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Anti-Dengue Therapeutic Potential of Medicinal plant, *Tinospora cordifolia*

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Abstract

Dengue, a significant viral disease spread by mosquitoes, is causing an increasing death rate due to inadequate treatments and preventative measures. However, there has been substantial advancement in the investigation of natural and traditional herbal remedies. Tinospora cordifolia has been extensively researched for its ability to treat dengue fever. This research aims to assess the current information on the use of T. cordifolia in treating dengue, emphasizing its clinical effectiveness, phytochemistry, and antiviral properties. The research methodology included an extensive examination of the literature on T. cordifolia's anti-dengue attributes in different databases utilizing appropriate keywords. Discoveries validate the effectiveness of T. cordifolia in fighting dengue by easing cytokine storms, decreasing vascular leakage, and blocking key viral proteins. Substances like berberine and magnoflorine obtained from the plant exhibit potential in this aspect. The research not only highlights but also underscores the significant potential of T. cordifolia as a beneficial treatment option for dengue, but additional computational and clinical studies are necessary to create effective and safe anti-dengue drugs. Moreover, it is crucial to have a more thorough comprehension of T. cordifolia's antiviral method in combating dengue virus infection.

Keywords: *Dengue Virus, Dengue Fever, Tinospora cordifolia, Viral Disease.*

Introduction

Dengue fever, also known as break-bone fever, is a mosquito-borne viral disease caused by the dengue virus, which belongs to the Flaviviridae family and is transmitted primarily by Aedes mosquitoes, mainly *Aedes aegypti.* The disease is prevalent in tropical and subtropical regions, affecting millions globally, with significant public health implications. Dengue fever can present a wide range of symptoms, from mild fever to severe conditions such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), characterized by high fever, headache, body aches, nausea, vomiting, swollen glands, rash, and in severe cases, bleeding, organ impairment, and shock [1]. The clinical progression of dengue involves increased vascular permeability, leading to plasma leakage and polyserositis, which can be detected through imaging methods like chest radiography and abdominal ultrasound, showing pleural effusion, thickened gallbladder wall, ascites, and hepatosplenomegaly. Diagnosis is often challenging, especially in endemic areas, and relies on clinical symptoms, physical examination, and laboratory tests such as total blood count, PCR, serology, and detection of NS1 antigen [1]. Hematological parameters, including platelet count, hematocrit, and liver function tests, are crucial for monitoring disease progression and differentiating between DF and DHF [2, 3]. Preventive measures focus on controlling the

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mosquito vector by eliminating breeding sites, using insect repellents, protective clothing, and bed nets, and employing advanced biotechnological methods like Wolbachia-infected and genetically modified Aedes mosquitoes to block virus transmission [1, 3]. Vaccination is a critical preventive strategy, with several live attenuated vaccines, such as CYD-TDV, TAK-003, and TV003/005, in advanced clinical trials, aiming to reduce the disease burden [4]. Despite the availability of the Dengvaxia vaccine in some countries, further safety evaluations are ongoing to ensure its efficacy and safety [1]. Management of dengue fever primarily involves supportive care, maintaining fluid balance, and symptom relief, with severe cases requiring hospitalization and intensive care. The rapid global spread of dengue, exacerbated by factors like long-distance travel, urbanization, and inadequate mosquito control, underscores the need for robust surveillance systems and primary healthcare approaches to detect and predict outbreaks early, as illustrated by the proposed epidemiological surveillance model in Colombia [5]. Increasing awareness among healthcare professionals and the general population is essential for early detection and appropriate management, particularly in regions where dengue is often misdiagnosed or overlooked due to symptoms overlapping with other febrile illnesses like malaria [1]. In conclusion, dengue fever remains a significant global health challenge, necessitating comprehensive strategies encompassing prevention, early diagnosis, effective management, and continuous research to mitigate its impact.

Different countries have launched various medications to combat dengue fever. At first, corticosteroids were seen as the primary form of protection, with *Dengvaxia* later becoming the first dengue vaccine [6]. Even though these vaccines have benefits, they have disadvantages like high prices, convenient availability, and adverse side effects. There has yet to be widely agreed upon dedicated medication for treating dengue in various healthcare systems [7]. Therefore, there was a need to develop advanced dengue vaccines derived from plants. Several medicinal plants like *Azadirachta indica*, *Carica papaya*, *Tinospora cordifolia*, and others have displayed effectiveness in treating dengue to a certain extent, demonstrating antiviral properties and immunomodulatory effects. These plants not only provide potential therapeutic benefits but also offer a sustainable and eco-friendly approach to vaccine development, leveraging their natural compounds to enhance immune responses against the dengue virus [8]. These plants have been discovered to boost blood platelet and white blood cell counts without negative impacts [9]. The active components in these plants act as potent immune system regulators and naturally promote overall health [10]. Furthermore, it is advisable to increase the intake of foods high in folate, iron, and vitamins B12, C, D, and K to help elevate platelet counts [1, 4]. *T. cordifolia* is commonly used as a medicinal plant for treating dengue, and it is particularly known for its ability to boost platelet levels rapidly, providing reassurance about its effectiveness in dengue treatment. Its traditional use for treating different health problems is supported by pharmacological research demonstrating its abilities to help with diabetes, reduce inflammation, and protect the nervous system. In addition, indigenous groups in India have mentioned utilizing *T. cordifolia* to treat conditions such as cancer, diarrhoea, and jaundice in their traditional healthcare methods [8, 10, 11]. The article explores the present situation of the dengue epidemic, offering information on the organization, spread, and impact of the dengue virus. In particular, it examines the therapeutic effects of *T. cordifolia* in dengue therapy, investigating clinical trials, and possible modes of action studies associated with this herb.

The dengue virus (DENV)

DENV is a single-stranded positive-sense RNA virus that poses a significant health risk, particularly in tropical and subtropical regions. The mature virion of DENV is composed of an icosahedral shell of envelope (E) and membrane (M) proteins surrounding a lipid bilayer, which encases a complex of the approximately 11 kb genomic RNA with capsid (C) proteins [12]. The viral genome, a key player in the viral life cycle, encodes a polyprotein that is processed into structural and nonstructural (NS) proteins, with NS2A, NS2B, NS4A, and NS4B being membrane proteins that play crucial roles in viral replication through interactions with viral or host proteins [13]. The NS3 protease, in tandem with the NS2B cofactor, is essential for the viral life cycle, and its structure has been elucidated to aid in the development of inhibitors [14]. The RNA genome of DENV contains conserved structural elements that are critical for replication, such as the 70 nucleotide stem-loop RNA structure (SLA) at the 5′-end, which functions as a promoter for viral replication by interacting with the viral polymerase NS5 [15].

Additionally, the genome contains higher-order structures that regulate viral fitness and replication, with at least ten conserved motifs identified as crucial for these processes [16]. The NS1 protein exists in multiple oligomeric states, including intracellular dimeric (iNS1) and extracellular secreted (sNS1) forms, with the latter contributing to dengue hemorrhagic fever (DHF) through its hexameric structure [17]. The interaction of C proteins with the viral RNA genome is essential for proper packaging. C proteins bind preferentially to RNA sites with low base pairing and long-range RNA-RNA interaction sites, thus coordinating fundamental interactions for viral assembly [12]. The structural insights into these various components of the dengue virus, including the SLA, NS proteins, and RNA-protein interactions, provide a foundation for developing targeted antiviral therapies and vaccines, highlighting the intricate and multifaceted nature of DENV's structure and replication mechanisms.

Dengue Transmission

DENV is mainly transmitted through bites from infected *Aedes aegypti* and *Aedes albopictus* mosquitoes found in tropical and subtropical regions, posing a significant global public health risk [3]. The virus can cause illnesses ranging from mild dengue fever to severe dengue hemorrhagic fever and dengue shock syndrome, affecting millions of people annually. The transmission dynamics are influenced by factors including mosquito density, climatic conditions, and human mobility patterns, which can complicate the prediction and control of outbreaks. DENV can also be transmitted through atypical routes such as needle stick injuries, vertical transmission from mother to child, and contaminated blood or organs. Studies have shown the potential for respiratory transmission, a route where the virus is expelled from the respiratory tract of an infected person and inhaled by another, although this route is not yet confirmed in humans and requires further research [3].

Infected mosquitoes are more attracted to hosts and bite more frequently, which enhances the virus's spread. There is also evidence of mechanical transmission, where mosquitoes can transmit the virus immediately after biting an infected host without an incubation period, potentially amplifying outbreak dynamics. Surveillance studies have detected DENV in mosquito populations even without reported human cases, indicating that the virus can be maintained through vertical transmission, where infected female mosquitoes pass the virus to their offspring. This underscores the importance of proactive vector surveillance [9]. One effective public health measure is the PSN 3M Plus program, which focuses on eliminating mosquito breeding sites and educating communities about preventive measures, thereby playing a crucial role in reducing dengue prevalence despite varying levels of compliance among populations. This community-driven initiative enhances the traditional 3M approach (drain, cover, and bury) by incorporating additional preventive strategies, such as improving drainage systems, raising fish that consume mosquito larvae, installing screens on windows and vents, collaborating on community clean-up efforts, inspecting water storage, properly storing used clothing, cleaning hard-to-drain areas, planting mosquito-repellent flora, and utilizing repellents [9].

Temperature fluctuations significantly impact DENV transmission, with higher temperatures and stable conditions enhancing mosquito proliferation and virus spread. Advanced predictive models integrating multiple factors, including mosquito behaviour, climatic conditions, and human movement, have shown promise in accurately forecasting dengue outbreaks, aiding in timely intervention and control efforts [3]. However, it is our understanding of the various transmission routes and factors influencing DENV spread that truly empowers us. This knowledge is essential for developing effective prevention and control strategies to mitigate the impact of dengue globally (Figure 1) [9].

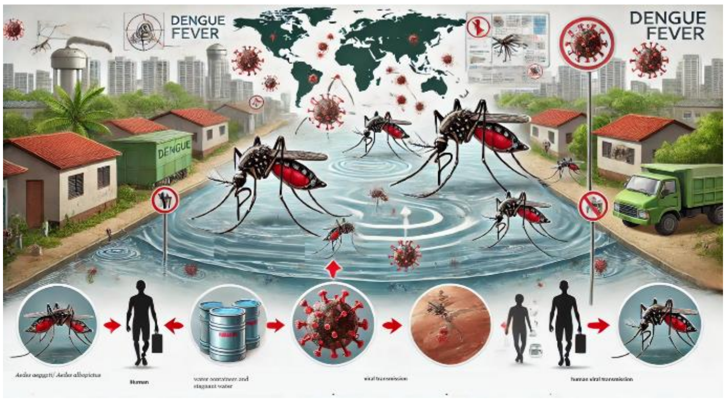

Figure 1. The Illustration shows Aedes Aegypti Mosquitoes Biting Humans, Water Sources in an Urban Setting, and a Map of Dengue Fever's Spread

Drawbacks of Current Treatments

Corticosteroids, including prednisone and dexamethasone, are the primary treatment for dengue, showing effectiveness in increasing platelet count within one week. Other options include platelet transfusion, growth factors, and bone marrow transplants, with splenectomy as a second-line treatment. The first licensed dengue vaccine, Dengvaxia, depends on serostatus and has limitations. Other vaccines, such as DENVax and LATV Δ30, are still in clinical trials. Butantan dengue vaccine has shown efficacy in preventing symptomatic DENV-1 and DENV-2. However, existing drugs like DENvax and TV003/TV005 are expensive, have side effects like nausea and vomiting, and only target dominant viral proteins, making them less effective over time due to viral evolution. Given these limitations, it is urgent to develop alternative plant-based drugs to effectively treat dengue.

Phytochemical and bioactivities of *T. cordifolia*

The herb being discussed falls under the category of a deciduous climbing plant that belongs to the Menispermaceae family. This remarkable botanical specimen, known for its medicinal attributes, is identified by various names such as Giloy, Guduchi, Rasayana, Amrita, heartleaf moonseed plant, and nectar of immortality [18]. It is characterized by a bitter taste and a juicy, thick stem that can display hues ranging from greyish brown to black, often adorned with thread-like fleshy aerial roots. The stem, which is both dry and softwooded, typically measures between 5 to 25 mm in diameter. Its unique heart-shaped leaves, called "cordifolia," have 5 to 10 cm dimensions. Small and yellow-green male flowers tend to grow in clusters, while the female flowers are solitary (Fig. 2) [19]. The fruits of this plant resemble peas in terms of shape and size, beginning as green and eventually ripening to a red colour. Despite its prevalence in tropical regions, its primary habitats are concentrated in countries such as India, Sri Lanka, China, Bangladesh, Indonesia, Myanmar, Thailand, Philippines, Malaysia, Borneo, and Vietnam. It can also be spotted in regions of North Africa, South Africa, and West Africa, thriving in dry deciduous forests situated at elevations of up to 1000 ft. This perennial herb is commonly found growing on fences and trees [18].

The therapeutic effectiveness of *T. cordifolia* is predominantly linked to its wide range of bioactive compounds, which include alkaloids, flavonoids, diterpenoid lactones, sesquiterpenoids, steroids, glycosides, lignans, polysaccharides, aliphatics, proteins, minerals (such as calcium and phosphorus), among others. These diverse properties, ranging from antidiabetic to anticancer effects, reassure us of its potential [20]. The ethnomedicinal knowledge surrounding this plant supports a broad spectrum of therapeutic uses, including aiding in metabolism, treating skin disorders, acting as an analgesic, alleviating general weakness, functioning as a carminative, reducing fever, displaying antiviral properties, treating jaundice, promoting diuresis, addressing seminal weakness, diarrhoea, bone fractures, asthma, vomiting, urinary tract infections, snake bites, reducing burning sensations, and exerting anti-inflammatory effects [7, 8, 10, 18, 19].

Furthermore, the plant enhances the immune system by boosting the activity of natural killer cells, B-cells, T-cells, and other components. It also demonstrates significant potential in combating dengue fever, a promising development that brings hope to many. It is often recommended locally for such purposes. Numerous clinical and computational studies have laid the foundation for further exploration of *T. cordifolia*'s anti-dengue capabilities. The immunomodulatory effects of *T. cordifolia* play a vital role in dengue prevention, increasing platelet count [21]. A blend of 125 mg *T. cordifolia* leaf and 375 mg *Carica papaya* leaf extract (Thrombobliss) can effectively address dengue [21]. Mishra et al. (2014) have suggested that consuming *T. cordifolia* with water or milk can assist in managing bleeding, a critical symptom of dengue [8, 18]. The study has observed that combining *T. cordifolia* and *B. diffusa* significantly raises platelet count and reduces body temperature [21].

Fig. 2. Morphology of *Tinospora cordifolia* Stem and Leaves

Anti-Dengue Activity and its Possible Mechanisms of *T. cordifolia*

T. cordifolia is known for containing various pharmacological agents with therapeutic potential, particularly against dengue. Studies have shown that Berberine and artemisinin tablets could effectively control dengue by enhancing berberine's efficacy [22]. Herbal formulations combining berberine and artemisinin have been suggested to remedy dengue symptoms [21]. Combinational therapies involving berberine, artemisinin, and loperamide have also shown promise in treating dengue fever [10]. Various studies have highlighted the presence of beneficial compounds like gallic acid, ellagic acid, palmitin, and berberine in Denguenil Vati, an effective anti-dengue formulation [8, 18]. The inhibitory effect of berberine chloride on viral nucleocapsid assembly has been noted, leading to fewer infectious viruses in treated cells. Additionally, magnoflorine has displayed dose-dependent inhibition of DENV and its NS1 antigen in mice, indicating the significant anti-dengue potential of *T. cordifolia* bioactives that warrants further investigation [7, 8, 10, 18].

The inflammatory response initiation in Dengue pathogenesis leads to the subsequent activation of infected cells for the production of nitric oxide and various inflammatory cytokines, such as tumour necrosis factor- α (TNF-α), interferon- γ (IFN-γ), interleukins (IL)-6, IL-8, IL-10, IL-12, and IL-18. These cytokines play a crucial role in enhancing the expression of leukocytes at the site of infection, thereby forming a protective barrier against viral intrusion [23]. Upon infection with Dengue virus (DENV), monocytes and dendritic cells stimulate the release of cytokines and TNF-α, which subsequently increase the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), ultimately activating platelet-activating factor (PAF). The secretion of vascular endothelial growth factor (VEGF) by mast cells acts on secretory phospholipase A2 (sPLA2), generating and releasing PAF [7, 8, 10, 18, 21].

Furthermore, the DENV virus can directly impact platelets, adding a layer of complexity to the pathogenesis process. Collectively, these intricate mechanisms are categorized under the phenomenon known as the "cytokine storm" observed during DENV infection, resulting in vascular leakage, heightened endothelial permeability, Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS). The integration of natural antiviral phytochemicals can impede the entry of DENV into host cells and regulate excessive cytokine production. These phytochemicals work by inhibiting nitric oxide synthases, thus reducing nitric oxide-mediated oxidative damage, enhancing the production of antiviral IFN-γ, stabilizing the cell membrane of infected cells, preventing platelet damage, thrombocytopenia, and bone marrow suppression [8, 10, 11, 20, 23, 24]. Moreover, they bolster the host immune system by augmenting the activity of macrophages, facilitating NF-κB translocation, and stimulating cytokine production [25]. In a separate investigation, Gupta et al. (2014) reported that *Tinospora cordifolia* enhances the immune response by boosting the activity of natural killer cells, T-cells, and B-cells, providing additional proof of its immunomodulatory characteristics [25]. Warowicka *et al.* elucidated the antiviral properties of berberine by highlighting its ability to impede viral replication and disrupt viral interaction with host cells. Berberine inhibits DNA synthesis and reverse transcriptase activity, while also modulating crucial signalling pathways like MEK-ERK, NF-κB, and AMPK/mTOR involved in viral replication [24]. Furthermore, Wan *et al.* (2020) demonstrated that berberine chloride interferes with capsid proteins and genomic RNA interaction, reducing the likelihood of viral infections [26]. Loaiza-Cano *et al.* examined the antiviral effects of flavonoids, showcasing their role in inducing cytokine 1 IFN via the

JAK/STATs pathway to modulate innate responses against DENV virus strains, emphasizing the need for further exploration into these mechanisms [8, 10, 11, 20, 23, 24, 27].

Conclusions and Future Perspective

Based on the data obtained from its clinical trials and molecular docking studies, the present study highlights the significant potential of *Tinospora cordifolia* in the fight against the dengue virus. Extensive research was conducted on berberine and magnoflorine for their potential in combating dengue, with the possibility of developing a revolutionary plant-based anti-dengue drug from *Tinospora cordifolia*. Potential anti-dengue treatments derived from this plant target the inhibition of the 'cytokine storm', preventing vascular leakage, and blocking various viral proteins. Further research is essential to confirm the specific antiviral mechanisms against dengue virus infection. Additionally, exploring the combined effects of bioactive compounds in Tinospora could reveal whether individual constituents or a combination of multiple bioactive contribute to the observed antiviral effectiveness. Investigating the biochemical and signaling pathways influenced by Tinospora's bioactive for potential dengue applications is also recommended. Modifying functional groups, like incorporating heterocyclic rings of diverse sizes into these compounds, may offer advantages in developing anti-dengue medications. Furthermore, thorough investigations are required to understand the complex interactions between active compounds and biological systems, elucidating their impact on the structure-function relationships in the context of dengue treatment.

Conflict of Interest

None.

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None.

Credit Authorship Contribution Statement

Malairaj Sathuvan: Conceptualization, Writing-original draft, Sai Laasya Reddy Iska: Writing- review and editing.

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