	−2.5	
			Tritetracontane	−2.3	
5.	*Dicentra cucullaria, Adlumia fungosa*	2FOM (Polyprotein)	Bicuculline	−8.8	Cadiz et al., 2020
	Chelidonium majus		(S)-stylopine	−8.5	
	Citrus aurantium, Citrus sinensis, Citrus unshiu, and Citrus mitis		Limonin	−9.3	
	Corydalis ternate and *Fumaria indica*		Pseudoprotopine	−9.0	
	Corydalis solida and *Corydalis racemosa*		Stylopine	−8.9	
	Strychnos colubrina		Angustidine	−9.4	
	Dicentra cucullaria, Adlumia fungosa	2JLQ (Serine protease)	Bicuculline	−9.4	
	Chelidonium majus		(S)-stylopine	−9.1	
	Citrus aurantium, Citrus sinensis, Citrus unshiu, and *Citrus mitis*		Limonin	−10.5	
	Corydalis ternate and *Fumaria indica*		Pseudoprotopine	−9.8	
	Corydalis solida and *Corydalis racemosa*		Stylopine	−9.3	
	Strychnos colubrina		Angustidine	−10.1	
6.	*PubChem, NPACT*	1OKE (Major envelope protein)	BOG	−8.3	Indu et al. (2021)
	Astragalus hoantchy and *Astragalus lepsensis*		Astragaloside III	−8.7	
			Astragaloside IV	−7.4	

(*continued on next page*)

Table 1 (*continued*)

S. no	*Source of ligands*	Protein (Target)	Phytocompounds (Ligands)	Docking score	References
			Astragaloside II	−5.0	
	Escherichia coli	1R6A (Genome polyprotein)	S-adenosyl-L-homocysteine	−11.6	
	Astragalus hoantchy and *Astragalus lepsensis*		Astragaloside IV	−7.2	
			Astragaloside II	−6.8	
			Astragaloside III	−5.9	
		1R6A (Genome polyprotein)	RPV	−8.00	
	Astragalus hoantchy and *Astragalus lepsensis*		Astragaloside IV	−9.1	
			Astragaloside II	−8.6	
			Astragaloside III	−6.3	
	Astragalus hoantchy and *Astragalus lepsensis*	4M9K (NS2B-NS3 protease)	Astragaloside III	−8.4	
			Astragaloside IV	−7.4	
			Astragaloside II	−6.7	
7.	*PubChem CID:92430*	5V13 (Mosquito Juvenile Hormone-binding protein)	Silafluofen	−10.9	Ononamadu et al. (2021)
	PubChem CID:10342051		Esfenvalerate	−10.7	
	PubChem CID:50980		Flucythrinate	−10.6	
	PubChem CID:5053		Resmethrin	−10.6	
	PubChem CID:71245		Ethofenprox	−10.6	
	PubChem CID:4767		Phenothrin	−10.5	
	PubChem CID:83975		Tetramethrin	−10.4	
	PubChem CID:123622		Imiprothrin	−10.5	
8.	*Salvia officinalis*	2FOM (Polyprotein)	Safficinolide	−6.3	Rahman et al. (2021)
	Salvia officinalis		Sageone	−6.9	
	Nigella sativa		Thymohydroquinone	−5.4	
	Thymus vulgaris, Acanthospermum austral and *Humulus lupulus,*		Thymol	−5.4	
	Thymus vulgaris and *Monarda fistulosa*		Thymoquinone	−5.6	
	Alpinia officinarum, Aframomum melegueta		Zingerone	−5.7	
	Alcea rosea		Cyanidin 3-glucoside	−8.0	
	Nigella sativa		Dithymoquinone	−7.3	
	Cuminum cyminum, Aframomum melegueta		Gingerol	−6.1	
	Glycyrrhiza glabra, Glycyrrhiza uralensis and *Ornithopus sativus*		Glabridin	−7.4	
	Hibiscus rosa sinensis		Hibiscus acid	−5.7	
	Callistemon citrinus, Perilla frutescens and *Origanum vulgare*		Carvacrol	−5.5	
	PubChem CID:11979606		Lopinavir	−7.4	
9.	*Salvia miltiorrhiza* and *Aspergillus duricaulis*	NS2B47-NS3 (Polyphenols)	Rosmarinic acid	−8.4	Rani et al. (2022)
	Curcuma longa L		Curcumin	−8.2	
	Camellia sinensis and *Paeonia obovata*		Catechin	−7.0	
10.	*Mangifera indica*	2J7U (RNA Dependent RNA Polymerase)	Mangiferin	−9.6	Kalaimathi et al. (2022)
		1UZG (Major Envelope Protein E)	Mangiferin	−9.7	
		3L6P (Fusion protein of nonstructural protein 2B and nonstructural protein 3)	Mangiferin	−8.0	
11.	*Azadirachta indica*	2J7W (Polyprotein)	Azadirachtin	−8.5	Rani et al. (2022)
	Curcuma longa L		Curcumin	−8.1	
	Allium fstulosum L. *Caricca Papaya* L		Apigenin	−7.3	
	Andrographis paniculata		Andrographolide	−6.0	
	Berberis vulgaris		Berberine	−5.1	
	Allium sativum L *and Allium ursinum* L		- (+)-*l*-Alliin	−4.0	
12.	*Tetradium ruticarpum* and *Zanthoxylum wutaiense*	2FOM (Polyprotein)	Rutaecarpine	−4.2	Shimu et al. (2022)
	Sesamum indicum L		Sesamin	−5.3	
	Choerospondias axillaris		Choerospondin	−6.3	
	Evodia rutaecarpa		Evodiamine	−4.7	
	Citrus sulcata and *Citrus reticulata*		Narirutin	−5	
	Strychnos colubrina		Angustidine	−4.6	
	Forsythia suspensa		Forsythoside A	−6.0	
	Laburnum anagyroides		Luteone	−5.8	

(*continued on next page*)

Table 1 (*continued*)

S. no	*Source of ligands*	Protein (Target)	Phytocompounds (Ligands)	Docking score	References
	Camellia sinensis, Spiranthes vernalis and *Galinsoga parviflora*		Quercimeritrin	−5.2	
	Salvia sclarea and *Salvia przewalskii*		Hydroxytanshinone	−5.1	
	Ophiopogon japonicus		Methylophiopogonanone A	−5.0	
	Salvia miltiorrhiza		Tanshinlactone	−4.6	
	Aristolochia galeata and *Lindera praecox*		Asarinin	−5.3	
	Magnolia grandiflora		Piperitylhonokiol	−4.6	
	Trypanosoma cruzi		Sanjoinine B	−4.3	
	Trypanosoma cruzi		Sanjoinine D	−3.7	
	Trypanosoma cruzi		Scutianine D	−3.4	
	Trypanosoma cruzi		Scutianine C	−4.1	
	Glycyrrhiza glabra L		6″-*o*-acetylliquiritin	−5.2	
	Phellodendron amurense		Phellodendroside	−5.1	
	Abies nephrolepis, Opuntia ficus-indica		Quercetin-7-*o*-rutinoside	−5.0	
	Forsythia koreana, Forsythia suspensa, and *Forsythia viridissima*		(S)-suspensaside	−4.7	
	PubChem SID:275700413		Paeonidanin B	−5.6	
	PubChem SID:274222159		Phellamuretin	−5.5	
	Salvia miltiorrhiza, Salvia przewalskii, and *Salvia yunnanensis*		Nortanshinone	−6.1	
	Angelica japonica and *Ostericum grosseserratum*		Sec-*o*-glucosylhamaudol	−4.4	
	Paeonia suffruticosa		Benzoyloxypaeoniflorin	−4.9	
13.	*Andrographis paniculata*	3WE1 (Envelope protein E)	14-deoxyandrographolide	−6.4	Gnaneswari et al. (2022)
			Andrograpanin	−6.4	
			14-acetylandrograpolide	−5.8	
		5B1C (Envelope protein E)	Andrographolide	−6.5	
			14-deoxyandrographolide	−6.0	
			Andrograpanin	−5.7	
		5EC8 (Genome polyprotein)	14-deoxy-11-oxoandrographolide	−5.9	
			Isoandrographolide	−5.8	
			Andrograpanin	−5.6	
		5IKM (NS5 Methyl Transferase)	Andrograpanin	−7.2	
			Neoandrographolide	−6.7	
			Andrographolide	−6.7	
	Azadirachta indica	3WE1 (Envelope protein E)	Meliaacinanhydride	−9.2	
			Nimbocinol	−6.6	
			Isomeldenin	−6.1	
		5B1C (Envelope protein E)	Nimbocinol	−6.7	
			Zafaral	−6.5	
			Meliaacinanhydride	−5.9	
		5EC8 (Genome polyprotein)	Nimbocinol	−8.0	
			Isomeldenin	−6.3	
			Meliaacinanhydride	−6.3	
		5IKM (NS5 Methyl Transferase)	Nimbocinol	−8.7	
			Meliaacinanhydride	−7.7	
			Zafaral	−7.5	
	Carica papaya	3WE1 (Envelope protein E)	Coumaric acid	−5.7	
			Caffeic acid	−5.6	
			Kaempferol	−5.0	
		5B1C (Envelope protein E)	Kaempferol	−4.8	
			Coumaric acid	−4.6	
			Protocatechuic acid	−4.5	
		5EC8 (Genome polyprotein)	Coumaric acid	−5.6	
			Caffeic acid	−5.2	
			Protocatechuic acid	−4.9	
		5IKM (NS5 Methyl Transferase)	Coumaric acid	−5.9	
			Citropten	−5.2	
			Kaempferol	−5.2	
	Tinospora cordifolia	3WE1 (Envelope protein E)	Tinosporide	−6.6	
			Berberine	−5.6	
			Palmatine	−5.4	
		5B1C (Envelope protein E)	Magnoflorine	−6.4	
			Berberine	−6.0	
			Tinosporide	−5.8	
		5EC8 (Genome polyprotein)	Berberine	−6.5	
			Tinosporide	−5.9	
			Tinocordifolin	−5.6	
		5IKM (NS5 Methyl Transferase)	Tinosporide	−7.5	

(*continued on next page*)

Table 1 (*continued*)

S. no	*Source of ligands*	Protein (Target)	Phytocompounds (Ligands)	Docking score	References
			Berberine	−7.3	
			Palmatine	−7.1	
		3WE1 (Envelope protein E)	Tinosporide	−6.6	
			Berberine	−5.6	
			Palmatine	−7.1	
14.	*Salvia miltiorrhiza* and *Hydrangea serrata*	2FOM (Polyprotein)	Quercetin	−8.2	Biswas et al. (2022)
	Solanum melongena		Melongoside P	−9.5	
	Solanum melongena		Melongoside O	−9.0	
	Solanum melongena		Melongoside G	−8.1	
	Solanum melongena		Melongoside N	−7.5	
	Solanum melongena		Melongoside F	−6.6	
	Solanum melongena		Melongoside H	−5.0	
	Solanum melongena		Melongoside B	−4.6	
15.	*Myrica rubra*	3VWS (Non-structural protein 5)	Myricetin	−10.4	
	Citrus unshiu, and *Citrus mitis*		Hesperidin	−9.8	
	Glycine max and *Streptomyces*		Fisetin	−9.7	
	Salvia miltiorrhiza and *Hydrangea serrata*		Quercetin	−8.5	
	Camellia sinensis		Galangin	−8.0	
	Camellia sinensis and *Salvia officinalis*		Hesperetin	−7.7	
	Camellia sinensis and *Humulus lupulus*		Naringenin	−5.6	
16.	*Ginseng* and *Notoginseng*	4R8S (Nonstructural protein NS5)	Isoquercitrin	−9.0	Jarerattanachat et al. (2022)
			Quercetin	−7.7	
			Adenosine	−7.4	
			Syringin	−7.3	
			P-Glucosyloxymandelonitrile	−7.2	
			Pancratistatin	−7.1	
			Dianthramine	−7.0	
			Protopanaxatriol	−6.9	
			Kaempferol	−6.8	
			Gypenoside-A	−6.7	
			Ramalic acid	−6.6	
			Suchilactone	−6.3	
			Celabenzine (H+)	−6.3	
			Protopanaxadiol	−6.3	
			Dencichin (H+)	−6.3	
			5-(E)-heptadec-12-enyl benzene-1,3-diol	−6.3	
			(3R,8E,10S)-10-hydroperoxyheptadeca-1,8-dien-4,6-diyn-3-ol	−6.2	
			(3S,5R,8R,9R,10R,14R,17S)-17-(2-hydroxy-6-methylhept-5-en-2-yl)-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[*a*]phenanthren-3-ol	−6.2	
			Ginsenoyne B	−6.2	
17.	*Phoenix dactylifera*	2FOM (Polyprotein)	Campesterol	−8.7	Al-Keridis et al. (2022)
			Isofucosterol	−6.2	
			Genistein	−8.8	
			Glycitin	−7.7	
			Pformonetin	−9.3	
			Matairesinol	−8.9	
			Lariciresinol	−8.8	
			Pinoresinol	−8.7	
			Secoisolariciresinol	−6.6	
			Coumestrol	−9.5	
18.	*Lantana camara*	1PZ4 (Sterol carrier protein)	Pectolinaringenin	−8.7	Anita and Selvaraj. (2022)
			Naphthalene, decahydro2,2-dimethyl	−7.9	
			Gamolenic acid	−7.8	
19.	*Commiphora gileadensis*	2J7W (NS5 RNA dependent RNA polymerase)	Guggulsterone	−5.4	Abdulhakim (2022)
			Ribavirin	−6.2	
		1L9K (Methyl-transferase)	Guggulsterone	−4.7	
			Ribavirin	−5.7	
		2VBC (NS3 protease-helicase)	Guggulsterone	−4.1	
			Ribavirin	−6.2	
		1OK8 (Dengue virus type 2 envelope glycoprotein)	Guggulsterone	−3.4	
			Ribavirin	−6.4	
20.	*Marine fungi*	2FOM (Polyprotein)	Chevalone E	−13.5	Hasan et al. (2022)
			Sterolic acid	−10.3	
			Brevione K	−9.2	

(*continued on next page*)

Table 1 (*continued*)

S. no	*Source of ligands*	Protein (Target)	Phytocompounds (Ligands)	Docking score	References
			Brevione F	−9.0	
			Lindgomycin	−8.7	
		61ZZ (NS5 methyltransferase)	Chevalone E	−12.0	
			Sterolic acid	−7.0	
			Brevione K	−7.4	
			Brevione F	−7.1	
			Brocazine A	−7.1	
21.	*Solanum torvum*	IPZ4 (Protease Sterol Carrier Protein-2)	5-Isopropyl-2-methylphenyl heptanoate	−8.0	Murugesan et al. (2023)
			Benzene, 1-(bromomethyl)-3-nitro	−6.5	
			Geranylacetone7.5	−7.5	
			Hexylamine, N, N-di(allyl)	−5.1	
			Myristic acid	−6.7	
			Neophytadiene	−9.3	
			N-Hexadecanoic acid	−6.9	
			Nonadecene	−6.5	
			Phytol	−7.9	
			7-tetradecyne	−6.3	
			Linolenic acid	−7.8	
			6,10,14,18,22-Tetracosapentaen-2-ol, 3-bromo-2,6,10,15,19,23-hexamethyl-, (all-E)	−8.7	
			Alpha-Tocopherol-beta-D-mannoside	−5.7	
			Campesterin	−10.0	
			Tetracosahexaen	−7.7	
22.	*Salvia miltiorrhiza* and *Aspergillus duricaulis*	4FFY (Single chain variable fragment)	Rosmarinic acid	−8.0	Murugesan et al. (2023)
		(2BMF) RNA helicase	Rosmarinic acid	−8.6	
		4O6B (Non-structural protein)	Rosmarinic acid	−7.9	
		2J7U (RNA dependent RNA polymerase)	Rosmarinic acid	−8.1	
23.	*Salvia miltiorrhiza* and *Aspergillus duricaulis*	2J7W (Polyprotein)	Rosmarinic acid	−10.0	Samy et al., 2023
		4OIG (Non-structural protein 1, NS1)	Rosmarinic acid	−7.2	
24.	*Carica papaya*	5E9Q (Genome polyprotein)	Rutin	−4.5	Shakya (2023)
	Curcuma longa L		Curcumin	−5.2	
	Magnolia officinalis and *Artemisia xerophytica*		D-camphor	−5.2	
	Salvia miltiorrhiza and *Hydrangea serrata*		Quercetin	−5.4	
			Amentoflavone	−6.0	
25.	*Commiphora wightti*	2J7U (NS5- Methyl transferase)	Commipherin	−8.2	Jain et al. (2023)
			Myrrhanone B	−8.0	
		3UZV (Envelope E-protein)	Myrrhanone A acetate	−11.8	
			Myrrhanone B	−11.1	
26.	*Carica papaya*	4O6B (Non-structural protein 1)	Olean-12-ene	−10.3	Banjan et al. (2023)
			Kaempferol 3-(200- rhamnosylrutinoside)	−9.4	
			Dehydrocarpaine_I	−9.2	
			Carpaine	−9.0	
			Manghaslin	−9.0	
			Obtusol	−9.0	
			Clitorin	−8.9	
			Pseudocarpaine	−8.9	
			Rutin	−8.9	
			Nicotiflorin	−8.5	
			Cardenolide	−8.5	
			Apigenin	−8.2	
			Stigmasterol	−8.2	
			Myricetin 3-rhamnoside	−8.1	
27.	*Centaurea spinosa*	1OKE (Major Envelope Protein E)	Malacitanolide	−7.0	Ragavan et al. (2023)
	Aspergillus ochraceopetaliformis and *Aspergillus versicolor*		Paclitaxel	−6.8	
			Ressantin E	−4.4	
	Aspergillus ochraceopetaliformis and *Aspergillus versicolor*	1R6A (Genome polyprotein)	Paclitaxel	−9.3	
	Centaurea spinosa		Malacitanolide	−6.1	
			Ressantin E	−5.8	
	Centaurea spinosa	1R6A (Genome polyprotein)	Malacitanolide	−5.2	
	Aspergillus ochraceopetaliformis and *Aspergillus versicolor*		Paclitaxel	−3.3	
	Centaurea spinosa	4M9K (NS2B-NS3 protease)	Malacitanolide	−4.0	
			Ressantin E	−3.9	
			Paclitaxel	−2.0	

(*continued on next page*)

Table 1 (*continued*)

S. no	*Source of ligands*	Protein (Target)	Phytocompounds (Ligands)	Docking score	References
28.	*Dracaena cinnabari*	4FFY (DENV1-E111 single chain variable fragment)	Stigmasterol	−7.1	Abutaha and Almutairi. (2023)
			Campesterol	−7.3	
			2-ethylacridine	−6.0	
		2FOM (Polyprotein)	Stigmasterol	−8.2	
			Campesterol	−7.9	
			2-ethylacridine	−7.0	
			Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2- (1-methylethenyl)	−7.2	
		3WE1 (Envelope protein E)	Stigmasterol	−6.8	
			Campesterol	−6.4	
			2-ethylacridine	−6.6	
			Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2- (1-methylethenyl)	−5.8	
		2J7U (RNA Dependent RNA Polymerase)	Stigmasterol	−8.2	
			Campesterol	−8.3	
			2-ethylacridine	−7.1	
			Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2- (1-methylethenyl)	−6.2	
		2BMF (RNA Helicase)	Stigmasterol	−7.3	
			Campesterol	−7.6	
			2-ethylacridine	−8.0	
			Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2- (1-methylethenyl)	−5.8	
		4V0Q (NS5 Polymerase)	Stigmasterol	−9.0	
			Campesterol	−7.8	
			2-ethylacridine	−7.4	
			Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2- (1-methylethenyl)	−8.0	
		4O6B (Non-structural protein 1)	Stigmasterol	−8.9	
			Campesterol	−8.1	
			2-ethylacridine	−6.3	
			Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2- (1-methylethenyl)	−5.8	
29.	*PMID: 28530609*	1OKE (Major Envelope Protein E)	1-*O*-β-D-glucopyranosyl sinapate	−7.7	Roney et al. (2023)
			Sinapoyl malate	−6.7	
30.	*Theobroma cacao*	DENV-3 NS5 (RdRp protein)	Panduratin A	−37.4	Huq et al. (2024)
			(+)-Catechin	−42.3	
			Amentoflavone	−50.8	
			Apigenin 7-*O*-glucoside	−55.0	
			Apigenin	−36.1	
			Caffeic acid	−28.9	
			Chlorogenic acid	−46.6	
			Coumaric acid	−27.6	
			Ferulic acid	−28.2	
			Gallic acid	−26.7	
			Hyperoside	−47.0	
			Isoorientin	−44.6	
			Isorhamnetin	−39.9	
			Isorhoifolin	−57.2	
			Isovitexin	−49.6	
			Kaempferol 3-*O*-β-D-glucoside	−49.5	
			Kaempferol-7-oneohesperidoside	−51.8	
			Luteolin	−39.2	
			Naringenin	−34.7	
			Naringin	−60.2	
			Nicotiflorin	−54.5	
			Orientin	−51.3	
			Protocatechuic acid	−25.3	
			Prunin	−54.6	
			Quercetin	−40.2	
			Quercitrin	−48.5	
			Rutin	−60.4	
			Luteolin 7-*O*-β-D-glucoside	−44.0	
			Isoquercetin	−44.5	
31.	*Daphnia pulex* and *Drosophila melanogaster*	6KR2 (Genome polyprotein)	S-adenosyl-L-homocysteine	−12.1	Mazri et al. (2024)
	PubChem CID:82972		1-Amino-4-((4-((dimethylamino)methyl) phenyl) amino) anthraquinone	−11.6	
	Aspergillus iizukae and *Silybum eburneum*		Silibinin	−11.3	

(*continued on next page*)

Table 1 (*continued*)

S. no	*Source of ligands*	Protein (Target)	Phytocompounds (Ligands)	Docking score	References
	Cinnamomum iners, *Cinnamomum aromaticum*, and *Cinnamomum verum*		Cinnzeylanine	−11.0	
	Valeriana officinalis		Valerenic acid	−10.0	
	Daphnia pulex and *Drosophila melanogaster*		S-adenosyl-L-homocysteine	−9.1	

Andrographolide from *A. paniculata*, tinosporide, and berberine from *T. cordifolia* also showed high efficiency against viral proteins (Gnaneswari et al., 2022).

Molecular docking was used to evaluate melongosides as possible inhibitors of the dengue virus NS2B-NS3 (serotype 2). Quercetin (control) exhibited a binding affinity of −8.2 kcal/mol, but melongoside P had the best fitting score of −9.5 kcal/mol. Other potential phytochemicals, such as melongoside O and melongoside G, exhibited docking values of −9.01 kcal/mol and −8.11 kcal/mol, respectively. The findings indicated that steroidal saponins (melongosides) are prospective DENV inhibitors, which, if confirmed in vivo and in clinical trials, might be therapeutic targets against DENV-2 (Biswas et al., 2022).

The interaction of 3VWS (Non-structural protein 5) with fisetin, galangin, hesperetin, hesperidin, myricetin, and naringenin was studied using molecular docking. The docking score of different compounds findings, with myricetin (−10.145 kcal/mol), hesperidin (−9.842 kcal/mol), fisetin (−9.796 kcal/mol), quercetin (−8.513 kcal/mol), galangin (−8.036 kcal/mol), hesperetin (−7.761 kcal/mol), and naringenin (−5.634 kcal/mol) showing strong performance. Among them, myricetin (−10.145 kcal/mol) has high docking score.

Lim et al. (2021) found that reports on medicinal plants against the dengue virus have not identified ginseng or notoginseng as viable herbs. However, a study was conducted to test the potential of compounds in Panax ginseng and/or Panax notoginseng as antiviral agents against dengue NS5 Methyltransferase (MTase). Isoquercitrin (−9.0) was identified as a single hit during the virtual screening process. Further analysis revealed that isoquercitrin may work as an inhibitor of the dengue NS5 protein at the MTase domain, proving its potential as an anti-DENV substance.

Hasan et al. (2022) identified 162 compounds from marine fungi with active bioavailability and examined compounds that could potentially inhibit the activity of dengue virus proteins. Of the 162 molecules, 41 were chosen for docking with NS5 methyltransferase and NS2B/NS3 protease (6IZZ and 2FOM, respectively). Chevalone E (−13.5 kcal/mol) and sterolic acid (−10.1 kcal/mol) showed greater binding energy against dengue NS2B/NS3 protease, but Chevalone E (−12.0 kcal/mol) and Brevione K (−7.3 kcal/mol) had higher binding affinity against NS5 methyltransferase. According to the study, Chevalone E is an effective inhibitor of NS5 methyltransferase and NS2B/NS3 protease.

(R)-(+)-Rosmarinic acid is recognized as a promising phytochemical in the field of pharmaceuticals due to its diverse pharmacological properties. The study aimed to evaluate the antiviral activity of (R)-(+)-rosmarinic acid against dengue viruses. The investigations revealed that (R)-(+)-rosmarinic acid had significant docking scores of −10.033 kcal/mol for NS5 and -7.259 kcal/mol for NS1, Rosmarinic acid suggesting potential therapeutic efficacy against dengue virus replication (Samy et al., 2023).

Theobroma cacao L. phenolic molecules bind to dengue RdRp protease. The results showed 29 phenolic compounds from *T. cacao*, with catechin having a high affinity with the active binding site of DENV3-NS5 RdRp protease (Huq et al., 2024). Mazri et al. (2024) conducted molecular docking on five compounds with the NS5 non-structural protein dengue protease, and the results indicated that the S-adenosyl-L-homocysteine (−12 kcal/mol) showed highly favorable docking with the NS5 protein.

4. Discussion and conclusion

In this view, predict the antiviral properties of various plant compounds. The viral activity and docking energy vary for various plant phytocompounds for various reasons, including plant species, parts of the plants used, age of the plants, and different viral proteins. In this literature review, ligands from various plants and other sources and dock with various dengue viral proteins, and docking energy is summarized in Table 1.

The majority of the investigation concentrated to testing dengue proteins against diverse phytocompounds exclusively using the in-silico approach. Conversely, just a few research have been undertaken in vivo and in vitro.

The challenge to of finding promising plant compounds, their deficient characterization, and a lack of knowledge about the molecular makeup of the active plants compounds that are responsible for diverse dengue virus inhibition are the main reasons of plant-based drug unsuccessful. In addition, various plant species need to be examined to uncover a diverse range of plants capable of controlling the dengue virus.

In conclusion, the global burden of dengue fever remains significant, with *Aedes* mosquitoes serving as primary vectors transmitting the virus to humans. Traditional control measures using synthetic chemicals have drawbacks, prompting exploration into alternative strategies utilizing plant-derived compounds. This review highlighted the promising antiviral properties of various phytochemicals against dengue virus proteins, as demonstrated through molecular docking studies. Compounds like apigenin, hesperidin, and kaempferol exhibited substantial binding affinities with viral proteins, suggesting their potential as therapeutic agents. Future research should focus on validating these findings through in vivo and clinical studies to advance their application in combating dengue fever effectively and sustainably. Integrating plant-based solutions into integrated vector management strategies could offer cost-effective and environmentally friendly alternatives to conventional control methods, thereby mitigating the impact of dengue outbreaks worldwide.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

K. Dass: Writing – review & editing, Writing – original draft,

Methodology, Investigation, Conceptualization. **N. Prakash:** Methodology, Conceptualization. **P. Manogar:** Validation, Data curation. **R. Murugesan:** Visualization, Validation, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

No acknowledgment.

References

Abdulhakim, J.A., 2022. Effect of guggulsterone, a sterol identified in *Commiphora gileadensis* (Becham), on the dengue virus enzymes: pharmacokinetics, molecular docking and molecular dynamics simulations studies. J. King Saud Univ. Sci. 1 (6), 102140 https://doi.org/10.1016/j.jksus.2022.102140, 34.

Abutaha, N., Almutairi, B.O., 2023. Exploring the therapeutic potential of GC–MS separated compounds from *Dracaena cinnabari* against dengue virus and *Aedes aegypti* using in silico tools. J. King Saud Univ. Sci. 1 (2), 102478, 35.

Agnihotry, S., Pathak, R.K., Srivastav, A., Shukla, P.K., Gautam, B., 2020. Molecular docking and structure-based drug design. Computer-aided drug design 115–131. https://doi.org/10.1007/978-981-15-6815-2_6.

Al-Keridis, L.A., Abutaha, N., AL-mekhlafi, F.A., Rady, A.M., Al-Khalifa, M.S., 2022. Larvicidal and antiviral nature of *Phoenix dactylifera* L. natural products by targeting dengue virus and *Aedes aegypti* L. Proteins through molecular docking. J. King Saud Univ. Sci. 1 (7), 102274 https://doi.org/10.1016/j.jksus.2022.102274, 34.

Anita, A., Selvaraj, D., 2022. In silico molecular docking study of plant-based compounds from medicinal plant *Lantana camara* L. against *Aedes aegypti* L. protein. International Journal of Mosquito Research 9 (6), 97–106. https://doi.org/10.22271/23487941.2022.v9.i6b.645.

Anwar, T., Kumar, P., Khan, A.U., 2021. Modern tools and techniques in computer-aided drug design. In: Molecular Docking for Computer-Aided Drug Design. Academic Press, pp. 1–30. https://doi.org/10.1016/B978-0-12-822312-3.00011-4.

Banjan, B., Krishnan, D., Koshy, A.J., Soman, S., Leelamma, A., Raju, R., Revikumar, A., 2023. In-silico screening and identification of potential drug-like compounds for dengue-associated thrombocytopenia from *Carica papaya* leaf extracts. J. Biomol. Struct. Dyn. 26, 1–9. https://doi.org/10.1080/07391102.2023.2230293.

Benfrid, S., Park, K.H., Dellarole, M., Voss, J.E., Tamietti, C., Pehau-Arnaudet, G., Raynal, B., Brûlé, S., England, P., Zhang, X., Mikhailova, A., 2022. Dengue virus NS1 protein conveys pro-inflammatory signals by docking onto high-density lipoproteins. EMBO Rep. 23 (7) https://doi.org/10.15252/embr.202153600.

Bharatam, P.V., 2021. Computer-aided drug design. Drug Discov. Dev.: From targets and molecules to medicines 137–210. https://doi.org/10.1007/978-981-15-5534-3_6.

Biswas, P., Hany Rumi, O., Ahmed Khan, D., Ahmed, M.N., Nahar, N., Jahan, R., Hasan Zilani, M.N., Paul, T.K., Hasan, A., Bondhon, T.A., Jannat, K., 2022. Evaluation of melongosides as potential inhibitors of NS2B-NS3 activator-protease of dengue virus (Serotype 2) by using molecular docking and dynamics simulation approach. J. Trop. Med. https://doi.org/10.1155/2022/7111786.

Cadiz, J.M., Susana, C.J., Endriga, M.A., Frio, E.J., 2020. Molecular Docking of Traditional Chinese Medicinal Compounds against Dengue Virus NS3 Protease and NS3 Helicase. IEEE International Conference on Bioinformatics and Biomedicine. https://doi.org/10.1109/BIBM49941.2020.9312980 (BIBM) 1901-1908.

Dass, K., Mariappan, P., 2014a. Larvicidal Activity of Aegle marmelos, Coleus aromaticus and Vitex negundo leaf extract against filarial vector Culex quinquefasciatus. Türk Tarım ve Doğa Bilimleri Dergisi 1 (1), 858–862, 2014.

Dass, K., Mariappan, P., 2018. Insecticidal activity of green synthesized silver nanoparticles using coleus aromaticus and wrightia tinctoria leaf extracts against Culex quinquefasciatus. Vector Biol J 3, 2. https://doi.org/10.4172/2473-4810.1000131.

Dass, K., Mariappan, P., 1998. A study on diversity of mosquito fauna in Thanjavur urban, Tamilnadu, India. Environ. Sci. J. Integr. Environ. Res. 2 (1), 7–16.

Dass, K., Mariappan, P., 2016. Larvicidal activity of Colocasia esculenta, Eclipta prostrata and Wrightia tinctoria leaf extract against Culex quinquefasciatus. Proc. Natl. Acad. Sci. India B Biol. Sci. 86, 139–143.

Dass, K., Mariappan, P., 2014b. Larvicidal activity of Lawsonia inermis and Murraya exotica leaves extract on filarial vector, Culex quinquefasciatus. Int J Mosq Res. 1 (2), 25–27.

Dass, K., Sujitha, S., Mariappan, P., 2022. Larvicidal activity of selected medicinal plants against dengue vector Aedes aegypti. International Journal of Mosquito Research 9 (1), 110–113. https://doi.org/10.22271/23487941.2022.v9.i1b.588.

Dass, K., 2020. Larvicidal and pupicidal activity of green synthesized silver nanoparticles using selected plants extract against Culex quinquefasciatus. International Journal of Mosquito Research 7 (6), 40–45.

Gnaneswari, D., Divya, D., Verma, A., Shraddha, S., Sharma, S., Mayandi, D.G., 2022. Molecular docking of potential Indian medicinal plant compounds against dengue viral proteins. Indian Journal of Traditional Knowledge 21 (3), 537–544.

Hasan, M., Mia, M.M., Munna, S.U., Talha, M.M., Das, K., 2022. Seawater fungi-derived compound screening to identify novel small molecules against dengue virus NS5 methyltransferase and NS2B/NS3 protease. Inform. Med. Unlocked 1 (30), 100932. https://doi.org/10.1016/j.imu.2022.100932.

Huq, A.M., Roney, M., Dubey, A., Nasir, M.H., Tufail, A., Aluwi, M.F., Ishak, W.M., Islam, M.R., Tajuddin, S.N., 2024. Phenolic compounds of Theobroma cacao L. show potential against dengue RdRp protease enzyme inhibition by In-silico docking, DFT study, MD simulation and MMGBSA calculation. PLoS One 19 (3). https://doi.org/10.1371/journal.pone.0299238.

Indu, P., Arunagirinathan, N., Rameshkumar, M.R., Sangeetha, K., Divyadarshini, A., Rajarajan, S., 2021. Antiviral activity of astragaloside II, astragaloside III and astragaloside IV compounds against dengue virus: computational docking and in vitro studies. Microb. Pathog. 152, 104563 https://doi.org/10.1016/j.micpath.2020.104563, 2021 Mar 1.

Jagtap, S., Pattabiraman, C., Sankaradoss, A., Krishna, S., Roy, R., 2023. Evolutionary dynamics of dengue virus in India. PLoS Pathog. 19 (4), e1010862, 2023 Apr 3.

Jain, P., Singh, Y., Kumari, R., 2023. In silico investigation and MD simulations of phytochemicals of C. wightii against dengue targets NS5 and E protein. Vegetos 6, 1–9. https://doi.org/10.1007/s42535-023-00658-6.

Jarerattanachat, V., Boonarkart, C., Hannongbua, S., Auewarakul, P., Ardkhean, R., 2022. *In silico* and *in vitro* studies of potential inhibitors against Dengue viral protein NS5 Methyl Transferase from Ginseng and Notoginseng. J Tradit Complement Med 13 (1), 1–10. https://doi.org/10.1016/j.jtcme.2022.12.002. PMID: 36685072; PMCID: PMC9845645.

Kalaimathi, K., Rani, J.M., Vijayakumar, S., Prakash, N., Karthikeyan, K., Thiyagarajan, G., Bhavani, K., Prabhu, S., Varatharaju, G., 2022. Anti-dengue potential of mangiferin: intricate network of dengue to human genes. Revista Brasileira de Farmacognosia 32 (3), 410–420. https://doi.org/10.1007/s43450-022-00258-6.

Kaushik, S., Kaushik, S., Kumar, R., Dar, L., Yadav, J.P., 2020. In-vitro and in silico activity of Cyamopsis tetragonoloba (Gaur) L. supercritical extract against the dengue-2 virus. Virusdisease 31, 470–478. https://doi.org/10.1007/s13337-020-00624-9Rahman.

Lee, M.F., Wu, Y.S., Poh, C.L., 2023. Molecular mechanisms of antiviral agents against dengue virus. Viruses 8 (3), 705. https://doi.org/10.3390/v15030705, 15.

Lim, S.Y.M., Chieng, J.Y., Pan, Y., 2021. Recent insights on anti-dengue virus (DENV) medicinal plants: review on in vitro, in vivo and in silico discoveries. Life 14 (1), 1e33. https://doi.org/10.1080/26895293.2020.1856192.

Malavige, G.N., Fernando, S., Fernando, D.J., Seneviratne, S.L., 2004. Dengue viral infections. Postgrad. Med. 80 (948), 588–601. https://doi.org/10.1136/pgmj.2004.019638.

Mazri, R., Ouassaf, M., Kerassa, A., Alhatlani, B.Y., 2024. Exploring potential therapeutics: targeting dengue virus NS5 through molecular docking, ADMET profiling, and DFT analysis. Chemical Physics Impact 1 (8), 100468. https://doi.org/10.1016/j.chphi.2024.100468.

Mgbemena, I.C., 2010. Comparative evaluation of larvicidal potentials of three plant extracts on Aedes aegypti. Journal of American Science 6 (10), 435–440.

Modis, Y., Ogata, S., Clements, D., Harrison, S.C., 2004. Structure of the dengue virus envelope protein after membrane fusion. Nature 427, 313–319. https://doi.org/10.1038/nature02165.

Murugesan, A., Manoharan, M., 2020. Chapter 16 - dengue virus. In: Emerging and Reemerging Viral Pathogens. Academic Press, pp. 281–359. https://doi.org/10.1016/B978-0-12-819400-3.00016-8.

Murugesan, R., Vasuki, K., Kaleeswaran, B., 2023a. A green alternative: evaluation of Solanum torvum (Sw.) leaf extract for control of Aedes aegypti (L.) and its molecular docking potential. Intelligent Pharmacy. https://doi.org/10.1016/j.ipha.2023.11.012.

Murugesan, R., Vasuki, K., Ramadevi, S., Kaleeswaran, B., 2023b. Rosmarinic acid: potential antiviral agent against dengue virus-In silico evaluation. Intelligent Pharmacy. https://doi.org/10.1016/j.ipha.2023.12.006.

Nasar, S., Rashid, N., Iftikhar, S., 2020. Dengue proteins with their role in pathogenesis, and strategies for developing an effective anti-dengue treatment: a review. J. Med. Virol. 92 (8), 941–955. https://doi.org/10.1002/jmv.25646. Aug.

Nwozo, O.S., Effiong, E.M., Aja, P.M., Awuchi, C.G., 2023. Antioxidant, phytochemical, and therapeutic properties of medicinal plants: a review. Int. J. Food Prop. 26 (1), 359–388. https://doi.org/10.1080/10942912.2022.2157425.

Ononamadu, C.J., Abdalla, M., Ihegboro, G.O., Li, J., Owolarafe, T.A., John, T.D., Tian, Q., 2021. In silico identification and study of potential anti-mosquito juvenile hormone binding protein (MJHBP) compounds as candidates for dengue virus-Vector insecticides. Biochemistry and Biophysics Reports 28, 101178. https://doi.org/10.1016/j.bbrep.2021.101178.

Patel, J.R., Joshi, H.V., Shah, U.A., Patel, J.K., 2022. A review on computational software tools for drug design and discovery. Indo Global J. Pharmaceut. Sci. 12, 53–81. https://doi.org/10.35652/IGJPS.2022.12006.

Paul, A., Raj, V.S., Vibhuti, A., Pandey, R.P., 2020. Larvicidal efficacy of Andrographis paniculata and Tinospora cordifolia against Aedes aegypti: a Dengue vector. Pharmacogn. Res. 12 (4), 352–360.

Qaddir, I., Majeed, A., Hussain, W., Mahmood, S., Rasool, N., 2020. An in-silico investigation of phytochemicals as potential inhibitors against non-structural protein 1 from dengue virus 4. Brazilian Journal of Pharmaceutical Sciences 7 (56), e17420. https://doi.org/10.1590/s2175-97902020000117420.

Ragavan, R.M., Purushothaman, I., Swaminathan, R., Almutairi, S.M., Hussein, D.S., Rasheed, R.A., Narasingam, A., 2023. Malacitanolide, reissantin E and paclitaxel compounds as inhibitors of envelope, NS5 and NS2B/NS3 target proteins of dengue virus: computational docking and molecular dynamics simulations studies. J. King Saud Univ. Sci. 35 (8), 102868 https://doi.org/10.1016/j.jksus.2023.102868.

Rahman, M.M., Biswas, S., Islam, K.J., Paul, A.S., Mahato, S.K., Ali, M.A., Halim, M.A., 2021. Antiviral phytochemicals as potent inhibitors against NS3 protease of dengue virus. Comput. Biol. Med. 134, 104492.

Rani, A.C., Sujitha, S., Kalaimathi, K., Vijayakumar, S., Varatharaju, G., Karthikeyan, K., Thiyagarajan, G., Sanjeevi, S.B., Prabhu, S., 2022. Uncovering of anti-dengue molecules from plants prescribed for dengue: a computational investigation. Chemistry Africa 5 (5), 1321–1336. https://doi.org/10.1007/s42250-022-00421-5.

Rani, J.M., Kalaimathi, K., Vijayakumar, S., Varatharaju, G., Karthikeyan, K., Thiyagarajan, G., Bhavani, K., Manogar, P., Prabhu, S., 2022. Anti-viral effectuality of plant polyphenols against mutated dengue protein NS2B47-NS3: a computational exploration. Gene Reports 27, 101546. https://doi.org/10.1016/j.genrep.2022.101546.

Roney, M., Dubey, A., Zamri, N.B., Aluwi, M.F., 2023. Inhibitory effect of Sinapic acid derivatives targeting structural and non-structural proteins of dengue virus serotype 2: an in-silico assessment. Aspects of Molecular Medicine 2, 100028. https://doi.org/10.1016/j.amolm.2023.100028.

Samy, C.R., Karunanithi, K., Sheshadhri, J., Rengarajan, M., Srinivasan, P., Cherian, P., 2023. (R)-(+)-Rosmarinic acid as an inhibitor of herpes and dengue virus replication: an in silico assessment. Revista Brasileira de Farmacognosia 33 (3), 543–550, 2023 Jun.

Shakya, A., 2023. Bioactive phytochemicals as inhibitors against dengue virus protein NS-5 methyltransferase: in silico molecular docking approach: bioactive phytochemicals as inhibitors against dengue virus protein NS-5 methyltransferase. J. Ayurveda Holist. Med. 11 (3). https://jahm.co.in/index.php/jahm/article/view/760.

Shimu, M.S., Mahmud, S., Tallei, T.E., Sami, S.A., Adam, A.A., Acharjee, U.K., Paul, G.K., Emran, T.B., Zaman, S., Uddin, M.S., Saleh, M.A., 2022. Phytochemical compound screening to identify novel small molecules against dengue virus: a docking and dynamics study. Molecules 27 (3), 653. https://doi.org/10.3390/molecules27030653, 20.

Sivaraman, D., Pradeep, P.S., 2020. Exploration of bioflavonoids targeting dengue virus NS5 RNA-dependent RNA polymerase: in silico molecular docking approach. J. Appl. Pharmaceut. Sci. 10 (5), 16–22. https://doi.org/10.7324/JAPS.2020.10503.

Tolle, M.A., 2009. Mosquito-borne diseases. Curr. Probl. Pediatr. Adolesc. Health Care 39 (4), 97–140. https://doi.org/10.1016/j.cppeds.2009.01.001.