JKKI: Jurnal Kedokteran dan Kesehatan Indonesia
Indonesian Journal of Medicine and Health
Journal homepage: https://journal.uii.ac.id/JKKI
P-ISSN 2085-4145 | E-ISSN 2527-2950

Indonesian medicinal plants' therapeutic potential against dengue virus infection: A literature review

Aisya Alma Asmiranti Kartika,[1*] Beti Ernawati Dewi,[2] Tjahjani Mirawati Sudiro[2]

[1]Master's Programme in Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2]Department of Microbiology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Article Info:

Keywords: medicinal plants, antivirus, anti-inflammatory, natural compounds, DENV

***Corresponding author:**
aisyaalmaasmiranti@gmail.com

Article History:

Received: November 23, 2023
Accepted: August 25, 2024
Online: December 27, 2024

DOI: 10.20885/JKKI.Vol15.Iss3.art11

Literature Review

ABSTRACT

Infections caused by the dengue virus (DENV) exhibit a wide range of clinical manifestations, from asymptomatic cases to severe, and sometimes life-threatening, conditions. Therefore, identifying effective antivirals and anti-inflammatory agents is a promising strategy to reduce the impact of these infections. Indonesia, with its rich biodiversity, particularly in medicinal plants, offers potential sources for such treatments. Most research on DENV antivirals in Indonesia has been conducted in vitro and has predominantly focused on DENV serotype 2 (DENV-2). However, in vivo research on medicinal plants, as well as studies on their anti-inflammatory properties, remains limited in Indonesia.Extracts that have been investigated in both *in vivo* and *in vitro* settings are limited to *Cassia alata* and *Curcuma longa*. Plants possessing antiviral properties originate from diverse botanical families, with leaves being the most utilized plant component. Flavonoids are found in most medicinal plants that have antiviral properties. Indonesia is known to have other natural compounds, including quercetin, isobutyl gallate, curcumin, and 6-gingerol, which have antiviral properties. Curcumin and 6-gingerol are the only natural compounds that have been subjected to testing against all four serotypes of dengue. This article provides a comprehensive review of medicinal plants in Indonesia, focusing specifically on their therapeutic potential against the dengue virus.

INTRODUCTION

The dengue virus is a primary causative agent responsible for the occurrence of dengue fever (DF) and Dengue Haemorrhagic Fever (DHF). According to data provided by World Health Organization (WHO), the annual incidence of dengue fever ranges from 50 to 100 million cases, with an additional 500,000 occurrences of DHF.[1] The dengue virus is recognized as having endemicity in over 100 countries globally, affecting up to 40% of the global human population, including the Caribbean, America, Africa, Eastern Mediterranean, Pacific, and Asia (around 70% of the global disease burden).[1,2] Infections of DENV are correlated with a broad and varied spectrum of clinical symptoms, spanning from a condition of mild intensity that typically resolves on its own identified as DF to severe and potentially fatal complications characterized by vascular leakage and bleeding, known as either DHF or dengue shock syndrome (DSS).[3] There are four globally circulating serotypes of the DENV, known as DENV-1, DENV-2, DENV-3, and DENV-4 (differences in the viral envelope protein of 25% to 40%).[3]

Dengue severity, strongly influenced by the occurrence of cytokine storms, can cause heightened capillary permeability, leading to plasma leakage and ultimately ending in death.[4] Considering the important role of pro-inflammatory cytokines in the severity of the dengue infections,[4] antiviral therapy that is both highly effective at inhibiting virion production and

cytokine storm occurrence is the most effective approach. Utilization of therapeutic herbs has been feasible since ancient times as the earliest recorded evidence of civilizations. In Indonesia, pharmaceutical products from natural sources are commonly referred as traditional or herbal medicines.[5] As a country that has high biodiversity, Indonesia has various kinds of medicinal plants that can be developed into antiviral[6] and anti-inflammatory agents.[5] Hence, several research activities have been conducted to investigate the prospective utilization of regional Indonesian medicinal flora. This literature review aims to provide a broader perspective on the advancement of research towards the development of therapeutic medications for dengue infections by discussing several studies in Indonesia that investigate the potential of local plants using various methodologies and a range of active chemicals.

METHODS

From April to October 2023, the authors conducted searches across databases housing scientific articles and research findings, such as PubMed, Science Direct, and Google Scholar. The search keywords used in this instance encompassed "dengue virus infection", "medicinal plants", "antivirus", "anti-inflammation", or "natural compounds". Included studies had to fulfil these criteria: research with quantitative methodologies, experimental study design, *in vitro* or *in vivo* studies, research conducted in Indonesia, and research published at least in 2014. Meanwhile, its excluded criteria were research with qualitative methodology, observational study design, and/or systematic reviews.

Dengue virus pathogenesis

Dengue virus is a type of RNA virus that possesses a positive-stranded RNA genome. It is classified within the *Flavivirus* genus (member of the *Flaviviridae* family). The DENV have some characteristics such as an enveloped virus with genome encased by a structure called capsid.[7] The Flavivirus genome, which is approximately 11 kilobases in size, contains untranslated regions (UTRs), positioned adjacent to the open reading frame (ORF).[8] The ORF encodes three structural proteins (C, prM, and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) of the DENV. Protein C is a component of nucleocapsids, and membrane protein (M) is synthesised inside the cells as a precursor protein (prM). The prM is subsequently cleaved by the enzyme furin to create a mature M protein. The protein envelope (E) plays a pivotal role as a structural protein in both its attachment to receptors on the cell membrane and fusing process with infected cells.[9]

The NS1 protein is involved in the process of RNA replication and is released from cells that have been infected. The NS2A plays an important role in the viral assembly and the recruitment of RNA to genome replication complexes. Additionally, NS2A functions as an interferon antagonist. The function of NS2B is as a cofactor for the protease activity of NS3, involved in the cleavage of protein C and all non-structural proteins except NS1.[7,9] The NS2B may inhibit the activation of the IFN-β promoter generated by RIG-I/MAVS.[10] The NS3 protein exhibits a distinct domain that serves as an RNA helicase. While the precise functions of two other non-structural proteins, namely NS4A and NS4B, which relate to the cell membrane, have yet to be definitively determined, both can inhibit type I interferon (IFN) signalling. The NS5 protein plays a crucial function in various biological processes. Notably, this versatile protein encompasses the core subunit of RNA-dependent RNA polymerase (Rdrp), with methyltransferases that are involved in the process of capping viral RNA.[7,9]

Dengue virus is transmitted to humans through female mosquito, especially from the *Aedes aegypti* species. Other mosquito species that play a role in transmitting the dengue virus, including *Aedes albopictus, Aedes polynesiensis,* and *Aedes scutellaris.*[8] Many species of mosquitoes that can be vectors are main factors contributing to the extensive global dissemination of the dengue virus. Replication of DENV starts from the mosquito's salivary glands, and then virions are released into the saliva which will be carried into human cells when the mosquito bites the human host. Numerous cell types have been found to be vulnerable to the DENV, encompassing fibroblasts, macrophages, epithelial cells, T cells, endothelial cells, dendritic cells, monocytes, B

cells, and hepatocytes.[8]

The process of DENV infections within cells starts with the attachment of the virus to the specific receptors located on the surface of the cell. Multiple receptor types have a role in facilitating the cellular entrance of DENV, including mannose receptors (MR), heparan sulphate, lipopolysaccharide complex (LPS)-CD14, dendritic cell-intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), phosphatidylserine (PS), T-cell Ig mucin (TIM).[8,11] The DENV has the ability to enter cells with the assistance of antibodies via the Fc receptor, known as Antibody Dependent Enhancement (ADE).[8]

Further internalization of the Dengue virus is facilitated through clathrin-mediated endocytosis. Once inside the host cell, the virus undergoes a series of endosomal processing stages, starting with early endosome formation and progressing to late endosome maturation. These steps are critical for the virus's successful entry into the cytoplasm, where it can initiate replication and infection. Furthermore, the phenomenon of uncoating or the liberation of the viral genome into the cytoplasm, along with the viral RNA that is characterized by a positive strand RNA, can be immediately utilized for protein translation and serve as a template for genetic material replication.[6] Next is the assembly process, which ultimately leads to the development of an immature viral particle. The maturation process occurring within the trans-Golgi network (TGN) is enhanced by the furin enzyme, resulting in the conversion of immature viral particles.[8]

During the initial phases of infection, resident immune cells in tissues become the main target of infection, including macrophage cells that are resident in the skin and dendritic cells. These infected cells will then go to the lymph nodes.[8] When the lymph nodes are infected, the infection is strengthened, and the virus is disseminated through the lymphatic system.[12] Viremia occurs when the virus has spread widely through the blood vessels and lymph nodes, so that infection can be observed in several organs such as the spleen, kidney, lung and liver through infected dendritic cells, monocytes and macrophages.[6] Infections of DENV exhibit a diverse array of clinical manifestations, spanning from instances with no apparent symptoms (which are prevalent) to a wide range of clinical manifestations, including a mild influenza-like illness known as DF, as well as the most severe manifestation of the disease.[13]

Vascular leakage is a significant characteristic of severe dengue, resulting from the compromised functionality of endothelial cells. A study shows that the mechanism of pathogenesis of DENV infection is quite complicated as well as the occurrence of vascular leakage which is influenced by several factors such as cytokines (e.g. TNF-α, has elevated levels during the crucial phase of dengue fever); NS1 protein (disrupts the endothelial glycocalyx); inflammatory mediators (platelet activating factor (PAF) and leukotrienes).[14] Multiple studies have shown that the DENV virus's non-structural protein NS1 plays an important role in the development and severity of the infection.[15–17] The activation of NS1 has the ability to activate the complement system and increase vascular permeability, resulting in vascular leakage.[18]

Indonesian medicinal plants and natural compound potential

Plant-based drugs are a popular substitute nowadays. According to WHO estimates, a significant proportion, about 80% of the population residing in developing countries, get their primary health care (PHC) from their traditional medicine.[19] Plants and their derivative products possess a number of advantages. They are not dangerous; these substances exhibit a higher degree of absorption and metabolic efficiency within the human body, making the treatment process more effective; they have minimal side effects; and they are abundant in nature.[20.21]

In terms of medicinal plants, Indonesia holds the fourth position globally as a prominent producer of medicinal plants, while also being recognized as the 19th largest exporter in the world, with a total of 6,000 of medicinal plants.[22,23] Indonesian people's ancestors utilized plants for treating numerous illnesses, although written evidence and related studies have been limited; everyday experience provides insights into the use of plants as medicine.[24] *Syzygium polyanthum*, also known as *salam,* is the plant most widely used to treat hypercholesterolemia in Kalimantan, Indonesia.[25] Several studies show that plants originating and widely used in Indonesia such as mangosteen, cinnamon and curcumin exhibit significant potential in the treatment of metabolic

syndrome including obesity, diabetes, hypertension, and hyperlipidemia.[26]

Nowadays, dengue treatment is mostly symptomatic and supportive, focusing on plasma fluid loss caused by increased capillary permeability and bleeding. Patients with DF can seek outpatient therapy, but patients with plasma leakage must be hospitalized in a standard treatment room, and instances of DHF need intensive care.[27] As a result, drugs discoveries to treat dengue infections are required to reduce case fatality rate. Medicinal plants consist of various chemical substances with biological activities, one of which suppresses viral multiplication. However, there is no approved medicine (antiviral) that targets the DENV currently.[21,27]

A comprehensive investigation has been conducted on numerous medicinal plant extracts and natural compounds found in Indonesia to explore the therapeutic attributes of indigenous medicinal plants. *In vitro* experiments (Table 1) and *in vivo* experiments (Table 2) have been conducted to study the potential of these plants in formulating pharmaceutical interventions for controlling infections caused by the DENV. Some of the plants that have been studied include the ethanolic extract from *Jatropha multifida* L (*jarak tintir*), *Psidium guajava* (*jambu biji*), *Carica papaya* (*pepaya*), *Cassia alata* (*ketepeng Cina*), *Annona squamosa* (*srikaya*), *Allium sativum* L. (*bawang putih*), and *Pterocarpus indicus* Willd (*sono kembang*). In addition, other plant species exhibiting antiviral properties have been effectively extracted by utilizing methanol as a solvent such as *Cymbopogon citratus* (*serai*), *Myristica fatua* (*pala hutan*), *Acorus calamus* (*dlingo*), and *Mangifera foetida* L (*mangga bacang*), *Curcuma longa* (*kunyit*). The other medical plants are, such as, *Piper betle* (*sirih*), *Pinus merkusii* (*pinus*), *Cosmos caudatus* (*kenikir*), *Ceiba pentandra* (*kapuk randu*), *Eugenia uniflora* (*ceremai Belanda*), and *Calophyllum nodosum* (*bintangur/nyamplung*) (Table 1).

Several studies conducted in Indonesia have shown significant progress in this field of research, namely around *in vitro* investigations utilizing cell lines (Table 1). Commonly utilized cell lines in research include Vero cells and Huh-7 it-1 cells, whereas the extensively investigated virus is DENV serotype 2. Additional research is necessary to examine the effectiveness of medicinal plants or natural compounds in treating all four dengue serotypes, with the goal of identifying the most promising botanical candidates. Flavonoids are commonly found in most medicinal plants that have been studied for their potential in DENV antiviral research in Indonesia (Table 1 and Table 2). Numerous phytochemicals are yielded through extraction using diverse solvents. Nevertheless, flavonoids and their derivatives stand out as commonly occurring phytochemicals in extracts with antiviral properties. Flavonoids have been extensively studied in various regions worldwide, revealing their potential as antiviral drugs capable of combating a wide range of viruses such as Japanese encephalitis virus, DENV, Chikungunya, hepatitis C virus (HCV), human immunodeficiency virus-1 (HIV-1), influenza, hepatitis B virus (HBV), enterovirus, poliovirus, and severe acute respiratory syndrome coronavirus 2 (SARS-Cov 2).[28]

Furthermore, various *in vitro* and/or molecular studies have investigated the effectiveness of specific chemical compounds obtained from plants as potential antiviral drugs for dengue infections. These compounds include quercetin, isobutyl gallate, curcumin, and 6-gingerol (Table 3). Curcumin and 6-gingerol have been extensively studied in scientific research for their potential antiviral properties against all serotypes of the DENV virus.[29]

Role of anti-inflammatory compounds in dengue infection

The severity of DF and the mechanism by which the DENV causes sickness are both significantly impacted by the inflammatory response that occurs within the host's body. Several inflammatory mediators, including prostaglandin E2 (PGE2), Tumor Necrosis Factor-α (TNF-α), interferon-γ (IFN-γ),interleukin-6 (IL-6), and IL-8 have been discovered to be more prevalent in severe dengue infection.[30-31] Furthermore, TNF-α levels exhibit positive correlations with disease's severity and known as the predominant cytokine responsible for inducing blood vessel permeability. *In vivo* investigations have demonstrated that TNF-α can induce endothelial dysfunction, characterized by elongation of endothelial cells and a decrease in their shape index.[32] A combination of TNF-α and IFN-γ also cause elongation of endothelial cells and the formation of gaps between endothelial cells.[33]

Table 1. *In vitro* studies Indonesia medicinal plants as antiviral against dengue virus infection

Scientific name (local name)/part used/family	Extract used/active constituents	Assay/method	Targeted DENV serotype and cell line used	Study parameters	Phytochemical
Jatropha multifida L (*jarak tintir*)/leaves/*Euphorbiaceae*[34]	Ethanolic	MTT assay RT-PCR	DENV-2, *Aedes albopictus* C6/36 and Vero cells	- CC_{50} = 651.8 µg/mL - Reduce copy number RNA	Flavonoid and terpenoid
Myristica fatua (*pala hutan*)/*Myristicaceae*[35]	Methanolic	MTT Assay FAA Molecular docking	DENV-2 strain New Guinea C (NGC), C6/36 and Huh-7 it-1 cell line	- CC50 = 474.42 µg/mL - EC50 = 25.33 µg/mL - SI = 18.73	Flavonoid; artesunic acid; homoegonol; and myriticin
Cymbopogon citratus (*serai*)/*Poaceae*[35]	Methanolic	MTT Assay FAA Molecular docking	DENV-2 strain NGC, C6/36 and Huh-7 it-1 cell line	- CC50 = 183.74 µg/mL - EC50 = 29.37 µg/mL - SI = 6.26	Terpenes; alcohols; ketones; aldehyde; and esters; citral α; citral β; nerol geraniol; citronellal; terpinolene; geranyl acetate; myrecene; and terpinol methylheptenone
Acorus calamus (*dlingo*)/*Acoraceae*[35]	Methanolic	MTT Assay FAA Molecular docking	DENV-2 strain NGC, C6/36 and Huh-7 it-1 cell line	- CC_{50} = 424.93 µg/mL	β-asarone; acoric acid; and calamusin D
Psidium guajava (*jambu biji*)/leaves/*Myrtaceae*[36]	Ethanolic	MTT Assay FAA	DENV-2 strain NGC, Huh7it-1 cell line	- CC50 = 153.18 µg/mL - IC50 = 7.2 µg/mL - SI = 21.28	Quercetin (derivate of flavonoid)
Carica papaya (*pepaya*)/leaves/*Caricaceae*[36]	Ethanolic	MTT Assay FAA	DENV-2 strain NGC, Huh7it-1 cell line	- CC50 = 244.76 µg/mL - IC50 = 6.57 µg/mL - SI= 37.25	Flavonoid; terpenoid; alkaloid; carbohydrate; phenol; glycoside; phytosterol; saponin; and tannin
Mangifera foetida L. (*mangga bacang*) Batu varieties/stem bark/*Anacardiaceae*[37]	Methanolic	MTT Assay Viral ToxGlo Assay	DENV-2, Vero cells	- CC_{50} = 133.78 µg/mL - IC50 = 8.14 µg/mL - SI= 16.43	Flavonoids (quercetin and catechins) and its derivative (mangiferin); polyphenolic compound (gallic acid)
Cassia alata (*ketepeng Cina*)/leaves/*Fabaceae*[38]	Ethanolic (from plants grow in	MTT Assay Time-of-addition test	DENV-2 strain NGC, Huh-7-it-1 cell line	- Early step inhibition: 96.04 %	5,7,2',5'-tetrahydroxyflavone; daturametelin H; kaempferol-3,7 diglucoside; 5,5-tetramethoxy-trans-

	Jakarta)			- Post infection inhibition 99.16 %	stilbene,25-dehydroxy-24-acetate alisol; β-sitosterol-3-0-β-D-glucopyranoside; digitopurpon; 3,3' deoxycholic acid.
Annona squamosa (*srikaya*)/leaves/*Annonaceae*[39]	Ethanolic	MTT Assay Viral ToxGlo Assay	DENV-2, Vero cells	- IC50= 73.78 µg/mL - CC50= 331.54 µg/mL - SI= 4.49	flavonoids; alkaloids; phytosterols; glycoside; saponins; phenolic compounds; and tannins.
Piper betle (*sirih*)/leaves/*Piperaceae*[40]	-	MTT Assay FAA	DENV-2 strain NGC, Huh7it-1 cell line	- IC50 = 17.662 µg/mL - CC50 = 486.404 µg/mL - SI = 24.3	Piperbetol; chavicol; hydroxychavicol; methylpiperbetol; chavibetol; piperol A; and piperol
Allium sativum L. (*bawang putih*)/tuber/*Amaryllidaceae*[41]	Ethanolic	MTT Assay FAA	DENV-2 strain NGC, Vero cells	- % Cell viability >90% - Dose 40 µg/mL has the highest inhibitory potency of 46.4%	Allyl methyl thiossulfinate and allicin
Pinus merkusii (*pinus*)/cone/*Pinaceae*[42]	-	Viral ToxGlo™ Assay CellTiter-Glo® Luminescent Cell Viability Assay	DENV-2 NCBI accession number: KT012509, Vero cells	- IC50 = 73.78 µg/mL - CC50 = 249.5 µg/mL - SI = 3.38	Proanthocyanidins (oligomeric and polymeric products from flavonoid biosynthetic pathway) as the most abundant; phenols; and terpenoids
Cosmos caudatus (*kenikir*)/leaves/*Asteraceae*[43]	-	MTT Assay FAA	DENV-2 strain NGC, Huh7it-1 cell line	- IC50 = 12.2 µg/mL - CC50 = 187.1 µg/mL - SI = 15.4	-
Pterocarpus indicus Willd (*sono kembang*/cendana merah)/*Leguminoceae*[44]	Crude Extract (ethanolic), hexane fraction, and ethyl acetate fraction	MTT Assay FAA	DENV-1 IDS 11/10, C6/36 cell line, Huh7it-1 cells	- Crude Extract - CC50= 174.31 µg/mL - IC50 = <0.125 µg/mL - SI = >1,392 - Hexane - CC50 = 35.67 µg/mL - IC50 = <0.125 µg/mL - SI = >285.36 - Ethyl acetate - CC50 = 21.07 µg/mL - IC50 = <0.125 µg/mL - SI = >168.56	Flavonoids
Curcuma longa	CDs-13	MTT Assay	DENV-2 strain NGC,	- CC50 = 85.4 µg/mL	Curcumin

(*kunyit*)/*Zingiberaceae*[45]	extract processed into methanol fraction	FAA	Huh7it-1 cell line	- IC50 = 17.91 µg/mL - SI = 4.8	
Ceiba pentandra (*kapuk randu*)/leaves/*Malvaceae*[46]	-	MTT Assay, FAA	DENV-2 strain NGC, Huh7it-1 cell line	- IC50 = 15.49 µg/mL - CC50 = 81.1 µg/mL - SI = 5.23	Flavonoids
Eugenia uniflora (*ceremai Belanda*)/leaves/*Myrtaceae*[46]	-	MTT Assay FAA	DENV-2 strain NGC, Huh7it-1 cell line	- IC50 = 19.83 µg/mL - CC50= 134.42 µg/mL - SI = 6.78	Flavonoids
Calophyllum nodosum (*bintangur/nyamplung*)/leaves /*Clusiaceae*[47]	Butanol fraction	MTT Assay FAA	DENV-2 strain NGC, Huh7it-1 cell line	- IC50= 5.6 µg/mL - CC50= 1,181.1 µg/mL - SI= 210.9	Flavonoids; xanthones; coumarin; chalcone; benzofuran; and triterpene

DENV: Dengue Virus; MTT: 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide; IC50: 50% inhibition concentration; CC50: 50% cytotoxicity concentrations; SI: selectivity index, FAA: focus forming assay; NGC: New Guinea C; CDs: carbon dots; RT-PCR: Reverse transcription polymerase chain reaction.

Table 2. In vivo studies Indonesia medicinal plants as antiviral against dengue virus infection

Scientific name (local name)/part used/family	**Extract used/active constituents**	**Assay/method**	**Targeted DENV serotype and animal model used**	**Study parameters/ results**	**Phytochemical**
Cassia alata (k*etepeng Cina*)/leaves/*Fabaceae*[48]	Ethanolic extract	FAA	DENV-2, 2-day-old Balb/C mice, Vero cell (for titration)	Decreasing of the DENV-2 titter	Flavonoids and alkaloids
Curcuma longa (k*unyit*)/*Zingiberaceae*[49]	CDs-13 extract processed into methanol fraction	ALT and liver histopathology examination	DENV-2, 8-weeks old male BALB/c mice	Reducing of the necroinflammatory activity	Curcumin
Curcuma longa (k*unyit*)/*Zingiberaceae*[45]	CDs-13 extract processed into methanol fraction	- Yamanaka S and Konishi E method - Serum analysis: SGPT, SGOT, ureum and creatinine - FAA	DENV-2, Male and female mice strain ddY 8-12 weeks old (and male mice strain ddY 2-4 weeks old	Antiviral effect at doses of 0.147 mg/mL and reduce viremia period	Curcumin

DENV: Dengue Virus; MTT: 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide; IC_{50}: 50% inhibition concentration; CC_{50}: 50% cytotoxicity concentrations; SI: selectivity index, FAA: focus forming assay; NGC: New Guinea C; CDs: carbon dots; RT-PCR: Reverse transcription polymerase chain reaction.

In addition to TNF-α, other cytokines IL-1β are also involved in the cause of vascular disease.[50] When dealing with a dengue infection, one method that can be implemented to prevent severe DF is to decrease the body's inflammatory response.

Certain naturally occurring compounds are known for their ability to function as immunomodulators. The compounds mentioned, such as alkaloids, carbohydrates, lectins, polyphenols, stilbenoids, and peptides, are all part of a group of medications called immunomodulatory drugs.[51] Phenolic compounds from plants can influence inflammation in the body and stop the multiplication of viral particles. Some of these derivatives do this by inhibiting the expression of NFκB (Nuclear factor kappa-light-chain-enhancer of activated B cells), while others boost IFN-α and NK (Natural Killer) cell production. Geranin (which comes from plants *Geranium thunbergii* and *Dimocarpus longan*), chebulagic acid and punicalagin (which come from the Genus *Geranium* and *Euphorbia*), and Curcumin (which comes from the plant *Curcuma longa* L.) are some of the phenolic compounds found in plants that have been discovered to have antiviral or anti-inflammatory effects.[52] Numerous active compounds that affect inflammation have been explored, but their molecular mechanisms are still uncertain. Mangosteen (*Garcinia mangostana* Linn.) pericarp extract contains α-MG (alpha mangostin), which inhibits DENV replication by targeting NS5 RdRp. Alpha mangostin inhibits the expression of cytokines and chemokines like TNF-α, RANTES (Regulated upon activation, normal T cell expressed and presumably secreted), IP-10 (interferon γ-induced protein 10 kDa), and IL-6 via the NFκB pathway by preventing NFκB translocation.[4]

Table 3. Indonesia natural compounds as antiviral against dengue virus infection

Compound name	Assay/method	Targeted DENV serotype and cell line used	Study parameters
Quercetin[53]	MTT assay, RT-PCR, molecular docking	DENV-2 strain NGC; Huh7it-1	- IC50= 1.1 µg/ml - CC50= 38.8 µg/ml - SI= 38
Isobutyl gallate[54]	MTT assay, FAA	DENV-2 strain New Guinea C (NGC); Huh7 it-1	- CC50= 167.19 µg/mL - IC50= 4.45 µg/mL - SI= 25.69
Curcumin[29]	MTT assay, plaque assay	- Virus: DENV-1 strain JMB-034; DENV-2 strain SUB-011; DENV-3 strain SUB-006; and DENV-4 strain SUB-007 - Cell line: alveolar epithelial carcinoma A549; fibroblast BHK-21	- IC50 ▪ DENV-1: 20.60 µM ▪ DENV-2: 13.95 µM ▪ DENV-3: 25.54 µM ▪ DENV-4: 12.35 µM - CC50= 108 µM
6-gingerol[29]	MTT assay, plaque assay	- Virus: DENV-1 strain JMB-034; DENV-2 strain SUB-011; DENV-3 strain SUB-006; and DENV-4 strain SUB-007 - Cell line: alveolar epithelial carcinoma A549; fibroblast BHK-21	- IC50 ▪ DENV-1: 14.70 µM ▪ DENV-2: 14.17 µM ▪ DENV-3: 78.76 µM ▪ DENV-4: 112.84 µM - CC50= 210 µM

DENV: Dengue Virus; MTT: 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide; IC_{50}: 50% inhibition concentration; CC_{50}: 50% cytotoxicity concentrations; SI: selectivity index, FAA: focus forming assay; NGC: New Guinea C; RT-PCR: reverse transcription polymerase chain reaction.

Research on the anti-inflammatory effects of medicinal plants against dengue virus (DENV) in Indonesia is limited. Although the severity of dengue infection is influenced by both viral load and the host's inflammatory response, there has been a lack of studies on the potential of natural substances and plant extracts to mitigate this inflammation. Given the critical role inflammation plays in dengue progression, it is important to thoroughly investigate the anti-inflammatory

properties of individual compounds and plant extracts to better understand their therapeutic potential against DENV infections.

CONCLUSION

Several medicinal plants and natural compounds in Indonesia have been empirically demonstrated to have antiviral activity, and several are also anti-inflammatory. The occurrence of flavonoids has been documented in a substantial proportion of medicinal plant species originally from Indonesia, which have demonstrated antiviral properties against DENV. Curcumin and 6-gingerol are the sole natural compounds that have undergone testing against all four serotypes of dengue. Hence, it is imperative to conduct additional investigations on the anti-inflammatory capabilities of Indonesian medicinal plants, encompassing both laboratory experiments (*in vitro*) and studies on living organisms (*in vivo*), with the aim of targeting all serotypes of the DENV. Hence, this leads to the development of the most potent antiviral and anti-inflammatory agent for the dengue virus infection treatment.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTION

AAAK designed the review methods, analysed the data, and drafted the manuscript. BED analysed the data and revised the manuscript; TMS revised the manuscript. All authors have read and approved the final manuscript.

LIST OF ABBREVIATIONS

DENV: Dengue Virus; DF: dengue fever; DHF: dengue haemorrhagic fever; DSS: dengue shock syndrome; CFR: case fatality rate; IR: incidence rate; IFN: Interferon; TNF-α: Tumour Necrosis Factor Alpha; α-MG: alpha mangostin; Rdrp: RNA-dependent RNA polymerase; NS: non-structural proteins; C: Capsid; prM: precursor membrane protein; E: Envelop protein; RNA: Riblonucleic acid; UTRs: untranslated regions ; ORF: open reading frame; RIG-I: retinoic acid-inducible gene I; MAVS: mitochondrial antiviral-signalling protein; LPS: lipopolysaccharide; DC-SIGN: Dendritic cell-intercellular adhesion molecule 3-grabbing nonintegrin; PS: Phosphatidylserine; TIM: T cell Ig mucin; ADE: Antibody Dependent Enhancement; TGN: Trans-Golgi Network; PGE2: prostaglandin E2; PHC: primary health care; NFκB: Nuclear factor kappa-light-chain-enhancer of activated B cells; IP-10: interferon γ-induced protein 10 kDa; ALT: Alanine Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; SGOT: Serum Glutamic Oxaloacetic Transaminase; RT-PCR: Reverse transcription polymerase chain reaction; MTT: 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide; IC50: 50% inhibition concentration; CC50: 50%cytotoxicity concentrations; SI: Selectivity Index, FAA: Focus Forming Assay; RANTES: Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted; HIV: Human Immunodeficiency Virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PAF: Platelet activating factor; HCV: hepatitis C virus; HBV: hepatitis B virus; NK: Natural Killer; NGC: New Guinea C; CDs: carbon dots.

REFERENCES

Murray PR, Rosenthal KS, Pfaller MA. Medical microbiology: Chapter 53. 9th ed. Philadelphia: Elsevier; 2021. 521–522 p.
2. World Health Organization. Dengue and severe dengue [Internet]. World Health Organization. 2022 [cited 2023 Feb 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.
3. Knipe DM, Howley PM, Cohen JI, Griffin DE, Lamb RA, Martin MA, et al., editors. Fields virology volume 1. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. 712–716, 923–926, 1244–1250, 1284–1287 p.
4. Tarasuk M, Songprakhon P, Chieochansin T, Choomee K, Na-Bangchang K, Yenchitsomanus P. Alpha-mangostin inhibits viral replication and suppresses nuclear factor kappa B (NF-κB)-mediated inflammation in dengue virus infection. Sci Rep. 2022;16:16088. DOI: 10.1038/s41598-022-20284-7.
5. Munaeni W, Mainassy MC, Puspitasari D, Susanti L, Endriyatno NC, Yuniastuti A, et al.

Perkembangan dan manfaat obat herbal sebagai fitoterapi. Swandari MTK, Mayer MAE, editors. Tohar Media; 2022. 1 p.
6. Lin LT, Hsu WC, Lin CC. Antiviral natural products and herbal medicines. J Tradit Complement Med. 2014;4(1):24–35. DOI: 10.4103/2225-4110.124335.
7. Flint J, Rall GF, Racaniello VR, Skalka AM, Enquist LW. Principle of virology, Volume I: Molecular biology. 4th ed. Washington DC: ASM Press; 2015. 510 p.
8. Nanaware N, Banerjee A, Bagchi SM, Bagchi P, Mukherjee A. Dengue virus infection: A tale of viral exploitations and host responses. Viruses. 2021;13(1967):1–20. DOI: 10.3390/v13101967.
9. Roy SK, Bhattacharjee S. Dengue virus: Epidemiology, biology, and disease aetiology. Can J Microbiol. 2021;7(10):687-702. DOI: 10.1139/cjm-2020-0572.
10. Nie Y, Deng D, Mou L, Long Q, Chen J, Wu J. Dengue Virus 2 NS2B Targets MAVS and IKKε to Evade the antiviral innate immune response. J Microbiol Biotechnol. 2023;33(5):600–6. DOI: 10.4014/jmb.2210.10006.
11. Dejarnac O, Hafirassou ML, Chazal M, Gaillard MV, Perera-Lecoin M, Umana-Diaz C, et al. TIM-1 ubiquitination mediates Dengue virus entry. Cell Rep. 2018;23(6):1779–93. DOI: 10.1016/j.celrep.2018.04.013.
12. Begum F, Das S, Mukherjee D, Mal S, Ray U. Insight into the tropism of Dengue virus in humans. Viruses. 2019;11(12):1136. DOI: 10.3390/v11121136
13. Dhanoa A, Hassan SS, Ngim CF, Lau CF, Chan TS, Adnan NAA, et al. Impact of dengue virus (DENV) co-infection on clinical manifestations, disease severity and laboratory parameters. BMC Infect Dis. 2016;16(406). DOI: 10.1186/s12879-016-1731-8.
14. Malavige GN, Ogg GS. Pathogenesis of vascular leak in dengue virus infection. Immunology. 2017;151(3):261–269. DOI: 10.1111/imm.12748.
15. Beatty PR, Puerta-Guardo H, Killingbeck SS, Glasner DR, Hopkins K, Harris E. Dengue virus NS1 triggers endothelial permeability and vascular leak that is prevented by NS1 vaccination. Sci Transl Med. 2015;7(304):304ra141. DOI: 10.1126/scitranslmed.aaa3787.
16. Chen J, Ng MML, Chu JJH. Activation of TLR2 and TLR6 by dengue NS1 protein and its implications in the immunopathogenesis of dengue virus infection. PLoS Pathog. 2015;11(7):e1005053. DOI: 10.1371/journal.ppat.1005053.
17. Glasner DR, Ratnasiri K, Puerta-Guardo H, Espinosa DA, Beatty PR, Harris E. Dengue virus NS1 cytokine-independent vascular leak is dependent on endothelial glycocalyx components. PLoS Pathog. 2017;13(11):e1006673. DOI: 10.1371/journal.ppat.1006673
18. Yong YK, Wong WF, Vignesh R, Chattopadhyay I, Velu V, Tan HY, et al. Dengue infection - recent advances in disease pathogenesis in the era of COVID-19. Front Immunol. 2022;13(889196):1–17. DOI: 10.3389/fimmu.2022.889196.
19. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4(177). DOI: https://doi.org/10.3389%2Ffphar.2013.00177.
20. Nasim N, Sandeep IS, Mohantycorresponding S. Plant-derived natural products for drug discovery: Current approaches and prospects. Nucl. 2022;65(3):399–411. DOI: 10.1007/s13237-022-00405-3.
21. Altamish M, Khan M, Baig MS, Pathak B, Rani V, Akhtar J, et al. Therapeutic potential of medicinal plants against dengue infection: A mechanistic viewpoint. ACS Omega. 2022;7:24048−24065. DOI: 10.1021/acsomega.2c00625.
22. Embassy of The Republic of Indonesia in Brussel. Indonesia's potential herbal products gain in the European market [Internet]. Brussel; 2021. Available from: https://kemlu.go.id/
23. Ansori ANM, Fadholly A, Proboningrat A, Jayanti S, Hayaza S, Susilo RJK, et al. Efficacy of *Allium cepa* (Amaryllidaceae) extract against dengue virus type-2 (Flaviviridae: Flavivirus) isolated from Surabaya, Indonesia. Biochem Cell Arch. 2020;20(2):4783–6. https://connectjournals.com/pages/articledetails/toc032318.
24. Henri, Sari DP, Hakim L. Medicinal plants for traditional treatment used by the Malays in South Bangka Regency, Indonesia. Biosaintifika. 2022;14(1):125–34. DOI:

10.15294/biosaintifika.v14i1.34455.
25. Rahmawati N, Mustofa FI, Haryanti S, Subositi D, Widodo H, Sholikhah IYM, et al. Ethnopharmacology study of medicinal plants utilized for hypercholesterolemia treatment in Kalimantan, Indonesia. J Tumbuh Obat Indones. 2022;15(1):1–15. DOI: 10.22435/jtoi.v15i1.5928.
26. Arozal W, Louisa M, Soetikno V. Selected Indonesian medicinal plants for the management of metabolic syndrome: Molecular basis and recent studies. Front Cardiovasc Med. 2020;8(72). DOI: https://doi.org/10.3389/fcvm.2020.00082.
27. Kementrian Kesehatan Republik Indonesia. Strategi nasional penanggulangan Dengue 2021-2025. Jakarta; 2021.
28. Badshah SL, Faisal S, Muhammad A, Poulson BG, Emwas AH, Jaremkob M. Antiviral activities of flavonoids. Biomed Pharmacother. 2021;140:111596. DOI: 10.1016/j.biopha.2021.111596.
29. Halim JAN, Halim SN, Denis D, Haryanto S, Dharmana E, Hapsari R, et al. Antiviral activities of curcumin and 6-gingerol against infection of four dengue virus serotypes in A549 human cell line in vitro. Indones J Biotechnol. 2021;26(1):41-47. DOI: 10.22146/ijbiotech.60174.
30. Bandara SMR, Herath HMMTB. Corticosteroid actions on dengue immune pathology; A review article. Clin Epidemiol Glob Heal. 2020;8(2):486–94. DOI: 10.1016/j.cegh.2019.11.001.
31. Chuang FK, Huang SM, Liao CL, Lee AR, Lien SP, Chiu YL, et al. Anti-inflammatory compound shows therapeutic safety and efficacy against Flavivirus infection. Antimicrob Agents Chemother. 2020;64(1):e00941-19. DOI: 10 .1128/AAC.00941-19.
32. Wang B, Chen R, Gao H, Lv X, Chen L, Wang W, et al. A comparative study unraveling the effects of TNF-α stimulation on endothelial cells between 2D and 3D culture. Biomed Mater. 2020;15(6):065018. DOI: 10.1088/1748-605x/ab95e3.
33. Seynhaeve ALB, Vermeulen CE, Eggermont AMM, ten Hagen TLM. Cytokines and vascular permeability an in vitro study on human endothelial cells in relation to tumor necrosis factor-α-primed peripheral blood mononuclear cells. Cell Biochem Biophys. 2006;44:157–169. DOI: 10.1385/CBB:44:1:157.
34. Yuniyanti MM, Nugrahaningsih DAA, Wahyuningsih MSH. Phytochemical screening and anti-dengue activity of J*atropha multifida* extract against DENV-2. Tradit Med J. 2022;27(1):77–84. DOI: 10.22146/mot.73368.
35. Rosmalena R, Elya B, Dewi BE, Fithriyah F, Desti H, Angelina M, et al. The antiviral effect of Indonesian medicinal plant extracts against Dengue virus in vitro and in silico. Pathogens. 2019;8(2):85. DOI: 10.3390/pathogens8020085.
36. Saptawati L, Febrinasari RP, Yudhani RD, Hudiyono, Faza AG, Luthfiani S, et al. In vitro study of eight Indonesian plants extracts as anti Dengue virus. Heal Sci J Indones. 2017;8(1):12–8. DOI: 10.22435/hsji.v8i1.6601
37. Fitmawati, Safitri M, Kholifah SN, Emrizal, Roza RM. *Mangifera foetida* L. (macang) source of potent antiviral activity of against Dengue virus serotype 2 (Anti DENV2). J Phys Conf Ser. 2021;(2049):012018. DOI:10.1088/1742-6596/2049/1/012018.
38. Angelina M, Hanafi M, Suyatna FD, Dewi BE. Drug of action *Cassia alata* leaves extract as antiviral to Dengue virus serotype-2 in vitro. Pharmacogn J. 2020;12(4):864–71. DOI: 10.5530/pj.2020.12.124.
39. Ansori ANM, Fadholly A, Proboningrat A, Antonius Y, Hayaza S, Susilo RJK, et al. Novel antiviral investigation of annona squamosa leaf extract against the Dengue virus type-2: In vitro study. Pharmacogn J. 2021;13(2):456–62. DOI: 10.5530/pj.2021.13.58.
40. Dewi BE, Tannardi K, Sudiro TM. The potency of *Piper betle* leave extract as antiviral drug to Dengue virus in vitro. Teikyo Med J. 2021;44(2):677–86. DOI: http://www.scopus.com/inward/record.url?scp=85108909507&partnerID=8YFLogxK.
41. Nupus Z, Apriyanto DR, Permatasari TO. Uji antivirus ekstrak bawang putih (*Allium sativum* L.) terhadap virus Dengue serotipe 2 strain New Guinea C. Indones J Biomed Heal Sci. 2022;1(1). https://jurnal.ugj.ac.id/index.php/inabhs

42. Ansori ANM, Fadholly A, Proboningrat A, Hayaza S, Susilo RJK, Naw SW, et al. In vitro antiviral activity of *Pinus merkusii* (Pinaceae) stem bark and cone against dengue Virus type-2 (DENV-2). Res J Pharm Technol. 2021;14(7):3706–9. DOI: 10.52711/0974-360X.2021.00641.
43. Prasetya SI, Tanujaya A, Ratnasari S, Desti H, Louisa M, Angelina M, et al. Antiviral activity of *Cassia alata* and *Cosmos caudatus* leaf extract to Dengue virus serotype-2 New Guinea C strain in Huh7-it1 cell. Adv Sci Lett. 2018;24(9):6388–92. DOI: 10.1166/asl.2018.12725.
44. Dewi BE, Angelina M, Meilawati L, Hartati S, Dewijanti ID, Santi MR, et al. Antiviral effect of *Pterocarpus indicus* willd leaves extract against replication of Dengue virus (DENV) in vitro. J Trop Life Sci. 2018;8(1):55–61. DOI: 10.11594/jtls.08.01.10.
45. Ichsyani M, Ridhanya A, Risanti M, Desti H, Ceria R, Putri DH, et al. Antiviral effects of *Curcuma longa* L. against Dengue virus in vitro and in vivo. IOP Conf Ser Earth Environ Sci. 2017;101:012005. DOI: 10.1088/1755-1315/101/1/012005.
46. Dewi BE, Angelina M, Ardiantara S, Prakoso AR, Desti H, Sudiro TM. Antiviral activity of *Ceiba pentandra* and *Eugenia uniflora* leaf extracts to Dengue virus serotype-2 in Huh 7it-1 cell line. AIP Conf Proc. 2019;2193:030003. DOI: 10.1063/1.5139340.
47. Salsabila S, Calista N, Desti H, Dewi BE. The effectivity of butanol fraction of *Calophyllum nodosum* as antiviral drug to Dengue virus serotype 2 in vitro. Bromo Conf Symp Nat Prod Biodivers. 2018; DOI: 10.5220/0009843100002406.
48. Angelina M, Hanafi M, Yuliani T, Suyatna F, Soediro TM, Dewi BE. The inhibitory activity of *Cassia alata* leaves extract on DENV-2 replication infected mice. Pharmacia. 2022;69(3):821–826. DOI: 10.3897/pharmacia.69.e86777.
49. Riani NWA, Utama IMS, Winaya IBO. The hepatoprotective effect of *Curcuma longa* extract on dengue virus serotype-2 infected BALB/c mice. Maced J Med Sci. 2023;11:111–6. DOI: 10.3889/oamjms.2023.8993.
50. Chunhakan S, Butthep P, Yoksan S, Tangnararatchakit K, Chuansumrit A. Vascular leakage in dengue hemorrhagic fever is associated with dengue infected monocytes, monocyte activation/exhaustion, and cytokines production. Int J Vasc Med. 2015;917143. DOI: 10.1155/2015/917143.
51. Singh P, Gupta E, Mishra N, Mishra P. Shikimic acid as intermediary model for the production of drugs effective against influenza virus. Phytochem as Lead Compd New Drug Discov. 2020;245–256. DOI: 10.1016%2FB978-0-12-817890-4.00016-0.
52. Loaiza-Cano V, Monsalve-Escudero LM, Filho CSMB, Martinez-Gutierrez M, Sousa DP. Antiviral role of phenolic compounds against Dengue virus: A review. Biomolecules. 2021;11(11). DOI: 10.3390/ biom11010011.
53. Dewi BE, Ratningpoeti E, Desti H, Angelina M. In vitro and in silico study to evaluate the effectiveness of quercitrin as antiviral drug to Dengue virus. AIP Conf Proc. 2019;2193:030004. DOI: 10.1063/1.5139341.
54. Dewi BE, Angelina M, Nuwwaaridya F, Desti H, Sudiro TM. Antiviral activity of isobutyl gallate to Dengue virus serotype 2 in vitro. IOP Conf Ser Earth Environ Sci. 2019;251:012018. DOI: 10.1088/1755-1315/251/1/012018.