Medicinal Plants against Malaria and Dengue: In-Silico Computational Drug Discovery Framework for Identifying Therapeutic Leads

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Abstract

Malaria and dengue contribute substantially to the global burden of infectious disease and pose serious health threats, particularly in tropical and subtropical regions. The growing resistance in these parasites against existing drugs and the absence of effective vaccine and targeted treatments for them highlights an urgent need for identifying new and effective therapies. Medicinal plants being rich in diverse bioactive compounds have long been used and hold great promise as potential solutions to these challenges. This chapter explains computational framework to drug discovery, with the main focus on phytochemicals and their potential targets reported in literature. Important steps of in-silico framework include selecting key protein targets related to malaria and dengue, screening of phyto-compounds reported against potential targets using molecular docking to predict their likely interactions. Molecular dynamics simulations are performed to understand behaviour of these interactions within the living system. This chapter highlights several natural compounds with strong binding affinity and encouraging pharmacokinetic profiles, suggesting their potential as therapeutic leads. By combining traditional knowledge with modern computational tools offers a fast and cost-effective way to identify new drug candidates. Present study underscores the value of integrating nature-based solutions into contemporary drug discovery efforts, offering hope for better treatments against dengue and malaria.

Keywords: Dengue, Malaria, In-silico, Computational drug discovery, Molecular docking, Molecular dynamics simulations

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Introduction

Malaria is an infectious disease caused by parasite *Plasmodium,* which belongs to the phylum protozoa. It affects millions of people globally and is spread by the bite of infected mosquito (female Anopheles). In humans, malaria is primarily caused by five *Plasmodium* species*: P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi.* Common clinical manifestation of malaria typically includes fever with chills along with headache, myalgia and arthralgia. *P. falciparum* is commonly linked to the severe and complicated form of malaria (Hay et al., 2007) considered as most lethal, because it can cause acute renal damage, severe iron deficiency and cerebral malaria (Mafethe et al., 2023). Whereas infections with *P. vivax* and *P. ovale* may involve hypnozoites that can become active after months or even after many years after the initial infection, that lead to relapse and recurring malaria (Toshihiro, 2020).

Malaria continues to be a major public health challenge, especially in tropical and subtropical regions worldwide (Nureye et al., 2020). According to the World Health Organization (2019), vector-borne parasite illnesses cause over 15% of all infectious diseases, with malaria accounting for over 50% of all fatalities worldwide. In 2022, WHO reported 249 million malaria cases globally, a 16 million increase from 2019. Pakistan, Papua New Guinea Ethiopia, Uganda, and Nigeria, accounted for most of the rise. Notably, 95% of cases occurred in 29 countries, with Nigeria, DR Congo, Uganda, and Mozambique contributing nearly half. The WHO Eastern Mediterranean Region saw a 92% surge in cases since 2015. India contributed 66% of cases in this region, with a 25% rise from 2021 to 2022, driven by 2.1 million additional cases in Pakistan. Climate change is a key factor in the rising incidence. Alarmingly, 61% of malaria deaths occur in children under five, and 125 million pregnant women remain at high risk (WHO, 2023).

The other most common and emerging mosquito-borne virus is dengue virus (DENV, spherical, single stranded positive sense RNA virus), is a part of the Flaviviridae family which is a mosquito-borne virus that affects millions of people globally (Torres et al., 2021). It spreads through *Aedes aegypti* mosquito bites (Ali et al., 2024). The most common symptoms include high fever, headaches, pain behind the eyes, body aches, skin rashes and mild bleeding (Trujillo-Correa et al., 2019). In some cases, Dengue hemorrhagic fever (DHF) is a very dangerous, causing plasma leakage and extreme bleeding. There are four serotypes of DENV: DEN-1, DEN-2, DEN-3, and DEN-4. Although these serotypes are closely related but antigenically, they are different. DENV has an 11kb genome, which is translated within the host cells, forming a single long

polyprotein having both structural and non-structural proteins (Sinha et al., 2024). This single long polyprotein is then cleaved into 10 different proteins, three structural proteins; envelope (E), precursor membrane/membrane (prM/M), capsid (C) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) (Nasar et al., 2020) (Figure 1).

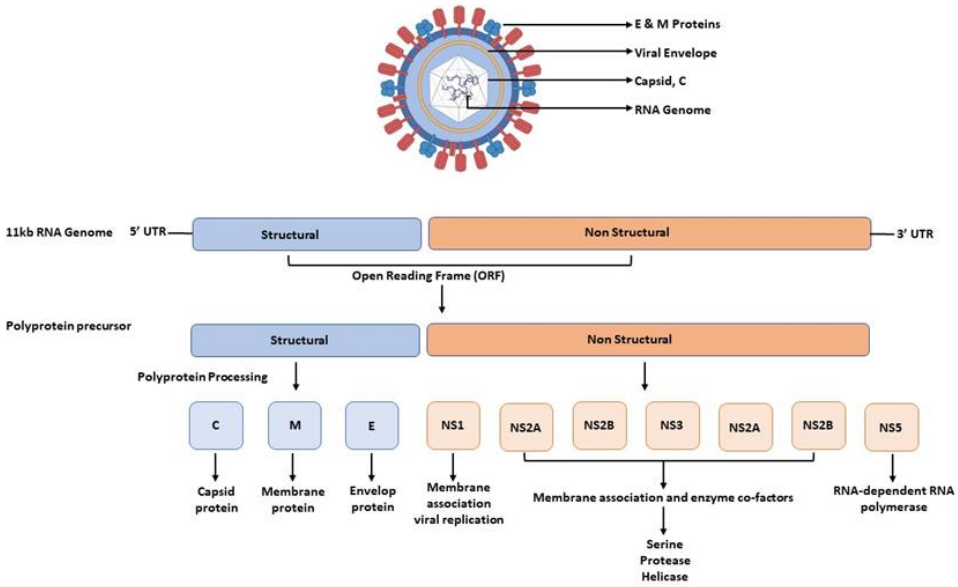

Fig. 1: Overview of the structural features of the Dengue Virus (DENV) genome

Like Malaria, Dengue is common around the world in tropical and subtropical areas, specifically in urban and semi-urban regions (Kularatne et al., 2022). Globally, an estimated 50 to 100 million dengue cases are reported each year, affecting about half of the world's population. Dengue is responsible for 20,000 deaths each year (Cucunawangsih et al., 2017). According to the NIH, confirmed dengue cases reached 48,906 in 2021, and by October 11, 2022, Pakistan had reported 41,746 cases, with progressively increasing each day (Dengue Worldwide Overview, 2023). The number of reported dengue cases is significantly higher in 2022 (between January and September) as compared to the same period during the four previous years.

In 2019, the dengue outbreak caused a direct loss of 716 million USD, which is 0.13% of the total GDP. The impact on industries supporting tourism led to an additional GDP decrease of 718 million USD, or 0.13% of the total GDP (Marczell et al., 2024). Pakistan has been endemic to dengue since 1994. In 2022, the number of reported cases increased, primarily because of heavy rainfall and flooding.

In-Silico Computational Drug Discovery Framework

Improvements in computer-aided drug discovery (CADD) have reformed the field to predict how bioactive Phyto-compounds interact with the target molecules (Chunarkar-Patil et al., 2024) commonly known as molecular docking. Researchers use this method to evaluate drug potential by analyzing the molecular interactions between drug candidates and their biological targets (Anwar et al., 2021).

Nowadays, three basic methods are utilized in drug discovery, which are cell-based, target-based and chemistry-based. The target-based method is the most commonly used as it saves both time and money. Moreover, the possibility of finding promising drug candidates is high in this method. The following outlines the general methodology, tools and databases (Table 1) for the phytocompounds screening and computational drug designing (Figure 2).

Target Selection and Preparation

Targets are usually protein molecules, which are a biological pathway related to disease progression at any stage (Gonzalez et al., 2012). Before heading to molecular docking, target proteins are cleaned; Heteroatoms including water molecules are removed, polar hydrogens and Kollman and Gasteiger charges are added to the and non-polar hydrogens are merged. If 3D structure of selected target is not available, it can be predicted by in-silico protein modeling

Ligands Selection and Screening

After target identification, potential drug candidates (ligands) are identified. The database provides canonical smiles and 3D structure of the potential bioactive ligand, which can be used for further screening and validation of drug. Drug candidates are also evaluated for their pharmacokinetic and drug-likeliness properties by performing ADMET analysis (absorption, distribution, metabolism, excretion, and toxicity). Several bioinformatic tools can estimate ADMET properties with great precisions (De Carlo et al., 2024).

Molecular Docking

Molecular docking is a computational method in structure-based drug design. It estimates how small molecules interact with macromolecular targets. It also predicts the binding affinity between ligands and receptor proteins (Agu et al., 2023). Molecular docking predicts the interaction of ligand with the target protein's binding site (Gohlke et al., 2002; Kitchen et al., 2004; Combs 2007; Coumar et al., 2009). Compounds with the lowest binding energy are prioritized for further optimization in computational drug discovery (Singh et al., 2024).

Molecular Dynamics Simulations

Molecular dynamics (MD) simulations are used for better understanding the relation between target and ligands by determining the stability, flexibility, and interactions of drug-target complexes over time under simulated physiological conditions. MD simulation helps to refine drug candidates and improve the understanding of their mechanism of action at the atomic level.

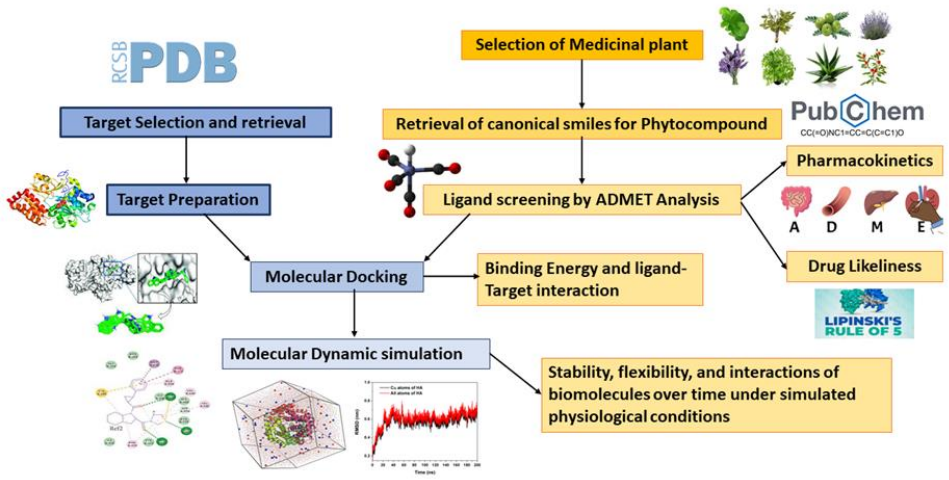

Fig. 2: Schematic representation of phytocompounds screening and computational drug discovery.

Table 1: Protein/receptor/target selection tools and software

Category	Tool/Software/Data base	Function
3D Structural Data Repositories	RCSB PDB (Protein Data Bank)	Repository for 3D structural data of biological macromolecules
Protein Information Databases	UniProt	Databases for protein sequences, functional data, and human genes
Chemical Structure Drawing and Conversion	ChemSketch, ChemDraw, Open Babel	Drawing and converting chemical structures and SMILES conversion
Molecular Visualization	MGL Tools, ChimeraX, PyMOL, Yasara, Dassault Systems Biovia Discovery Studio	Visualization and analysis of molecular structures and enzyme preparation
Active Site and Structural Analysis	CASTp, SAVES Server, ProSA Web Server	Analyzes structure and quality of protein models
Docking and Ligand Binding	AutoDock, PyRx, BIOVIA Discovery Studio, MOE (Molecular Operating Environment)	Molecular docking and ligand binding affinity calculations
Molecular Dynamics Simulation	NAMD Version 2.14, CHARMM-GUI Solution Builder, GROMACS	Conducts molecular dynamics simulations and modeling of PDB structures
Ligand Binding Site Identification	LigandScout	Identifies and visualizes ligand binding sites on proteins
ADMET and Toxicity Prediction	SwissADME, admetSAR	Predicts (ADMET)
Biological Activity Prediction	PASS Server	Predicts biological activities and drug-likeness properties
Chemical and Compound Databases	PubChem, ChemSpider, IMPPAT	Databases for chemical substances and phytocompounds
Drug Target Databases and Interactions	DrugBank, Therapeutic Target Database (TTD), Comparative, ChEMBL	Provides information on drug targets, interactions between chemicals, genes, and diseases
Protein Interaction Networks	Cytoscape, STRING, HAPPI	Visualizes complex protein-protein interaction (PPI) networks
Sequence Analysis	BLASTp	Bioinformatics tool for comparing protein sequences

Medicinal Plants: Exploring Natural Alternatives

Currently, malaria is treated with numerous kinds of drugs with different approaches depending upon the P*lasmodium* species and level of severity of infection. Artemisinin-based and quinine-based combination treatments are used for uncomplicated malaria and severe or complicated malaria, respectively (Jinying et al., 2023; Magwaza et al., 2023). However, in some regions, the resistance against artemisinin-based treatments is increasing. (Hoarau et al., 2023). Similarly, for dengue corticosteroids were found as the first line of defense, while Dengvaxia became the first licensed dengue vaccine, but there are several drawbacks of vaccines (Sinha et al., 2024). But so far, there are no specific globally accepted treatments for dengue fever in any medical system (Singh et al., 2017). The increase in viral resistance to antiviral drugs shows the importance of discovering new and effective antiviral treatment (Altamish et al., 2022).

Medicinal plants have been an essential part of healthcare since ancient times. Phytomedicines have been utilized to treat several diseases all over the world (Sofowora et al., 2013; Abbas et al., 2025). The availability, affordability, safety, and effectiveness of natural goods are the reasons for their success (Okoh, 2019). Several natural phytocompounds are studied as a new potential therapeutic target for malaria. Several medicinal plants have shown potential antimalarial properties because of their several bio-active compounds. According to the WHO, approximately 80% of low- and middle-income countries rely on medicinal plants for basic healthcare requirements (Bhat, 2022).

Andrographis paniculata

A. paniculata extracts contain phytochemicals having anti-malarial and antiviral properties. (Mishra et al., 2007; Ukpanukpong et al., 2018). Various potential ligand like, DSM1, 7a-Isopropenyl-4, 5-dimethyloctahydroinden-4-yl, 6-methoxy-2-methyl-quinoline-3-carboxylic acid-2-dimethylamino-ethylester, Andrographolide, 2-ethylacridine, Phytol have been reported (Deborah et al., 2021; Olaosebikan et al., 2023; Afolayan et al., 2024). PfDHODH, DHFR-TS, M1 alanyl aminopeptidase, Purine nucleoside phosphorylase, Gametocyte surface protein are reported as possible target for malarial prevention by *A. paniculata* phytochemicals (Deborah et al., 2021; Olaosebikan et al., 2023; Afolayan et al., 2024).

Tinospora cordifolia

T. cordifolia is a commonly used medicinal plant for treating dengue, known for its ability to significantly elevate platelet counts in a relatively short period. Among the alkaloids, Magnoflorine and Berberine exhibited the strongest binding affinities. The anti-dengue activity of *T. cordifolia* has been primarily attributed to Berberine, followed by Magnoflorine, which demonstrated notable potential in combating the dengue virus. Different potential protein targets have been reported in literature for therapeutic inhibitors to control dengue fever. For example, NS3 (Non-structural protein 3) and NS2B (Non-structural protein 2B) Glycoprotein E, NS2B-NS3 complex and NS1 have been identified as key targets (Yennamalli et al., 2009; Bency et al., 2018).

Pharmacological targets for Malaria

Dihydrofolate Reductase (DHFR)

In *Plasmodium falciparum*, dihydrofolate reductase (PfDHFR) plays a significant role in folate metabolism, and thymidine synthesis, both are vital for the parasite's survival and growth. This enzyme is essential for the production of deoxythymidine monophosphate (dTMP) that act as a DNA base (Singh & Mishra, 2018; Ojo, 2021). The process starts with the reduction of Dihydrofolate (DHF) to Tetrahydrofolate (THF) by utilizing NADH co factor in the presence of DHFR. THF converts into 5, 10-methylene-tetrahydrofolate, that contributes a methyl group to deoxyuridine monophosphate in a reaction mediated by thymidylate synthase (TS), produces dTMP. This reaction not only produces dTMP but maintains folic acid homeostasis by regenerating the DHF and completing the cycle. This step is vital because dTMP is crucial for DNA replication and parasite proliferation (Hyde, 2005). By inhibition of DHFR, it disrupts the process that leads to the shortage of dTMP and increase in the dUTP. The higher level of dUTP leads to the incorporation of uracil into DNA that triggers cell toxicity and ultimately cell death (Ojo, 2021).

Dihydroorotate Dehydrogenase (DHODH)

Dihydroorotate dehydrogenase (DHODH) has an essential role in the *denovo* pyrimidine synthesis pathway (Liu et al., 2000; Phillips et al., 2010). DHODH uses flavin mononucleotide (FMN) as a cofactor during an oxidation reaction that converts dihydoorotateto orotate. The following reaction produces orotate, that is the precursor of uridine monophosphate (UMP). During the erythrocytic stage, parasite utilizes all these monophosphates to synthesize all other pyrimidines required for rapid DNA and RNA synthesis.

Variation in the active and binding sites of DHODH between species facilitates the development of inhibitors that specifically target the parasitic enzyme, not the human hosts DHODH. By blocking PfDHODH, orotate production can be limited, that limits the pyrimidine synthesis. This ultimately leads to the disruption in the DNA and RNA synthesis and eventually leads to cell death (Rodrigues et al., 2011).

Falcipains

Plasmodium falciparum's falcipains (FPs) are cysteine proteases that break down hemoglobin during erythrocytic stage that facilitates the parasite development (Rawlings et al., 2006; Tyagi et al., 2013). An acidic vacuole, hydrolyzes approximately 75% of host hemoglobin, supplies amino acids, regulates osmotic balance, and facilitates parasite growth (Francis et al., 1997; Gil et al., 2011), within this vacuole, hemoglobin is degraded into heme and globin. Heme is detoxified into hemozoin, while globin is used in protein synthesis. According to Sijwali and Rosenthal (2004) FPs are important targets for antimalarial drugs because they disrupt hemoglobin degradation and ultimately parasitic survival (Sijwali and Rosenthal, 2004). Table 2 shows therapeutic phytocompounds for malaria.

Table 2: Therapeutic Phytocompounds for Malaria

Plant	Common name	Target	Top Ligand	Reference
Andrographis paniculata	Creat or green chiretta	DHFR-TS	7a-Isopropenyl-4,5-dimethyloctahydroinden-4-yl	(Afolayan et al., 2024)
		M1 alanyl aminopeptidase, Purine nucleoside phosphorylase, Gametocyte surface protein	7a-Isopropenyl-4,5-dimethyloctahydroinden-4-yl N-Ethyl-3-methoxy-4-methy	
		PfDHODH	6-methoxy-2-methyl-quinoline-3-carboxylic acid-2-dimethylamino-ethylester Andrographolide 1-(6-purinyl)-2-pyrrolidinecarboxylic acid 2-ethylacridine	(Olaosebikan et al., 2023)
		Plasmepsin II, DHODH	Phytol	(Deborah et al., 2021)
Azadirachta indica	Neem	Pf GST	IMPHY000093, IMPHY001448, IMPHY005310	(Al-Malki 2024)
		PfTIM	Gedunnin Nimbinene Salanin Azadirachtin Nimbandiol Quercetin	(Areh et al., 2022)
		Gephyrin E	Azadirachtin, Artesunate	(Okoh et al., 2021)
Chromolaena odorata	Siam weed	DHFR	Falcarinol	(Archana et al., 2014)
		Pf GST Pf falcipain 2 Pf falcipain 3	Quercetin Luteolin Naringenin	(Maduakolam-Aniobi et al., 2024)
Chrysophyllum albidum	Star Apple	PfLDH	β-D-Mannofuranoside	(C & Roland, 2024)
Strophanthus hispidus		Plasmepsin II PfDHFR-TS	Pityriacitrin	(Faloye et al., 2024)
Citrus aurantifolia	Lime	20S α proteasome Choline kinase Phosphocholine Cytidylyltransferase	Limonin Luteolin Myricetin	(Elmaidomy et al., 2024)
Saussurea pulchella	lizard's tail,	Plasmepsin X	Pinoresinol 4-glucoside	(Gholam et al., 2024)
Artocarpus sericicarpus	Pedalai,	Falcipain-2	Dihydrochalcone	(Tumewu et al., 2023)
Phyllanthus amarus	Gale of the wind	P. *falciparum*thioredoxin reductase *P. falciparum* enoyl-acyl carrier protein reductase *PfLDH*	Amarulone, Amariin	(FID et al., 2023)
Barleria buxifolia Linn	Box-Leaved Barleria	Phosphatidylinositol-4-kinase III β	1-[2-(benzhydryloxy) ethyl]-4-(3-phenylpropyl) piperazine	(Abisek et al., 2024)
Cymbopogon citratus	Lemon grass	PfMSP1 PfCSP PfEMP1	Swertiajaponin Quercetin	(Evbuomwan et al., 2023)
Dissotis rotundifolia		Plasmepsin II PfDHFR-TS	Dimethylmatairesinol Flavodic acid Sakuranetin Sesartemin	(Adams et al., 2023)
Cyperus rotundus	Coco grass	DHFR	Beta-Sitosterol	(Luxy and Sumathi 2023)
Zingiberaceae		PfLDH	Sulcanal, Quercetin, Shogosulfonic acid C, Galanal A, Naringenin,	(Heikal et al., 2023)
Piper betle Linn	Betel fruit/ betel or sire	Plasmepsin 1 Plasmepsin 2	Androstan-17-one, ethyl-3-hydroxy-, (5-alpha)	(Fatimawali et al., 2021)

Pharmacological Targets for Dengue

Envelop Protein

The E protein comprises three domains: the central domain I (EDI), the finger-like domain II with the fusion loop (EDII), and the immunoglobulin-like domain III (EDIII) (Modis et al., 2003). To penetrate the cellular membrane, the virus need attachment to host cell receptors and injects its viral RNA genome into cytosol (Yennamalli et al., 2009). A decrease in penetration inhibits the dengue virus's ability to spread. E-protein's critical role in viral attachment and host cell entry (Hsieh et al., 2014).

Non-Structural Protein 3

The NS3 protein of the dengue virus is vital for viral replication and pathogenesis, exhibiting protease (NS3pro), helicase (NS3hel), and RNA triphosphatase function (Nasar et al., 2020). The N-terminal part of NS3 works closely with another protein called NS2B (co-factor), forming a complex known as NS2B3 (Nasar et al., 2020).

NS3 (and NS5) enter the host cell and move to the endoplasmic reticulum (ER) membrane (site of protein synthesis in the host cell) to operate the cellular pathways for viral replication (Alomair et al., 2021). It behaves like a protease by using NS2B as a co-factor, cleaving the polyprotein at specific sites and host proteins that would impair dengue infection (Sinha et al., 2024). The central part of NS2B aids with its proteolytic activity, which means it plays a role in breaking down proteins. The treatment of cells with a peptide that suppress NS2B-NS3 protease reduces the chance of dengue virus infection by 80% (Oliveira et al., 2014). NS3 is a main protein in the dengue virus (DENV) which is very similar across all four serotype, with 77% of its amino acids being same. This resemblance presents it as a good target for making vaccines, that's why NS3 protease is known as an excellent target for antiviral inhibitors (Niyomrattanakit et al., 2004)

Non-Structural Protein 5

Another important enzyme-based drug target is NS5 protein. It is the most protectd as well as largest protein (102 kDa) shown by dengue virus. It has two spots, at its N-terminal end, a methyltransferase domain (MTase) and at its C-terminus an RNA-dependent RNA polymerase (RdRp) (El Sahili et al., 2017). It a good target for both vaccine as well as for antiviral drug development. If we Target NS5, it could pave a productive approach to making antiviral drugs (Nasar et al., 2020). Table 3 elaborates therapeutic phytocompounds for dengue fever.

Table 3: Therapeutic Phytocompounds for Dengue Fever

Plant	Common name	Target	Top Ligand	Reference
Commiphora wightti	Guggul	E protein NS5 Methyl transferase	Myrrhanone A acetate Guggulsterol-Y	(Jain et al., 2024)
Tinospora cordifolia	Heart-leaved moonseed	Envelop protein NS3	Magnoflorine Berberine	(Singh et al., 2024)
Kaempferia galanga	Aromatic ginger	NS2B NS3	Cystargamide B	(Kumar A et al., 2020)
Carica papaya	Papaya	NS2b/NS3pro NS3, NS5	Oleic acid, stearic acid, palmitic acid Kaempferol, Quercetin, Chlorogenic acid	(Saqallah FG et al., 2022) (Madushanka A et al., 2022)
Azadirachta indica	Neem	NS2B NS3pro	Nimbin Desacetylnimbin desacetylsalannin	(Dwivedi et al., 2016)
Psidium guajava	Guava	NS5 Envelope protein	Naringin Hesperidin	(Trujillo-Correa et al., 2019)
Raw papaya fruit	Papaya	E protein	Papain	(Saranya V et al., 2021)
Andrographis paniculata	Green chiretta	NS5	Andrographolide	(Kaushik S et al., 2021)

Conclusion

Medicinal plant-derived phytocompounds are promising therapeutic approach against the treatment of malaria and dengue, especially in low middle-income countries. By integrating in-silico computational drug discovery approach with traditional medical plant phytocompounds can accelerate early-stage drug discovery. Later the best phytocompounds can provide a foundation for further experimental validation and development of plant-based treatments. These natural drugs will be more accessible, especially in the endemic regions of these vector-borne diseases and will help to reduce the overall cost of discovery and production of drugs.

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