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Review Article

Potential Pharmacological Activities of Medicinal Plants and Their Phytochemicals Against Dengue Virus Serotypes: A Review

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Abstract

Introduction: The dengue virus (DENV), with four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4), continues to pose a threat to global public health, with no effective antiviral treatment. This review aimed to analyze the published evidence, including in vitro, in vivo, and in silico research, about medicinal plants and plant-derived compounds tested against the different serotypes of the DENV.

Methods: Scientific databases, including NIH, PubMed, ScienceDirect, Google Scholar, Scopus, and EBSCO, were thoroughly searched for relevant publications through June 2025. Different keywords, such as dengue virus, DENV serotypes, antiviral activity of plants, anti-dengue activity of medicinal plants, potential anti-dengue phytochemicals, and plant compounds having anti-dengue activity, were included in the search strategy to find the most relevant studies, reviews, and literature.

Results: Compound of medicinal plants (e.g., andrographolide), flavonoid compounds (e.g., quercetin and kaempferol), methyl gallate and anacardic acid, and several triterpenoids were predicted by docking and phytochemical analyses, indicating that they bind to the NS2B-NS3 protease enzyme of the DENV and are important leads with multi-serotype or strong serotype-specific inhibition . In general, most high-quality experimental data are available only from in vitro tests, which often use DENV-2, and there are few comprehensive in vivo or clinical assessments.

Conclusion: Anti-dengue drugs can be derived from a variety of plant compounds and phytochemicals.

Keywords: Dengue virus serotype, Medicinal plants, *Aedes aegypti*, DENV-2, Bio-active phytocomponents

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Introduction

Dengue virus (DENV) serotypes (i.e., DENV-1, DENV-2, DENV-3, and DENV-4) can cause dengue fever. Mosquitoes transmit this virus and remain one of the most globally urgent public health issues (1-3). Dengue, mainly transmitted by Aedes aegypti and Aedes albopictus mosquitoes, affects millions of people each year in tropical and subtropical regions worldwide. Dengue fever manifests with a variety of symptoms, ranging from mild fever to severe dengue hemorrhagic fever and dengue shock syndrome (4). Currently, no approved, effective antiviral treatment is available for dengue illness, despite intensive research efforts, and the effectiveness of existing vaccines varies by serotype (5). Thus, finding safe, efficient, and affordable therapeutic substitutes is becoming a top priority in dengue therapy.

Traditional healthcare systems and the general public have long used many medicinal herbs (Figure 1), which have recently attracted considerable interest as the potential sources of antiviral phytochemicals that may combat the DENV. Several studies have shown that extracts from a few plants and their bioactive components, including phenolic compounds, alkaloids, terpenoids, and flavonoids, have inhibitory effects against dengue serotypes, including the inhibition of protein synthesis, viral replication, and viral entry. These phytochemicals interfere with viral enzymes, preventing viral attachment to host cells and modifying host immune responses (6-8).

This review will provide a concise summary of medicinal plants and their phytochemicals, including their activity against DENV serotypes, given the growing body of evidence demonstrating the antiviral potential of substances derived from medicinal plants. Moreover, the pharmacological potential, possible mechanisms of action of phytochemicals, dengue serotypes, specific activity of phytochemicals, and clinical use are highlighted

Figure 1. Few Natural Products Having Anti-Dengue Activities: *Andrographis paniculata* **(A)**, *Ocimum sanctum* **(B)**, *Lonicera japonica* **(C)**, *Azadirachta indica* **(D)**, *Glycyrrhiza glabra* **(E)**, *Cassia grandis* **(F)**, *Plumeria alba* **(G)**, *Hibiscus rosa-sinensis* **(H)**, *Euphorbia hirta* **(I)**, *Taraxacum officinale* **(J)**, *Vernonia cinerea* **(K)**, *Carica papaya* **(L)**, *Muntingia calabura* **(M)**, and *Scutellaria baicalensis* **(N)**

in this article.

Materials and Methods

A computerized literature search was conducted to identify relevant studies on medicinal plants and phytochemicals with pharmacological activities against DENV serotypes. Different databases, including PubMed, NIH repository, Google Scholar, ScienceDirect, EBSCO and Scopus, were thoroughly searched for studies published up until June 2025. Search strings, including 'dengue virus, DENV serotypes, antiviral activity of plants, anti-dengue activity of medicinal plants, potential anti-dengue phytochemicals, natural compounds having activity against DENV serotypes, were used for all the mentioned databases and for the search method to find the majority of relevant reviews and studies. The search priorities included studies that clearly stated the DENV serotype tested with plant extract or a specific phyto-compound, in vitro studies that identified active phyto-compounds, and in silico docking studies with target hypotheses. Additionally, the inclusion criteria were ethnopharmacological research, review papers, a few clinical studies, and case reports reporting the antiviral effectiveness of medicinal plant extracts or isolated phytochemicals against any DENV serotype, using in vitro, in vivo, and in silico studies. In addition, the inclusion list included the published literature written only in English. However, substances not derived from plants, lacking experimental confirmation, unpublished preprints, and literature not related to the anti-dengue activity of medicinal plants were in the excluded research list.

Results and Discussion

Medicinal Plants and Phytochemicals Act Against Dengue Virus Serotypes

A variety of medicinal plants (Table 1) and phytochemicals (Table 2) have been shown to have anti-dengue activities, as demonstrated by real-time quantitative polymerase chain reaction -based replication assays, viral antigen suppression, and in vitro plaque reduction assays. However, most studies reported that potential phyto-compounds act against the DENV-2 serotype, which is frequently used as a representative laboratory strain. The efficacy against DENV-1, DENV-3, and DENV-4 serotypes remains inadequately elucidated due to a relative scarcity of clinical research.

Extensive research has demonstrated that flavonoids, phenolic acids, terpenoids, alkaloids, and xanthones are the phytochemicals that consistently exhibit antiviral effects (Table 3). These compounds block the entry and fusion of the DENV, inhibit viral enzymes (e.g., the NS2B-NS3 protease and NS5 polymerase), alter host immune and oxidative pathways, and have a direct virucidal effect.

Recent studies have highlighted the potential of *Glycyrrhiza glabra*'s aqueous root extract to exhibit antiviral effects against all four serotypes of the DENV. The half maximal inhibitory concentration (IC_{50}) of the four dengue serotypes (10–50 µg/mL) indicated moderate inhibition by the aqueous root extract. Overall, 98–100% inhibition of all dengue serotypes was observed with the aqueous extract at the maximum nontoxic dose (9). Experiments revealed that the replication of DENV-1, DENV-2, DENV-3, and DENV-4 in Vero cell cultures

Table 1. Medicinal Herbs' Action Against Dengue Virus Serotypes

Biological Name of the Medicinal Plant	Type of Extract Examined	Potential Effectiveness Against the DENV Serotype	Type of Research	References
Glycyrrhiza glabra	Aqueous root extract	DENV-1, DENV-2, DENV-3, and DENV-4	In vitro study	(9)
Andrographis paniculata	Ethanolic extract and isolated andrographolide	DENV-2 and DENV-4	In vitro study	(10-12)
Euphorbia hirta	Ethyl-acetate extract	DENV-1 and DENV-2	In vitro study	(13)
Taraxacum officinale	Methanolic extracts	DENV-2	In vitro (cell culture replication assays)	(14)
Lonicera japonica	Aqueous extract	DENV-2	In vitro study	(15, 16)
Carica papaya	Plant extracts rich in quercetin	DENV-2	In vitro study	(17-19)
Plumeria alba, Ancistrocladus heyneanus, Bacopa monnieri	Crude extracts	DENV (serotype not always specified) and some of the reported anti-dengue activities	In vitro study	(8)
Cassia alata and *Cassia grandis*	Ethanolic extracts	DENV-2	In vitro and animal studies	(20, 21)
Azadirachta indica	Isolated triterpenoids from crude extracts	DENV-1, DENV-2, DENV-3, and DENV-4	In silico docking; some in vitro reports	(22-24)
Hibiscus rosa-sinensis	Crude extracts	DENV-2 (most cell-based screening panels used DENV-2)	In vitro study	(25)
Ocimum sanctum	Crude extracts	DENV-1	In vitro (cell culture)	(26, 27)
Scutellaria baicalensis	Root extract	DENV-2	In vitro studies	(28)
Muntingia calabura	Methanolic extract	DENV (serotype not specified)	In vitro study	(29)
Anacardium occidentale	Ethanolic extracts	DENV-2	In vitro study	(30)
Vernonia cinerea	Crude extract containing Chrysoeriol	DENV-2	In silico study	(31)

Note. DENV: Dengue virus.

Table 2. An Overview of Phytochemicals and Their Action Against Dengue Serotypes

Phytochemicals	Molecular Formula	Mechanism of Action	Demonstrated Activity Against DENV Serotypes	Experimental Model	References
Andrographolide	$C_{20}H_{30}O_5$	Inhibiting NS3 helicase and NS2B-NS3 protease and reducing viral RNA synthesis	DENV-2	In vitro	(32, 33)
Quercetin	$C_{15}H_{10}O_7$	Preventing viral entrance by binding to NS5 polymerase and NS2B-NS3 protease	DENV-2 and DENV-3	In vitro	(28, 34)
Kaempferol	$C_{15}H_{10}O_6$	Inhibiting NS5 RNA-dependent RNA polymerase and furin protease	DENV-2	In vitro	(35, 36)
Glycyrrhizin	$C_{42}H_{62}O_{16}$	Inhibiting viral adsorption and replication	DENV-1, DENV-2, DENV-3, and DENV-4	In vitro	(9, 37)
Nimbin	$C_{30}H_{36}O_9$	Blocking polyprotein cleavage by NS2B-NS3 protease inhibition	DENV-1, DENV-2, DENV-3, and DENV-4	In vitro	(22, 38)
Methyl gallate	$C_8H_8O_5$	Inhibiting NS5 polymerase and possessing virucidal and antioxidant activities	DENV-2	In vitro	(39, 40)
Curcumin	$C_{21}H_{20}O_6$	Downregulating MAPK and NF-κB pathways	DENV-2	In vitro	(41, 42)
Luteolin	$C_{15}H_{10}O_6$	All four DENV serotypes' ability to replicate is inhibited by luteolin	DENV-1, DENV-2, DENV-3, and DENV-4	In vitro	(43)
Baicalein	$C_{15}H_{10}O_5$	Inhibiting NS3 protease and viral replication	DENV-2	In vitro	(28)
Epigallocatechin gallate	$C_{22}H_{18}O_{11}$	Blocking the E protein–cell receptor interaction, which demonstrates an anti-dengue effect	DENV-2	In vitro	(44, 45)
Ursolic acid	$C_{30}H_{48}O_3$	Inhibiting NS5 RNA-dependent RNA polymerase; it also enhances host antiviral enzymes	DENV-2	In vitro	(46, 47)
Geraniin	$C_{41}H_{28}O_{27}$	Inhibiting NS3 protease and viral adsorption	DENV-2	In vitro	(48-50)
Apigenin	$C_{15}H_{10}O_5$	Binding NS2B-NS3 protease and inhibits viral replication	DENV-2	In vitro	(51, 52)
Phyllanthin	$C_{24}H_{34}O_6$	Suppressing NS5 polymerase; modulates interferon response	DENV-2	In vitro	(53, 54)
Betulinic acid	$C_{30}H_{48}O_3$	Blocking the replication of virus serotypes by NS3 protease inhibition	DENV-1, DENV-2, DENV-3, and DENV-4	In vitro	(55)

Note. MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor-kappa B; DENV: Dengue virus.

was notably inhibited without any significant cytotoxic effects at concentrations < 100 μg/mL. Furthermore, phytochemical analysis identified compounds like glycyrrhizin, liquiritigenin, and isoliquiritigenin, which are known to influence host inflammatory responses and viral replication. These compounds work by suppressing RNA replication and disrupting viral attachment, possibly by modifying the host's nuclear factor-kappa B signaling pathways (56).

According to experimental and computational research, triterpenoids, such as nimbin, azadirachtin, and salannin, which are found in *A. indica*, may decrease NS2B-NS3 protease activity in all dengue serotypes. Strong binding affinities (-8 to -10 kcal/mol) to the catalytic residues of the protease and NS5 polymerase are shown by docking (Autodock) analysis (57). Despite the lack of direct in vitro evidence, many studies suggest that chemicals derived from neem plant may function as pan-serotype inhibitors by blocking viral protease enzyme (24).

Andrographolide is a diterpenoid lactone isolated from *A. paniculata*. It is one of the phytochemicals that has received significant attention for its association with DENV-2 inhibition. Panraksa et al (32) and Paemanee et al (33) demonstrated that andrographolide strongly inhibits DENV-2 replication in HeLa, HepG2, and Vero cells, with half maximal effective concentration values ranging from 20 μM/mL to 25 μM/mL (33). By lowering the synthesis of intracellular viral RNA and proteins, this substance successfully prevents viral replication. Its significant binding affinity for the DENV NS3 helicase domain is revealed by molecular docking experiments, which offer a mechanistic understanding of its inhibitory activity (58).

Euphorbia hirta extracts have represented remarkable inhibitory effects on DENV-1 and DENV-2. In one study, a specific extract of *E. hirta* showed IC_{50} values of 33.84 μg/mL for DENV-1 and 33.55 μg/mL for DENV-2 (13). The ethyl-acetate fraction of *E. hirta* significantly decreased the formation of plaques when tested on infected Vero cells. This process is aided by polyphenolic chemicals, which either bind to viral envelope proteins or prevent the synthesis of viral RNA. *E. hirta* is a promising ethnobotanical candidate for fighting DENV-2, even though its precise active constituents are still unknown.

Based on laboratory experiments, although the *Carica papaya* leaf extract has a moderate antiviral impact against DENV-2, its main benefit is that it has potential to help dengue patients having thrombocytopenia. Given its antioxidant qualities, quercetin and other flavonoids found in the extract may help maintain platelet levels and indirectly prevent viral multiplication. Its advantages in hematology, along with its antioxidant and antiviral properties, turn it an adjuvant treatment, even if we still need more conclusive clinical data to support its antiviral efficacy. Some clinical studies have been performed in

Table 3. Prominent Phytochemicals Having Anti-Dengue Activities, Along With Their Chemical Structure

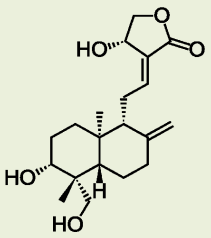
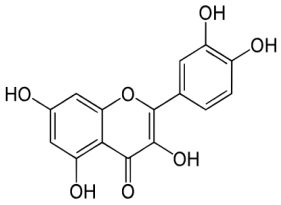
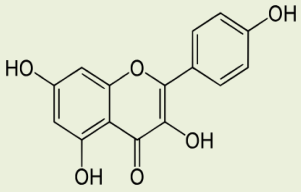
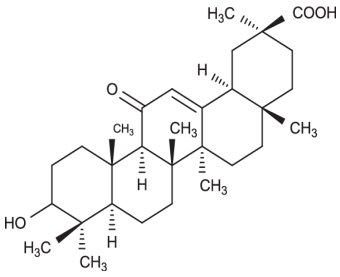
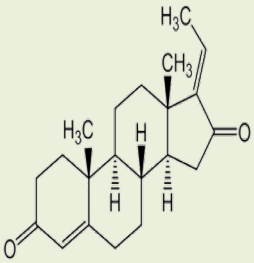
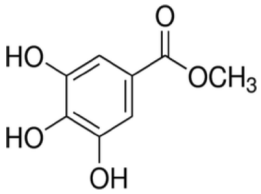
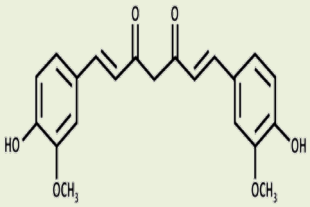
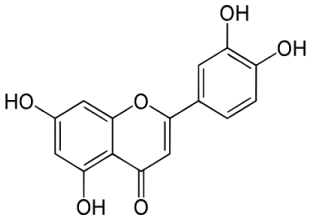
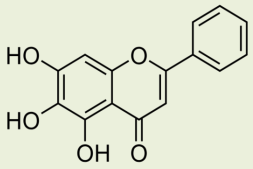
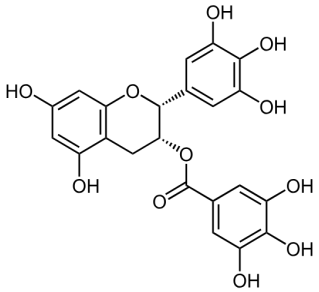
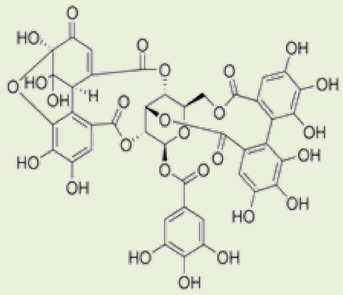
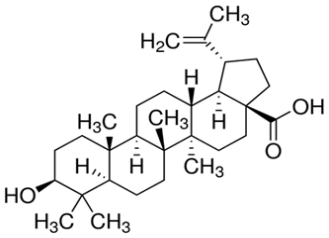
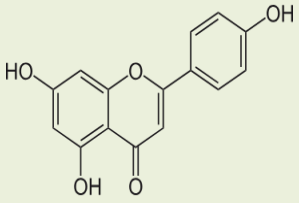
Phytochemical Name	Chemical Class	Molecular Weight	Chemical Structure	Hazard Identification
Andrographolide	Terpenoid	350.45 g/mol		Usually safe under the GHS, but slight skin irritation and eye irritation may occur.
Quercetin	Flavonoid	302.236 g/mol		This chemical does not meet GHS hazard criteria for 1.3%; acute toxicity.
Kaempferol	Flavonoid	286.23 g/mol		This chemical does not meet GHS hazard criteria for 1.3%. It may possess acute toxicity.
Glycyrrhizin	Terpeniod	822.94 g/mol		This chemical does not meet GHS hazard criteria for 100%; it is usually safe.
Nimbin	Terpenoid	540.6 g/mol		Based on GHS classification, nimbin has a low acute toxicity and is slightly hazardous to aquatic life.
Methyl gallate	Phenolic compound	184.15 g/mol		It causes skin and serious eye irritation and potentially an allergic skin reaction.
Curcumin	Curcuminoids	368.38 g/mol		This chemical does not meet GHS hazard criteria for 7.4%; mild-to-moderate toxicity is observed at high concentrations

Table 3. Continued.

Phytochemical Name	Chemical Class	Molecular Weight	Chemical Structure	Hazard Identification
Luteolin	Flavonoid	286.24 g/mol		This chemical does not meet GHS hazard criteria for 2%; causes irritantion.
Baicalein	Flavonoid	270.24 g/mol		This chemical is quite safe according to GHS hazard.
Epigallocatechin gallate	Flavonoid	458.372 g/mol		This chemical does not meet GHS hazard criteria for 60%; it is normally safe.
Geraniin	Polyphenol	952.6 g/mol		Geraniin is not classified as a dangerous substance under the GHS.
Betulinic acid	Terpenoid	456.7 g/mol		This chemical does not meet GHS hazard criteria for 96.7%; it is typically safe.
Apigenin	Flavonoid	270.0528 g/mol		This chemical does not meet GHS hazard criteria for 24.5%; at high concentrations, it can be hazardous.

Note: GHS: Globally Harmonized System. GHS hazards refer to the classifications and communication standards for chemical dangers under the GHS. These hazards are grouped into health, physical, and environmental categories.

South Asia to demonstrate the effectiveness of papaya in case dengue fever, reporting its positive effects by enhancing platelet count in patients (Table 4).

Anacardic acid, which comes from the *Anacardium occidentale*, and methyl gallate, which is found in Terminalia and Phyllanthus species, are potent inhibitors of DENV-2 replication, according to in vitro screening tests. They reduce plaque formation in a dose-dependent manner by blocking the NS2B-NS3 protease enzyme and interfering with envelope protein fusion. Owing to their

Table 4. Specific Clinical Studies of Papaya Herbal Formulation for the treatment of Dengue

Products	Study Type and Phase	Country	Description	Outcomes	References
Carica papaya leaf extract (CPLE)	Double-blind, randomized, placebo-controlled (phase II/III)	India	300 adult dengue patients across 5 centers; CPLE tablet 1100 mg, 3 times daily for 5 days + standard care; control: placebo + standard care.	A significant increase in platelet count ($P < 0.01$) was found compared with a placebo, and no serious adverse effects were reported.	(67)
Carica papaya leaf extract (for severe thrombocytopenia)	Pilot randomized controlled trial	India	Fifty-one confirmed dengue adults were selected (26 were treated, while 25 were placebo). The study evaluated platelet recovery, cytokine changes, and NS1 clearance.	Platelets rose at 482% ± 284 on day three (treatment) compared to 331% ± 370 on day three (placebo), $P = 0.007$; platelets recovered more quickly to ≥ 50,000/μL	(68)
Ayurvedic polyherbal formulation (LNS)	Double blind RCT (phase II)	Sri Lanka	The safety and effectiveness of a traditional herbal mixture for the treatment of dengue have been investigated. The results are based on biomarkers and dose determination.	Ongoing; results pending	Sri Lanka Clinical Trials Registry (SLCTR/2024/015); Link: https://slctr.lk/trials/slctr-2024-015

Note. RCT: Randomized controlled trial.

relative simplicity and ease of synthesis, these phenolic acids make good candidates for optimizing structure-activity correlations (30).

Betulinic acid is also a pentacyclic triterpenoid that is found in some medicinal plant barks and leaves. It has demonstrated efficacy against several DENV serotypes, notably DENV-1 and DENV-4. According to a research by Loe et al (55), betulinic acid significantly inhibits the replication of the virus at the post-entry stage, as evidenced by a considerable decrease in intracellular viral RNA levels and the generation of infectious virions across all tested serotypes. Accordingly, this acid is a good option for creating novel dengue fever medicines. Few tropical and subtropical plants have shown a mild-to-moderate capacity to halt DENV reproduction in laboratory research. Among them, *Taraxacum officinale*, *Urtica dioica*, *Plumeria alba*, *Vitex negundo*, and *Muntingia calabura* are remarkable. It is crucial to remember that the majority of these results are based on crude extracts that do not identify the active components or specific serotypes.

Limitations in the Evidence Base and Knowledge Gap: While there are promising findings in pharmacological and phytochemical research, translating these discoveries into real-world clinical applications faces several serious hurdles. Most studies conclude with in vitro results, and after oral intake, the effective concentrations observed in cell cultures frequently exceed what can actually be achieved in plasma or tissues. Additionally, different parts of plants, the climatic conditions under which they are harvested, the solvents used for extraction, and the methods of processing can all lead to the variations of chemical features in the resulting crude extracts. On the other hand, many studies lack proper chemical characterization (e.g., measurements of specific chemical markers), which complicates the comparison and reproduction of results across studies (59, 60). Blind outcome assessments, cytotoxicity adjustments, and proper controls, including vehicle and positive antiviral controls, are not comprehensively explained in most of the research. In addition, biases in selective reporting and limited sample sizes exacerbate this lack of clarity (61).

The toxicological profiling of phytochemicals is inadequate in many cases. Furthermore, the immunopathology of dengue may worsen due to the limited therapeutic windows of certain phytochemicals, hepatotoxic potential, drug-drug interactions (via cytochrome P450), or unfavorable immunomodulatory effects (62, 63). A notable deficiency in high-quality randomized controlled trials is the lack of studies examining variables such as fatality rates, length of hospital stays, and progression to severe dengue. While some clinical studies have shown an increase in platelets with papaya leaf juice consumption, these studies are interesting. Nonetheless, there are not enough data or controlled trials to support its use in medical practice without appropriate safety data (64-66).

Future Directions

For future research, it is essential to use standardized extraction techniques, detailed phytochemical profiles, and reliable quality control procedures. Moreover, drug development efforts might be streamlined by linking specific phytochemicals to their antiviral properties. It is recommended that advanced molecular docking, enzyme inhibition assays, and omics-based techniques (e.g., transcriptomics and proteomics) be used to determine which viral and host targets are inhibited by these bioactive chemicals. The development of antivirals or synergistic formulations that are based on the potency of phytochemicals will be made possible by molecular understanding (69, 70). To establish promising phytochemicals closer to clinical use, the field requires appropriate steps and considerations (Figure 2).

To truly advance translational research, more reliable toxicological and pharmacokinetic data are essential. Additionally, researchers must investigate immunotoxicity, genotoxicity, and chronic toxicity to ensure safety, especially since dengue infection already triggers complex immune responses that herbal remedies may help regulate. Although most of the currently available information comes from in vitro studies, future research should prioritize in vivo validation using relevant dengue infection models. Ultimately, standardized formulations

Figure 2. Steps in Advancing Medicinal Plant Research

and early-phase clinical studies are necessary to assess therapeutic potential and establish the optimal dosage and safety profile.

Conclusion

Medicinal plants contain bioactive chemicals that provide a variety of natural antiviral substances effective against different serotypes of the DENV. Numerous studies have demonstrated the effects of substances, including flavonoids, alkaloids, terpenoids, and phenolic acids, on the host's immune responses and on various viral life cycle stages, including entry, replication, and protein synthesis. Nonetheless, there are a wide variety of unanswered questions regarding toxicity, the proper mechanism of these substances, their efficacy, standardization, and clinical validation. Accordingly, careful experimental design, proper characterization of extracts, an understanding of the underlying mechanisms, and closely observed investigations in both humans and animals should be the main priorities of future studies. Those approaches are necessary to convert these plant-derived substances into potent medications. Phytochemists, virologists, pharmacologists, and clinical researchers can work together to fill the gap between what can be used in treatment and what can be conducted in laboratory research. Finally, the development of high-quality, evidence-based data that satisfy current scientific and regulatory criteria is necessary if medicinal plants and phytochemicals continue to be utilized as antiviral medicines, particularly in the fight against dengue.

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Authors' Contribution

Conceptualization: Majedul Hoque
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Formal Analysis: Majedul Hoque
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Methodology: Majedul Hoque
Project Administration: Majedul Hoque
Resources: Majedul Hoque
Software: Majedul Hoque
Supervision: Majedul Hoque
Validation: Majedul Hoque
Visualization: Majedul Hoque
Writing–Original Draft: Majedul Hoque
Writing–Review and Editing: Majedul Hoque

Competing Interests

The author declares no competing interests.

Ethical Approval

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