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Traditional Knowledge and Molecular Evidence of Medicinal Plants for Multi-Target Dengue Therapy: A Review

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Abstract

Dengue fever continues to intensify as a major global public health challenge, driven by climate change, rapid urbanization, and expanding vector habitats, while the absence of a universally safe and effective antiviral therapy remains a critical limitation. Unlike conventional single-target antivirals, plant-based interventions offer a multi-target therapeutic strategy capable of simultaneously inhibiting viral replication, modulating immune dysregulation, reducing oxidative stress, stabilizing endothelial function, enhancing platelet recovery, and contributing to vector control. A wide range of phytochemicals, including flavonoids, alkaloids, tannins, polyphenols, polysaccharides, and bioactive enzymes, have been reported to interact with key dengue viral proteins such as NS2B-NS3 protease and NS5 RNA-dependent RNA polymerase, while also regulating host inflammatory and immunological pathways. Integration of ethnopharmacological data with molecular docking, network pharmacology, and preclinical studies provides mechanistic validation for traditionally used plants, particularly *Carica papaya*, *Andrographis paniculata*, and *Tinospora cordifolia*. Additionally, analysis of plant diversity, parts used, phytochemical classes, and conservation status highlights both therapeutic promise and sustainability concerns. Despite promising in-vitro and in-silico evidence, clinical translation remains constrained by lack of standardized formulations, limited in-vivo validation, and insufficient large-scale clinical trials. This review comprehensively integrates epidemiological trends, dengue virus biology, pathogenesis, traditional knowledge, and modern molecular evidence to evaluate the therapeutic potential of medicinal plants in dengue management. Overall, this review underscores medicinal plants as evidence-based, multi-target candidates for next-generation dengue therapeutics, offering a sustainable and affordable pathway to mitigate the escalating global dengue burden.

Keywords: Antiviral; Dengue; Ethnomedicine; Immunomodulation; Medicinal Plants; Phytotherapy.

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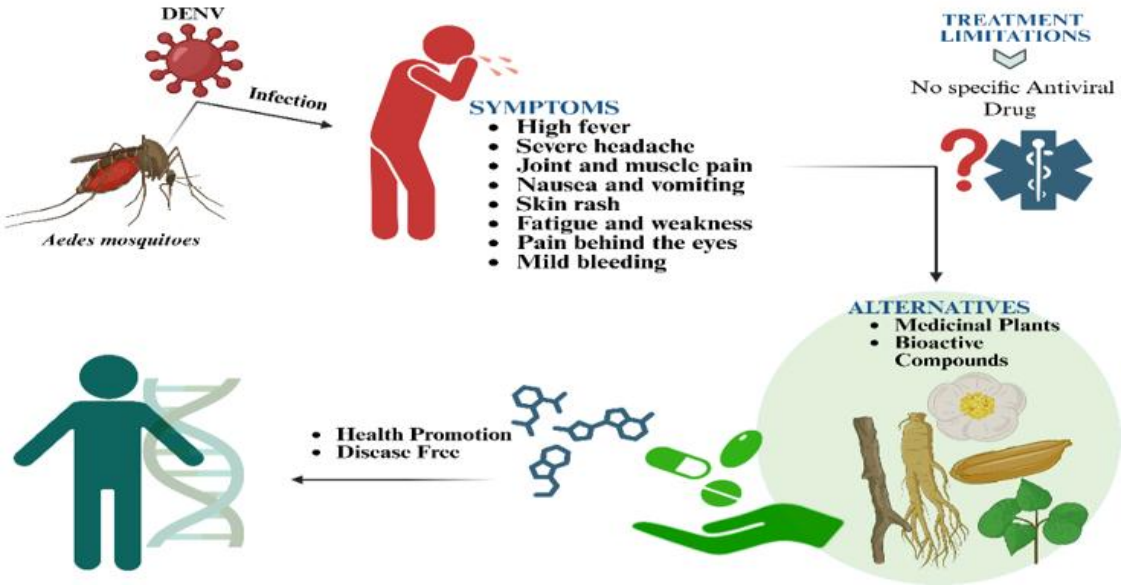

Schematic Abstract

Introduction

Viruses are emerging as the most infectious entities capable of producing a broad spectrum of diseases in nearly all life forms. This marks Antiviral medicines vital because Drug development doesn't follow a smooth path due to the simple structure of viruses, their dependency on the host cell machinery, and their rapid mutation rate (1). Viruses are intracellular parasites, some of which cause mild infections, while others co-exist with their hosts to cause severe outbreaks (2). They are composed of nucleic acid, enzymes, and a protein coat, or sometimes enclosed in an envelope (3). The COVID-19 pandemic, with over a million deaths in 2020 alone, creates an immediate need for the development of significant antiviral drugs. In addition, phytomedicines also show promising results in the inhibition of viral replication and the cure of viral infections (4). Among the viruses, dengue fever is one of the fastest spreading mosquito-borne infections, especially in tropical and subtropical parts of the world. The World Health Organization (WHO) reported that dengue cases increased from 500,000 in the year 2000 to 5.2 million in 2019, covering 129 countries. Half the world population is at risk, with 100-400 million infections per year. This makes research into plant medicines more vital since, despite so much investigation, there is no clear antiviral treatment yet (5,6).

Despite several studies conducted on dengue, an effective and safe therapy against the disease is not yet available. In contrast, a significant amount of plant species showing good results, the experimental data generated for this purpose is mostly based on in vitro and in silico experiments. Thus, there exists a definite need to bridge the gap between traditional practices and molecular evidence for developing multiple targets for dengue treatment using medicinal plants.

Dengue Virus

Structure and Virology of Dengue Virus

Dengue virus (DENV) is a single-stranded RNA virus that belongs to the genus *Flavivirus* under the family *Flaviviridae* (7). Flaviviruses such as Dengue, yellow fever, Zika, and West Nile are globally emerging health threats that replicate despite interferon-based immunity and invade before the activation of host defences (8). Dengue infection is caused by five antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, DENV-4, and the newly discovered DENV-5. These serotypes are genetically similar, sharing around 65% of their DNA, yet each triggers a unique immunological response. DENV-1 to DENV-4 are well-established in human populations. DENV-5 was identified in a 37-year-old farmer in Sarawak, Malaysia, in 2007 and officially reported in 2013. At first, the illness was thought to be sylvatic DENV-4, which spreads among primates and *Aedes nivalis* in forests in Southeast Asia (9). The virus enters the host cell by adherence of its envelope (E) protein to receptors which are found in the cells among dendritic cell-specific intercellular adhesion molecule-

3-grabbing non-integrin (DC-SIGN), mannose receptors, and glycosaminoglycans. Then it infects the host cell through receptor-mediated endocytosis, after which the acidification of the endosome induces conformational changes in the E protein, leading to fusion of the viral and endosomal membranes, ultimately releasing viral RNA into the cytoplasm. The positive-sense single-stranded RNA genome is translated into a polyprotein that is cleaved into structural (C, prM, E) and non-structural (NS1–NS5) proteins. Replication occurs on the endoplasmic reticulum membrane, and mature virions are assembled after cleavage of prM by the host protease furin in the Golgi apparatus. The viral NS2B/NS3 and NS5 proteins inhibit the JAK-STAT pathway, which is crucial for interferon signalling, allowing immune evasion (10).

Transmission Dynamics and Global Burden

Dengue is transmitted through *Aedes aegypti* and *Aedes albopictus* mosquito bites. These mosquitoes thrive in urban, rural, and forest environments. They bite people infected with dengue and subsequently infect another uninfected healthy person by biting (12,13). According to annual reports, DENV has accounted for the highest number of infections with widespread distribution worldwide over the past seven decades (12,14). In 2019, there were 56.9 million cases and over 36,000 deaths (12,13). Dengue cases rose by 85.5% from 1990 to 2019, especially in Southern Asia (15). Current estimates indicate that climate change will put over 6 billion people at risk by the year 2080 (16). Poor waste management, stagnant water, and unplanned urbanisation create appropriate conditions for mosquito breeding. The eggs of *Aedes* mosquitoes can survive in dry conditions for several months, which helps their populations to sustain themselves even when they are devoid of water sources. Outbreaks of dengue are associated with almost regular peaks during the monsoon seasons in South and Southeast Asia. However, is spreading into previously unaffected areas due to climate change, deforestation, and traveling throughout the world (17,19).

Pathogenesis and Immunological Response

Dengue virus infects different cells, such as dendritic cells, monocytes, and endothelial cells. The viral proteins thus inhibit host interferon responses, leading to viral replication and immune evasion (10). The antibody-dependent enhancement (ADE) thus facilitates viral replication and elevated vascular permeability and worsens with host factors and immune dysfunction like low platelet counts and leukopenia, leading to multiorgan failure (20). Dengue haemorrhagic fever (DHF) is a fever among haemorrhagic manifestations, thrombocytopenia, and increased vascular permeability, usually resulting from bone marrow suppression (21) and may be due to immune-mediated destruction of platelets (22-24). Two principal hypotheses have been mentioned regarding the pathogenesis of DHF: one includes ADE in heterotypic secondary infections, and the other comprises a multifactorial interplay of viral load, strain virulence, and host immune response (25-28).

Clinical Symptoms and Disease Progression

Clinically, symptoms such as fever, malaise, arthralgia, myalgia, retro-orbital pain, and rash are seen due to dengue infection after an incubation period of 4-7 days (29). Dengue progresses through three distinct phases:

i. **Febrile Phase:** High fever, headache, muscle pain, rash, and low platelet counts.
ii. **Critical Phase:** Life-threatening plasma leakage, internal bleeding, and circulatory failure.
iii. **Recovery Phase:** Skin rash, fatigue, and fluid reabsorption.

It develops most severely into Dengue Haemorrhagic Fever (DHF) or Dengue Shock Syndrome (SDS) and is associated with a considerably amplified risk of organ failure and death (18). Laboratory findings are thrombocytopenia, leukopenia, increased liver enzymes (AST and ALT), and dyspnoea associated mostly with pulmonary capillary leakage (23-31).

Diagnostic Approaches and Treatment Options

With no antiviral treatment exists, the symptom management goes on. The recommendation is paracetamol administration in case of fever, while aspirin and NSAID use must be avoided to eliminate possible bleeding risks. Fluids are very important in extreme cases to prevent shock, and platelet transfusions are only

done in a very severe management situation where extreme haemorrhagic conditions are present (5). In other words, no antiviral treatment means supportive clinical management, with particular attention to fluid resuscitation and symptomatic treatment with acetaminophen, while non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated (4).

Vector Ecology and Innovative Control Strategies

Asia alone accounts for 70% of cases of dengue, followed by 14% in the Americas and 16% in Africa. The conventional control of mosquitoes is based largely on the removal of breeding habitats and the application of insecticides; however, resistance to the chemicals has resulted in decreased efficacy of these methods. Advanced techniques include genetically modified mosquitoes engineered to prevent reproduction and *Wolbachia* biocontrol, where bacteria are introduced to the mosquitoes, preventing the transmission of the virus. Insecticide-treated window screens and mosquito nets provide indoor protection (32). Plant-wise mosquito repellents, such as neem, citronella, and eucalyptus oil, are congenial to nature as opposed to synthetic insecticides. Some plant extracts also have larvicidal actions, controlling the immature stages of mosquitoes before they develop into adults (19).

Medicinal Plants with Antiviral and Immunomodulatory Properties

Currently, there exists only one approved vaccine for dengue, called CYD-TDV (Dengvaxia). It is, however, not recommended for persons without prior dengue infections because of the danger of an ADE, which can result. Furthermore, there is pre-screening before being vaccinated, limiting its use (6). NS3 protease and NS5 polymerase inhibitors are emerging as promising compounds for antiviral medicinal drug development. There are no approved marketed medicines yet. However, studies are ongoing on the development of plant-based antiviral compounds as safer alternatives (19). The new hope, therefore, seems to emanate from medicinal plants, given their role in antivirals, immune boosters, and mosquito repellents, thereby constituting an area of increasing research interest (32). The compiled Table.1-3 presents medicinal plant species validated through Plants of the World Online (POWO), ensuring nomenclatural accuracy by updating accepted names and identifying synonyms. This taxonomic verification strengthens the reliability of species identification, which is essential for ethnopharmacological studies and dengue treatment research (33). Figures 3-6 collectively indicate that anti-dengue medicinal plants listed from the review of literature are taxonomically concentrated in families such as Zingiberaceae, Lamiaceae, and Fabaceae, with leaves being the most used plant part. Most species fall under *Not Evaluated (NE)* or *Least Concern (LC)* categories of the International Union for Conservation of Nature (IUCN) Red List, highlighting limited conservation assessment despite extensive use. The predominance of flavonoids, alkaloids, and polyphenols further supports a multi-target therapeutic potential combining antiviral, immunomodulatory, and antioxidant effects.

Phytoconstituents with Anti-Dengue Activity and Their Action Mechanism

Numerous plants and plant-derived chemicals contain crucial biological activities, such as antibiotic, anticancer, and antiviral properties, which have helped treat millions of people suffering from serious illnesses. Flavonoids, polysaccharides, hemicelluloses, and hydrophilic colloids as listed in table.4 have all been discovered as important components of medicinal plants exhibiting antiviral effects. The structure and chemical properties of these bioactive compounds, as described in recent research, highlight their potential as viable candidates for future therapeutic use (50).

Molecular Basis of Dengue Infection and Therapeutic Targets

Dengue is a mosquito-borne viral disease caused by dengue virus (DENV), a positive-sense single-stranded RNA virus of the genus *Flavivirus* (family *Flaviviridae*). Globally, dengue causes approximately 100-400 million infections annually, with Asia contributing the largest share, and India representing a major endemic region (12, 63). Rapid urbanization, climate change, and vector adaptability have further intensified dengue transmission (64). The DENV genome (~10.7 kb) encodes a single polyprotein cleaved into three structural

proteins capsid (C), premembrane/membrane (prM/M), and envelope (E) and seven non-structural proteins (NS1–NS5) (65). Viral entry occurs via receptor-mediated endocytosis in dendritic cells and monocytes, followed by pH-dependent membrane fusion mediated by the envelope protein (66). Viral replication occurs on endoplasmic reticulum membranes, with NS2B–NS3 protease and NS5 RNA-dependent RNA polymerase/methyltransferase playing central roles in polyprotein processing and genome replication (67, 68). A hallmark biochemical feature of dengue infection is thrombocytopenia, resulting from bone marrow suppression, immune-mediated platelet destruction, platelet aggregation, and direct infection of megakaryocytes via FcγRII receptors (69). Additionally, immune dysregulation characterized by excessive cytokine release (TNF-α, IL-6, IFN-γ), oxidative stress, and endothelial dysfunction leads to plasma leakage and hemorrhagic manifestations (70-71). Current dengue management remains largely supportive, as antiviral drugs and vaccines have shown limited success or safety concerns (72-74). This therapeutic gap has driven renewed interest in medicinal plants, which often act through multi-target antiviral and host-modulatory mechanisms.

Molecular Docking and In-Silico Evidence Supporting Medicinal Plants

Molecular docking and in-silico studies have provided mechanistic validation for traditional medicinal claims by identifying phytochemicals that interact with key dengue viral targets. Numerous studies demonstrate that compounds from *Carica papaya, Andrographis paniculata,* and *Tinospora cordifolia* bind effectively to NS2B-NS3 protease and NS5 polymerase (75-77).

Flavonoids such as quercetin, kaempferol, and chlorogenic acid from papaya leaf extracts show strong binding affinity toward NS2B-NS3 protease, supporting a direct antiviral mechanism alongside platelet-enhancing effects (75,76). Andrographolide exhibits high binding affinity to NS5 polymerase, correlating with significant viral inhibition observed in cell-based assays (78). Similarly, berberine and tinosporide from *T. cordifolia* demonstrate stable interactions with viral proteins in docking studies (77).

Network pharmacology analyses further suggest that medicinal plants act through multiple host and viral pathways, including modulation of oxidative stress, autophagy, unfolded protein response, and immune signaling cascades (79,80). While molecular docking alone cannot replace experimental validation, it provides a critical mechanistic bridge between traditional knowledge and modern drug discovery. When integrated with *in-vitro, in-vivo*, and clinical evidence as seen most clearly for papaya leaf extract it strengthens the scientific rationale for plant-based dengue therapeutics.

Traditional Knowledge in Dengue Management

Indian Traditional Knowledge for Dengue Treatment

India possesses a rich heritage of traditional medicine systems such as Ayurveda, Siddha, Unani, and regional folk practices. Among Indian remedies, *Carica papaya* (papaya; Papita, Papayi) leaf extract is the most extensively studied traditional treatment for dengue. Numerous clinical trials, case reports, and meta-analyses have demonstrated that papaya leaf extract significantly increases platelet count and reduces hospitalization duration in dengue patients (81-83). A recent systematic review and meta-analysis reported a significant mean increase in platelet count and shorter hospital stay following papaya leaf extract treatment (83). The proposed mechanisms include membrane-stabilizing effects on blood cells, stimulation of thrombopoietic cytokines such as IL-6 and stem cell factor, and antioxidant protection (84).

Tinospora cordifolia (Giloy, Guduchi, Amrita) is a classical Ayurvedic rasayana traditionally used for fever and immune enhancement. Experimental studies indicate that its alkaloids and diterpenoid lactones modulate cytokine balance, suppress inflammatory responses, and inhibit viral structural and non-structural proteins (85,86). Although clinical data remain limited, in-vitro and in-silico studies support its potential role in dengue management (77). *Andrographis paniculata* (Kalmegh, Nilavembu) is widely used in Ayurveda and Siddha medicine for febrile illnesses. Its bioactive compound andrographolide exhibits antiviral, anti-inflammatory,

and immunomodulatory activities. Multiple in-vitro studies demonstrate significant inhibition of dengue viral replication, and clinical relevance is suggested by its immune-modulating effects (79,87).

Other Indian medicinal plants such as *Azadirachta indica* (Neem) and *Ocimum tenuiflorum* (Tulsi) are traditionally used for viral fevers and immune support. Neem phytochemicals show antiviral and immunomodulatory properties, while tulsi extracts reduce viral-induced cytopathic effects and enhance host immunity (77,88).

Worldwide Traditional Knowledge for Dengue Treatment

Globally, traditional medicinal systems also employ plant-based remedies for dengue-like illnesses. In Traditional Chinese Medicine (TCM), polyherbal formulations containing *Curcuma longa*, *Zingiber officinale*, and *Lonicera japonica* are used to treat viral fevers and inflammation, emphasizing synergistic multi-target actions (89,90). In Africa, ethnobotanical surveys report extensive use of Fabaceae and Lamiaceae species for febrile and viral conditions, although direct anti-dengue validation remains limited (91). In Latin America and the Philippines, *Euphorbia hirta* (Tawa-tawa), *Psidium guajava* (Guava), and *Momordica charantia* (Bitter gourd) are widely used folk remedies, with guava leaf decoctions reported to improve platelet recovery and antioxidant status (92,93). Overall, Indian traditional medicine is distinguished by the availability of clinical evidence particularly for papaya leaf extract whereas many global remedies remain largely ethnobotanical or preclinical. Nevertheless, all systems converge on the principle of multi-component therapy suited to the complex pathophysiology of dengue.

Knowledge Gap

Despite extensive ethnomedicinal documentation and promising in-vitro and in-silico evidence, most medicinal plants proposed for dengue therapy lack standardized formulations, validated dosages, comprehensive toxicity and pharmacokinetic data, and robust clinical validation, with mechanistic insights largely limited to predicted interactions with viral targets such as NS3 and NS5 rather than experimentally confirmed pathways.

Future Scope

Future research should focus on developing standardized, quality-controlled plant extracts, validating their multi-target antiviral and immunomodulatory mechanisms through in-vivo and multi-serotype studies, and advancing the most promising candidates into well-designed clinical trials, supported by network pharmacology, multi-omics approaches, and innovative delivery systems to enable safe and effective plant-based dengue therapeutics.

Table 1: List of major medicinal grass and herbs used in the treatment of dengue.

Sl. No.	Scientific Name	Habit	Family	Local Name	IUCN Status	Parts Used	Bioactive Compounds	Mechanism of Action	Ref.
1.	*Acorus calamus* L.	Herb	Acoraceae	Sweet Flag	NE	Leaves	α-Asarone, β-Asarone, Eugenol, Acorenone	Disrupts viral enzymes, antioxidant activity	(34)
2.	*Aloe barbadensis* Miller	Herb	Asphodelaceae	Aloe Vera	NE	Leaves, Gel	Aloin, Aloe-emodin, Acemannan, Chrysophanol	Soothes inflammation, supports immune function	(35)
3.	*Alpinia galanga* L.	Herb	Zingiberaceae	Greater Galangal	NE	Rhizome	Galangin, 1′-Acetoxychavicol acetate, Kaempferide	Suppresses viral load, enhances immunity	(36)
4.	*Alternanthera philoxeroides* Mart.	Herb	Amaranthaceae	Alligator Weed	NE	Whole Plant	Flavonoids, Phenolic acids, β-Sitosterol	Antioxidant, inhibits viral RNA synthesis	(34)
5.	*Andrographis paniculata* (Burm. f.) Wall. ex Nees	Herb	Acanthaceae	Kalmegh	NE	Leaves	Andrographolide, Neoandrographolide, Deoxyandrographolide	Suppresses viral replication, enhances immunity	(34)

6.	*Boesenbergia rotunda* (L.) Mansf.	Herb	Zingiberaceae	Chinese Ginger	NE	Rhizome	Panduratin A, Pinostrobin, Boesenbergin	Inhibits dengue NS3 protease	(37)
7.	*Curcuma longa* L.	Herb	Zingiberaceae	Turmeric	LC	Rhizome	Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin	Inhibits inflammatory pathways, modulates immunity, Inhibits viral protein synthesis, anti-inflammatory	(36)
8.	*Amphilophium elongatum* (Vahl) L.G.Lohmann	Herb	Bignoniaceae	Distictella	NE	Whole Plant	Flavonoids, Iridoids	Promotes platelet production, inhibits viral proteins	(34)
9.	*Euphorbia hirta* L.	Herb	Euphorbiaceae	Asthma Weed	NE	Whole Plant	Quercetin, Rutin, Gallic acid	Platelet enhancement, antiviral activity	(34)
10.	*Gastrodia elata* Blume	Herb	Orchidaceae	Japanese Orchid	VU	Rhizome	Gastrodin, Vanillyl alcohol	Inhibits dengue virus entry	(35)
11.	*Kaempferia parviflora* Wall. ex Baker	Herb	Zingiberaceae	Black Galingale	NE	Rhizome	Methoxyflavones, Kaempferol	Directly inactivates dengue virus particles	(36)
12.	*Kaempferia galanga* L.	Herb	Zingiberaceae	Aromatic Ginger	NE	Rhizome	Ethyl p-methoxycinnamate, Kaempferol	Reduces oxidative stress, antiviral activity	(36)
13.	*Matricaria chamomilla* L.	Herb	Asteraceae	Chamomile	NE	Flowers	Apigenin, Bisabolol, Chamazulene	Anti-inflammatory, relaxes muscles, soothes fever	(35)
14.	*Mentha* × *piperita* L.	Herb	Lamiaceae	Peppermint	NE	Leaves	Menthol, Menthone, Rosmarinic acid	Cooling effect, reduces fever, inhibits viral enzymes	(35)
15.	*Ocimum tenuiflorum* L.	Herb	Lamiaceae	Holy Basil	NE	Leaves	Eugenol, Ursolic acid, Rosmarinic acid	Binds to NS1 and NS5, inhibits viral replication	(34)
16.	*Oldenlandia affinis* (Roem. & Schult.) DC.	Herb	Rubiaceae	Small-Egg Plant	NE	Whole plant	Cyclotides (Kalata B1), Peptides	Inhibits dengue NS2B-NS3 protease	(39)
17.	*Pimpinella anisum* L.	Herb	Apiaceae	Anisuan	NE	Seeds	Anethole, Estragole	Larvicidal action	(41)
18.	*Salvia officinalis* L.	Herb	Lamiaceae	Sage	NE	Leaves	Carnosic acid, Rosmarinic acid	Reduces airway inflammation, blocks viral proteins	(35)
19.	*Scutellaria baicalensis* Georgi	Herb	Lamiaceae	Baikal Skullcap	NE	Root	Baicalein, Baicalin, Wogonin	Blocks viral adsorption, entry inhibition	(35)
20.	*Silybum marianum* L.	Herb	Asteraceae	Milk Thistle	NE	Seeds	Silymarin, Silibinin	Protects liver cells, boosts antioxidant levels	(36)
21.	*Tacca palmata* Blume	Herb	Dioscoreaceae	Tacca	NE	Tuber	Steroidal saponins, Taccalonolides	Blocks viral entry, cytotoxic to infected cells	(34)
22.	*Zingiber officinale* Roscoe	Herb	Zingiberaceae	Ginger	NE	Rhizome	Gingerols, Shogaols, Zingerone	Suppresses inflammation, reduces prostaglandins, Enhances immune response, antioxidant	(34)
23.	*Cymbopogon citratus* (DC.) Stapf	Grass	Poaceae	Lemongrass	NE	Leaves	Citral, Geraniol, Myrcene	Disrupts viral proteins, antioxidant	(36)
24.	*Cymbopogon nardus* (L.) Rendle	Grass	Poaceae	Citronella Grass	NE	Leaves	Citronellal, Citronellol, Geraniol	Repels *Aedes aegypti* mosquitoes	(42)

Abbreviations: NE, Not Evaluated; LC, Least Concern; VU, Vulnerable; DENV, Dengue virus; NS, Non-structural protein.

Table 2: List of major medicinal climbers and shrubs used in the treatment of dengue.

Sl. No.	Scientific Name	Habit	Family	Local Name	IUCN Status	Parts Used	Bioactive Compounds	Mechanism of Action	Ref.
1.	*Azadirachta indica* A. Juss.	Tree	Meliaceae	Neem	NE	Leaves	Azadirachtin, Nimbin, Nimbolide, Quercetin	Inhibits viral replication, modulates immune response	(34)
2.	*Camellia sinensis* L.	Tree	Theaceae	Green Tea	NE	Leaves	Epigallocatechin gallate (EGCG), Catechins, Theaflavins	Strengthens immune cells, reduces oxidative stress	(35)
3.	*Carica papaya* L.	Tree	Caricaceae	Papaya	LC	Leaves	Carpaine, Quercetin, Kaempferol, Papain	Increases platelets, inhibits viral replication	(34)
4.	*Castanospermum australe* (A.Cunn. & C.Fraser ex Hook.)	Tree	Fabaceae	Moreton Bay Chestnut	LC	Seeds	Castanospermine, Alkaloids	Disrupts viral glycosylation, inhibits viral maturation. DENV-1, -2, -3, -4 inhibition	(34)
5.	*Cinnamomum verum* J.Presl	Tree	Lauraceae	Cinnamon	NE	Bark	Cinnamaldehyde, Eugenol, Procyanidins	Enhances blood flow, inhibits pro-inflammatory cytokines	(35)
6.	*Eucalyptus globulus* Labill.	Tree	Myrtaceae	Eucalyptus	LC	Leaves	1,8-Cineole, α-Pinene, Limonene	Mosquito-repellent activity	(42)
7.	*Eurycoma longifolia* Jack	Tree	Simaroubaceae	Tongkat Ali	NE	Root	Quassinoids (Eurycomanone), Alkaloids	Inhibits NS5 RNA polymerase, antiviral activity	(34)
8.	*Ficus septica* Burm.f.	Tree	Moraceae	Hauili	NE	Roots, Fruits, Latex	Phenanthroindolizidine alkaloids	Inhibits DENV in several cell types	(40)
9.	*Garcinia mangostana* L.	Tree	Clusiaceae	Mangosteen	LC	Fruits	α-Mangostin, γ-Mangostin, Xanthones	Reduces inflammation, inhibits viral enzymes	(34)
10.	*Myristica fatua* Houtt.	Tree	Myristicaceae	Nutmeg	NE	Seeds	Myristicin, Elemicin	Inhibits viral replication, reduces inflammation	(36)
11.	*Quercus faginea* Lam.	Tree	Fagaceae	Mazu Phal	LC	Bark	Tannins, Quercetin	Inhibits dengue virus replication	(43)
12.	*Syzygium aromaticum* L.	Tree	Myrtaceae	Clove	NE	Buds	Eugenol, β-Caryophyllene	Prevents viral attachment, reduces inflammation	(34)

Abbreviations: NE, Not Evaluated; LC, Least Concern; DENV, Dengue virus; NS, Non-structural protein; EGCG, Epigallocatechin gallate.

Table 3: List of major medicinal trees used in the treatment of dengue.

Sl. No.	Scientific Name	Habit	Family	Local Name	IUCN Status	Parts Used	Bioactive Compounds	Mechanism of Action	Ref.
1.	*Cuspidaria pulchra* (Cham.) L.G.Lohmann	Climber	Bignoniaceae	Arrabidaea	NE	Leaves	Flavonoids, Phenolic acids	Suppresses viral proliferation, antioxidant activity	(34)
2.	*Flagellaria indica* L.	Climber	Flagellariaceae	-	NE	Leaves	Saponins, Phenolic compounds	Inhibits DENV-2 by 45.52%	(44)
3.	*Momordica charantia* L.	Climber	Cucurbitaceae	Bitter Melon	NE	Fruit	Charantin, Polypeptide-P, Vicine	Modulates cytokines to reduce inflammation in severe dengue	(45)
4.	*Piper betle* L.	Climber	Piperaceae	Betel Leaf	NE	Leaves	Chavicol, Eugenol, Hydroxychavicol	Prevents viral attachment, antimicrobial	(36)

5.	*Piper longum* L.	Climber	Piperaceae	Pippli	LC	Fruit	Piperine, Piperlongumine	Strong larvicidal activity	(46)
6.	*Tinospora cordifolia* (Willd.) Hook.f. & Thomson	Climber	Menispermaceae	Giloy	NE	Stem, Leaves	Berberine, Tinosporide, Cordifolioside	Eases cytokine storm, reduces vascular leakage, blocks key viral proteins	(34)
7.	*Uncaria tomentosa* (Willd. ex Schult.) DC.	Climber	Rubiaceae	Cat's Claw	LC	Stem Barks	Oxindole alkaloids, Quinovic acid	Suppresses viral replication, modulates immune response	(34)
8.	*Anacolosa pervilleana* Baill.	Shrub	Olacaceae	Anacolosa	NE	Leaves	Alkaloids, Flavonoids, Terpenoids	Inhibits viral polymerase, modulates cytokines	(34)
9.	*Annona muricata* L.	Shrub	Annonaceae	Soursop	NE	Fruit	Acetogenins (Annonacin), Quercetin, Kaempferol	Inhibits viral attachment, immune modulation	(34)
10.	*Caesalpinia pulcherrima* (L.) Sw.	Shrub	Fabaceae	Peacock Flower	NE	Leaves	Flavonoids, Saponins, Tannins	Repels *Aedes aegypti*	(47)
11.	*Cladogynos orientalis* Zipp. ex Span.	Shrub	Euphorbiaceae	Cladogynos	NE	Whole Plant	Terpenoids, Flavonoids	Blocks viral entry, anti-inflammatory effects	(34)
12.	*Clerodendrum indicum* (L.) Kuntze	Shrub	Lamiaceae	Glory Bower	NE	Leaves	Clerodin, Flavonoids, Phenolics	Modulates immune response, antiviral properties	(36)
13.	*Flacourtia indica* (Burm.f.) Merr.	Shrub	Salicaceae	Governor's Plum	NE	Stem Barks	Flavonoids, Coumarins, Phenolics	Inhibits NS5 polymerase, anti-inflammatory action, Inhibits DENV RNA Polymerase	(34)
14.	*Hippophae rhamnoides* L.	Shrub	Elaeagnaceae	Sea Buckthorn	LC	Leaves	Flavonoids, Vitamin C, Carotenoids	Antioxidant, modulates immune response	(34)
15.	*Murraya koenigii* (L.) Spreng.	Shrub	Rutaceae	Kari Patah	NE	Leaves	Carbazole alkaloids, Limonene	Causes larval and pupal abnormalities	(48)
16.	*Pemphis acidula* J.R.Forst. & G.Forst.	Shrub	Lythraceae	Mentigi	LC	Leaves	Triterpenoids, Flavonoids	Larvicidal, ovicidal, repellent	(49)
17.	*Carapichea ipecacuanha* (Brot.) L.Andersson	Shrub	Rubiaceae	Ipecac	NE	Root	Emetine, Cephaeline	Prevents viral protein synthesis, immune modulation	(34)
18.	*Sambucus nigra* L.	Shrub	Adoxaceae	Black Elderberry	LC	Fruits	Anthocyanins, Rutin, Quercetin	Blocks viral replication, enhances immune response	(34)

Abbreviations: NE, Not Evaluated; LC, Least Concern; DENV, Dengue virus; NS, Non-structural protein.

Table 4: Presents a comprehensive list of these bioactive compounds identified from medicinal plants in dengue treatment.

Sl. No.	Compound Name	Class	Mechanism of Action	Effect	Ref.
1.	5,7-Dimethoxycoumarin	Coumarin	Inhibits viral replication	Disrupts viral replication machinery	(51)
2.	Apiofuranoside	Glycoside	Flavanone glycoside; controls DENV replication; reduces infected cells and viral RNA	12% infected cells; 67% RNA reduction in HepG2 cells	(52)
3.	Baicalein	Flavonoid	Metabolite of baicalin, with similar antiviral effects	Interacts with NS3–NS2B, E, NS5 proteins	(53)
4.	Baicalin	Flavonoid	Inhibits DENV-2 replication post-infection, direct inactivation of DENV-2, binds host cell	Inhibits NS2B/NS3 protease, E, and NS5 proteins	(54)
5.	Carpaine	Alkaloid	Increases platelet count, modulates immune response	Enhances platelet production, reduces thrombocytopenia	(55)
6.	Castanospermine	Alkaloid	Inhibits glycoprotein processing by blocking glucose residue removal	Inhibits prM & E folding, NS1 accumulation in ER; blocks host-virus interaction	(56)
7.	Celgosivir (prodrug)	Iminosugar derivative	Butylated prodrug cleaved into castanospermine, a glucosidase inhibitor	NS1 accumulation, host protein alteration, misfolded viral proteins	(57)
8.	Chebulagic acid	Tannin	Inhibits viral entry and replication	Blocks glycoprotein interactions, prevents viral fusion	(58)
9.	Chlorogenic acid	Phenolic acid	Reduces oxidative stress, antiviral properties	Neutralizes free radicals, reduces cellular damage	(59)
10.	Chymopapain	Proteolytic enzyme	Inhibits viral replication by interfering with protease function	Blocks viral proteases essential for replication	(59)
11.	Papain	Proteolytic enzyme	Inhibits viral replication by interfering with protease function	Blocks viral proteases essential for replication	(59)
12.	Curcumin	Polyphenol	Bioactive compound with virucidal property	Similar to EGCG and delphinidin	(35)
13.	Dehydrocarpaine I	Alkaloid	Anti-inflammatory, enhances platelet production, restricts viral replication	Regulates immune response, reduces oxidative stress	(59)
14.	Dehydrocarpaine II	Alkaloid	Anti-inflammatory, enhances platelet production, restricts viral replication	Regulates immune response, reduces oxidative stress	(59)
15.	Delphinidin	Anthocyanidin	Polyphenol with virucidal effects and inhibits DENV production	Acts on viral life cycle entry and attachment	(60)
16.	Epigallocatechin	Flavanol	Bioactive compound; repressive effect on viral growth	Virucidal action via surface protein interaction	(60)
17.	Epigallocatechin Gallate	Flavanol	Virucidal effect by direct binding to the DENV surface; prevents early viral entry	Approx. 90% reduction in DENV antigen	(60)
18.	Gallic Acid	Phenolic acid	Inhibits DENV surface protein binding and receptor attachment	Acts as antiviral agent	(61)
19.	Geraniin	Tannin	Binds to DENV-2 envelope domain III, inhibiting viral entry	Prevents viral attachment to host receptors	(58)
20.	Kaempferol	Flavonoid	Inhibits viral replication by interacting with viral RNA	Binds viral RNA, preventing translation and replication	(59)
21.	Pectolinarin	Flavonoid	DENV-2 inhibitory activity	EC50 = 86.4 µg/ml	(62)
22.	Protocatechuic acid	Phenolic acid	Antiviral, anti-inflammatory	Modulates immune response, inhibits viral spread	(59)
23.	Punicalagin	Tannin	Blocks viral entry by inhibiting glycosaminoglycan interaction	Reduces viral infectivity and prevents cell entry	(58)

24.	Quercetin	Flavonoid	Inhibits viral entry and replication	Inhibits viral RNA polymerase, blocks replication	(59)
25.	Sinococuline	Alkaloid	Inhibits NS1 antigen secretion, reduces viremia, suppresses TNF-α and IL-6 cytokines	Reduces fever symptoms, suppresses inflammation	(59)

Abbreviations: DENV, Dengue virus; NS, Non-structural protein; ER, Endoplasmic reticulum; RNA, Ribonucleic acid; EC50, Half maximal effective concentration.

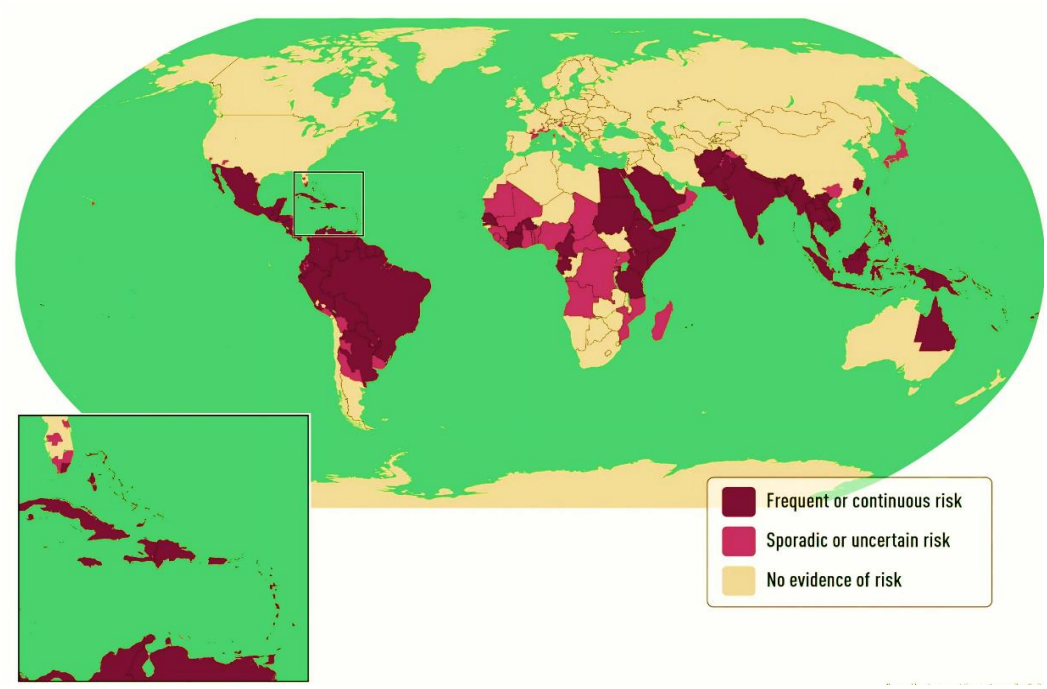

Figure 1: Worldwide distribution map of areas with rick of Dengue.

Worldwide geographic distribution of dengue virus transmission highlighting endemic and high-risk regions across tropical and subtropical areas. The figure illustrates the expanding burden of dengue influenced by climate change, urbanization, and vector adaptability (92).

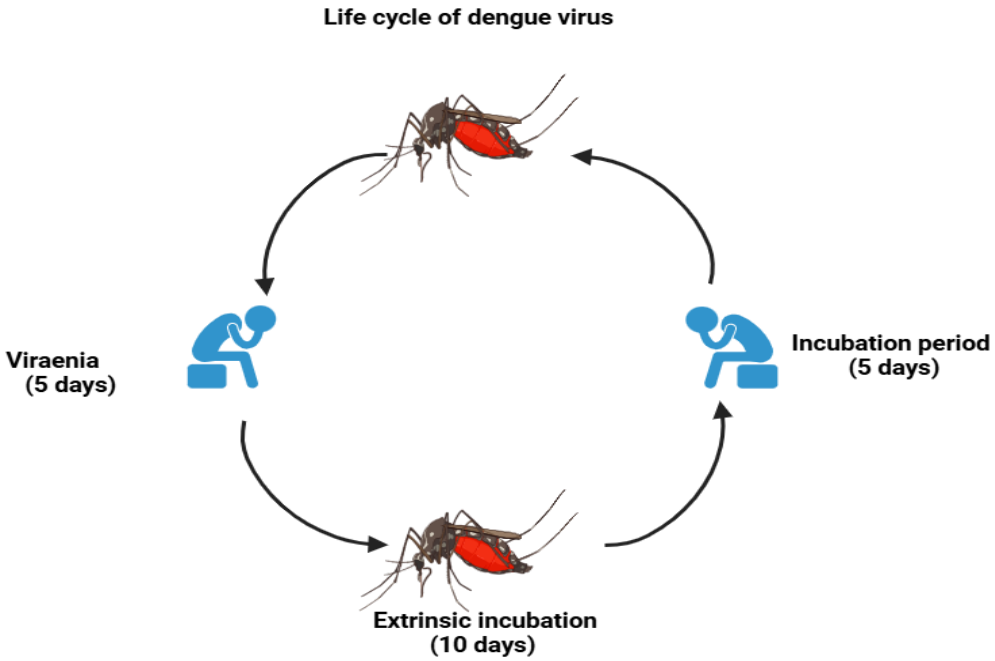

Figure 2: Life cycle of dengue virus within the host cell.

Schematic representation of dengue virus entry, replication, assembly, and release in host cells. The virus enters through receptor-mediated endocytosis, undergoes membrane fusion, polyprotein translation, and replication mediated by NS2B–NS3 protease and NS5 polymerase, followed by virion maturation and release.

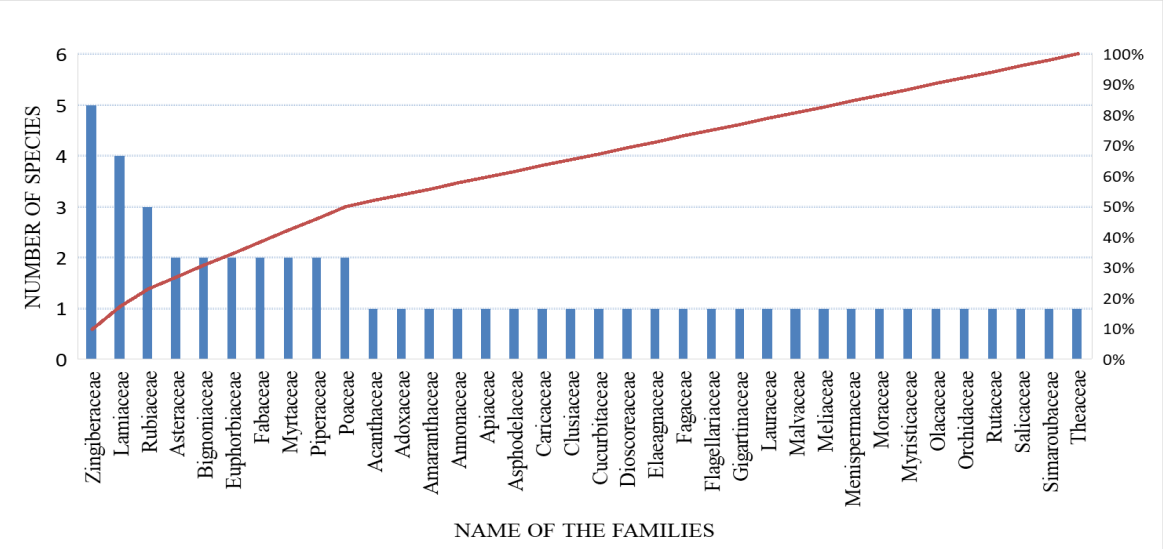

Figure 3: Distribution of medicinal plant species used in dengue management across plant families.

Graph showing the proportion of major 56 medicinal plant species listed from review of literature belonging to different botanical families reported for dengue treatment, highlighting the dominance of families such as Zingiberaceae, Lamiaceae, and Fabaceae.

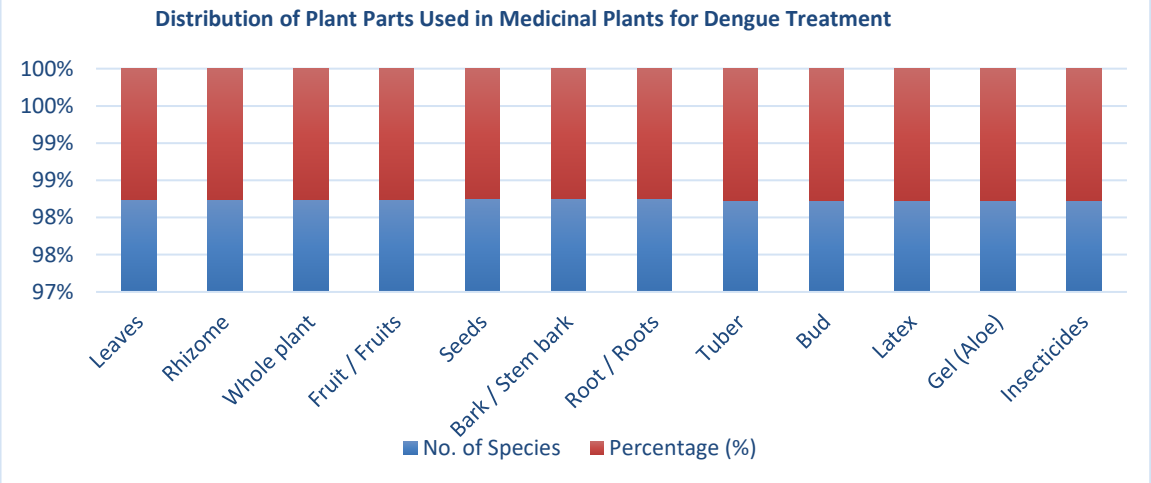

Figure 4: Distribution of plant parts used in dengue treatment from review of literature.

Graph showing the relative proportion of different plant parts (leaves, rhizomes, fruits, bark, roots, seeds, and whole plant) utilized in traditional and experimental dengue management. Leaves emerge as the most frequently used plant part.

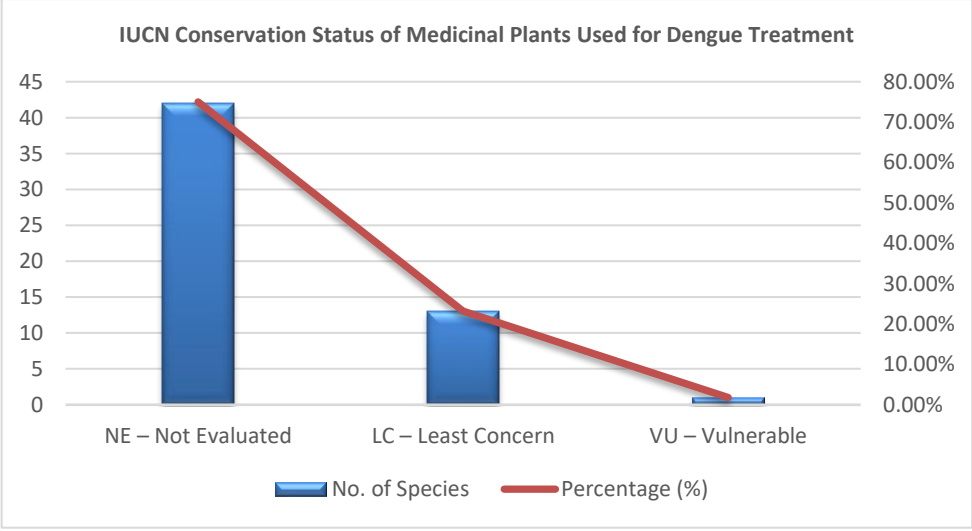

Figure 5: Distribution of medicinal plant species used in dengue management according to International Union for Conservation of Nature (IUCN) Red List categories.

It shows predominance of Not Evaluated (NE) and Least Concern (LC) species, with a small proportion classified as Vulnerable (VU).

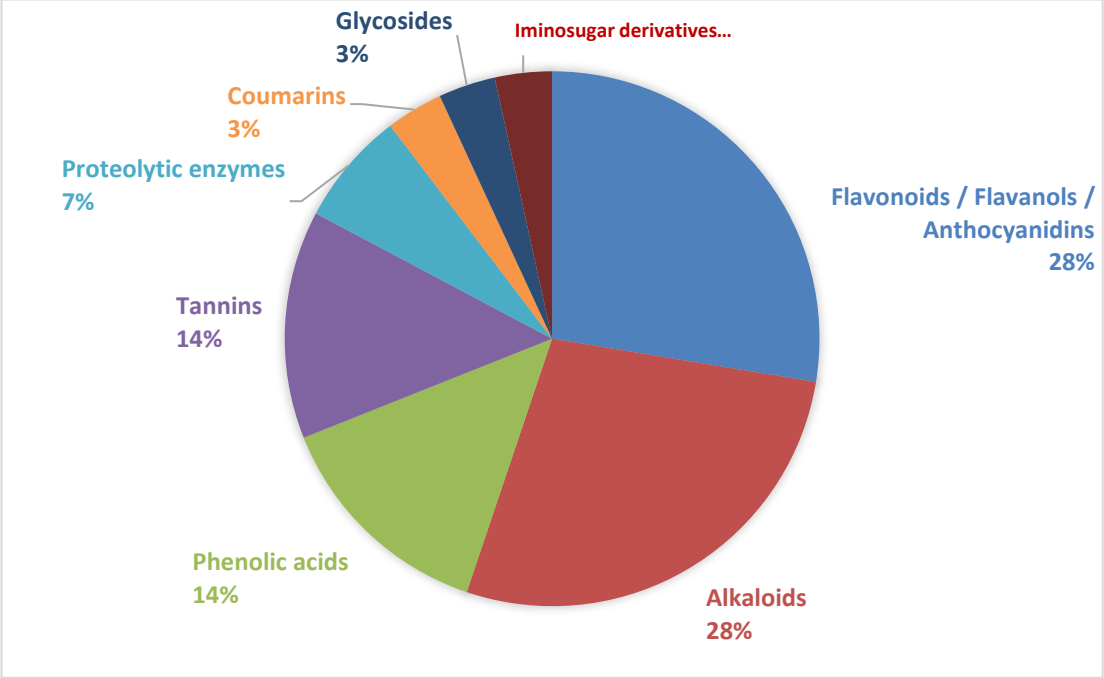

Figure 6: Distribution of major classes of bioactive compounds involved in anti-dengue activity listed from review of literature.

Graph depicting the major classes of phytochemicals reported from medicinal plants used in dengue treatment, including flavonoids, alkaloids, tannins, polyphenols, glycosides, and polysaccharides, highlighting their chemical diversity and therapeutic relevance.

Conclusion

Dengue fever has become one of the most rapidly expanding mosquito-borne viral diseases worldwide, driven by climate change, urbanization, and vector adaptability. Despite sustained research efforts, dengue management remains largely supportive, as the development of safe and universally effective antivirals or vaccines is limited by viral serotype diversity, antibody-dependent enhancement, and complex host–virus interactions. This review integrates epidemiological insights, molecular virology, pathogenesis, traditional knowledge, and modern pharmacological evidence to establish medicinal plants as a scientifically credible resource for dengue management.

By elucidating the molecular basis of dengue infection, this review identifies key therapeutic targets, particularly the NS2B-NS3 protease and NS5 RNA-dependent RNA polymerase, that are repeatedly addressed by plant-derived phytochemicals. Ethnopharmacological and experimental studies demonstrate that medicinal plants exert multi-target actions, combining direct antiviral effects with immunomodulation, antioxidant protection, endothelial stabilization, platelet recovery, and vector control. Such integrated mechanisms are particularly suited to the multifactorial nature of dengue pathogenesis involving viral replication, immune dysregulation, oxidative stress, thrombocytopenia, and vascular leakage.

Analysis of medicinal plant diversity reveals taxonomic clustering within families such as Zingiberaceae, Lamiaceae, and Fabaceae, with leaves being the most frequently utilized plant part. Conservation assessment shows that most plants used in dengue treatment are classified as Not Evaluated or Least Concern under the International Union for Conservation of Nature Red List, highlighting a gap between widespread medicinal use and formal conservation evaluation. At the molecular level, the predominance of flavonoids, alkaloids, tannins, polyphenols, and polysaccharides supports a convergent therapeutic strategy targeting both viral and host pathways. Molecular docking and in-silico studies provide mechanistic support for traditional claims; however, clinical translation remains limited by lack of standardized formulations, insufficient in-vivo validation, incomplete safety profiling, and scarcity of large-scale clinical trials.

Overall, this review concludes that medicinal plants represent evidence-based, multi-target candidates for next-generation dengue therapeutics, offering a promising, affordable, and sustainable approach to addressing the global dengue burden.

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