

Medicinal plants as a source of antiviral agents against dengue, chikungunya, zika and yellow fever: A narrative review

Plantas medicinais como fonte de antivirais contra dengue, chikungunya, zika e febre amarela:

Uma revisão narrativa

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Received: 11/24/2025 | Revised: 12/02/2025 | Accepted: 12/03/2025 | Published: 12/05/2025

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Abstract

Arboviruses represent a growing challenge to global public health, with dengue, chikungunya, zika, and yellow fever standing out due to their epidemiological impact in tropical and subtropical regions. The control of these infections is still limited by the absence of specific antiviral therapies and the increasing resistance of vectors, reinforcing the need for new therapeutic approaches. In this context, the bioprospecting of medicinal plants has gained attention due to the antiviral potential of their secondary metabolites. This study aims to summarize the current evidence on medicinal plant species with confirmed antiviral activity against arboviruses, emphasizing their mechanisms of action. Thus, this narrative review compiled updated evidence on phytochemicals with anti-arboviral activity, describing their mechanisms of action against Dengue virus (DENV), Chikungunya virus (CHIKV), Zika virus (ZIKV), and Yellow Fever virus (YFV). The results showed that essential oils, saponins, flavonoids, alkaloids, and diterpenoid derivatives may act through virucidal activity, inhibition of viral replication, and modulation of the host cell. Therefore, plant-derived compounds represent promising alternatives for the development of innovative therapeutic agents against arboviruses transmitted by mosquitoes.

Keywords: *Aedes aegypti*; Antiviral action; Arboviruses; Medicinal plants; Natural compounds.

Resumo

As arboviroses representam um desafio crescente para a saúde pública global, com dengue, chikungunya, zika e febre amarela se destacando devido ao seu impacto epidemiológico em regiões tropicais e subtropicais. O controle dessas infecções ainda é limitado pela ausência de terapias antivirais específicas e pela crescente resistência dos vetores, reforçando a necessidade de novas abordagens terapêuticas. Nesse contexto, a bioprospecção de plantas medicinais tem ganhado destaque devido ao potencial antiviral de seus metabólitos secundários. Este estudo tem como objetivo sintetizar as evidências atuais sobre espécies de plantas medicinais com atividade antiviral confirmada contra arbovírus, com ênfase em seus mecanismos de ação. Assim, esta revisão narrativa compilou evidências atualizadas sobre fitoquímicos com atividade antiarboviral, descrevendo seus mecanismos de ação contra o Vírus da Dengue (DENV), Vírus Chikungunya (CHIKV), Vírus Zika (ZIKV) e Vírus da Febre Amarela (YFV). Os resultados mostraram que óleos essenciais, saponinas, flavonoides, alcaloides e derivados de diterpenos podem atuar por meio de atividade virucida,

inibição da replicação viral e modulação da célula hospedeira. Portanto, compostos de origem vegetal representam alternativas promissoras para o desenvolvimento de agentes terapêuticos inovadores contra arbovírus transmitidos por mosquitos.

Palavras-chave: Ação antiviral; *Aedes aegypti*; Arboviroses; Compostos naturais; Plantas medicinais.

Resumen

Las arbovirosis representan un desafío creciente para la salud pública mundial, destacándose el dengue, chikungunya, zika y fiebre amarilla debido a su impacto epidemiológico en regiones tropicales y subtropicales. El control de estas infecciones aún se ve limitado por la ausencia de terapias antivirales específicas y por la creciente resistencia de los vectores, lo que refuerza la necesidad de nuevas estrategias terapéuticas. En este contexto, la bioprospección de plantas medicinales ha ganado relevancia debido al potencial antiviral de sus metabolitos secundarios. El objetivo de este estudio es sintetizar la evidencia actual sobre especies vegetales medicinales con actividad antiviral confirmada contra arbovirus, con énfasis en sus mecanismos de acción. De este modo, esta revisión narrativa recopiló evidencia actualizada sobre fitoquímicos con actividad antiarboviral, describiendo sus mecanismos de acción contra el Virus del Dengue (DENV), el Virus Chikungunya (CHIKV), el Virus Zika (ZIKV) y el Virus de la Fiebre Amarilla (YFV). Los resultados demostraron que los aceites esenciales, saponinas, flavonoides, alcaloides y derivados diterpenoides pueden actuar mediante actividad virucida, inhibición de la replicación viral y modulación de la célula hospedera. Por lo tanto, los compuestos de origen vegetal representan alternativas prometedoras para el desarrollo de agentes terapéuticos innovadores contra arbovirus transmitidos por mosquitos.

Palabras clave: Acción antiviral; *Aedes aegypti*; Arbovirosis; Compuestos naturales; Plantas medicinales.

1. Introduction

According to the World Health Organization (WHO), infectious diseases remain a major global public health burden, ranking as the sixth leading cause of mortality worldwide. Among these infectious diseases, arboviruses have long been recognized as a significant threat to human health (Saleh & Kamisah, 2020). Arboviruses comprise a group of viral diseases transmitted by arthropods, including ticks and mosquitoes, which are responsible for several clinically important pathogens, particularly those belonging to the *Aedes* genus in urban settings (Weaver et al., 2018). Notably, dengue, chikungunya, zika virus infection, and yellow fever continue to afflict tropical and subtropical regions, where humans serve both as the primary amplifying hosts and main victims of their pathological consequences (Patterson & Sammon, 2016; Wu et al., 2019; de França Cirilo et al., 2023; Malik et al., 2023; Monteiro et al., 2024).

Focusing on dengue, the disease is transmitted through the bite of *Aedes aegypti* infected with one of the four Dengue virus serotypes (DENV 1-4). Dengue outbreaks represent a major concern for international public health authorities, as it is considered the most prevalent and dangerous emerging arbovirus globally, according to the WHO. The disease predominantly affects tropical and subtropical regions, particularly densely populated urban and peri-urban areas, which poses major challenges to vector control (Frederico et al., 2017). It is estimated that more than 300 million new cases occur annually, resulting in approximately 22,000 deaths. The disease is endemic in over 100 countries across the Americas, Africa, Asia, the Eastern Mediterranean, and the Western Pacific (Saleh & Kamisah, 2020).

Another arboviral disease of global concern is chikungunya, caused by an alphavirus belonging to the family *Togaviridae*, the Chikungunya virus, also transmitted primarily by *A. aegypti*. Its name derives from the word “kungunyala” from the Makonde language, meaning “to become contorted,” referring to the severe arthralgia frequently experienced by affected individuals (Kumar et al., 2021). Epidemiological reports indicate that, since 2004, multiple outbreaks have spread throughout Africa and Asia, with the first confirmed case in the Western Hemisphere reported in 2013 (Patterson & Sammon, 2016). By 2014, approximately one million cases had been documented in the Americas (Kumar et al., 2021). An infectivity rate ranging from 34% to 45% has been reported (Patterson & Sammon, 2016), corroborating its classification as a rapidly expanding global health concern (Kumar et al., 2021).

Additionally, Zika virus infection, caused by a flavivirus also transmitted predominantly by *A. aegypti*, is relevant to public health due to its impact in tropical and subtropical regions (Acquadro et al., 2020; Haddad et al., 2019). For decades, zika

remained a relatively neglected disease because of its lower incidence compared to other arboviruses. However, the emergence of a major epidemic in the Americas in 2015 marked a turning point, raising international alarm and gaining broad media coverage (Patterson & Sammon, 2016; Cruz-Arreola et al., 2022). Zika virus infection has since been associated with severe neurological disorders in adults, including Guillain-Barré syndrome and meningoencephalitis, as well as congenital malformations, most notably microcephaly, in newborns from infected mothers (Haddad et al., 2019; Acquadro et al., 2020; Kumar et al., 2021). In 2016, WHO declared Zika a Public Health Emergency of International Concern (Patterson & Sammon, 2016; Haddad et al., 2019).

Yellow fever also remains a major arboviral disease of significance. The Yellow Fever virus is transmitted by *A. aegypti* in urban cycles and by *Haemagogus* and *Sabethes* spp. in sylvatic environments. Urban yellow fever outbreaks can severely disrupt local economies, including tourism, and may lead to quarantine procedures and trade restrictions. Even smaller sylvatic outbreaks have considerable epidemiological implications, highlighting vaccination as a cornerstone measure for preventing viral dissemination. Furthermore, yellow fever is subject to compulsory notification under the International Health Regulations, requiring nations to report confirmed cases to ensure timely preventive actions (Monath, 2001; Vasconcelos, 2003).

Given the significant negative impact of these arboviral diseases, it has become increasingly evident that new therapeutic and preventive strategies must be developed. Among emerging approaches, natural bioactive products represent a promising field of research. Since ancient times, natural medicinal resources have played an essential role in disease management due to the wide pharmacological potential of numerous plant species. Regarding arboviruses transmitted by *Aedes* mosquitoes, several studies have investigated phytotherapeutic agents aiming to identify antiviral properties. Thus, the exploitation of medicinal plants represents a viable, long-term complementary strategy for arbovirus control (Frederico et al., 2017; Lee et al., 2018; Kumar et al., 2021).

Therefore, the purpose of the present narrative review is to summarize the current evidence on medicinal plant species with confirmed antiviral activity against arboviruses, emphasizing their mechanisms of action.

2. Methodology

A non-systematic, qualitative bibliographic review was conducted (Snyder, 2019; Pereira et al., 2018), using the following search terms: “arboviruses”, “medicinal plants”, “natural compounds”, “antiviral action”, and “*Aedes aegypti*”. This narrative review was conducted using scientific articles published between 2010 and 2024, indexed in the PubMed and SciELO databases, focusing on studies investigating plant-derived compounds with antiviral activity against Dengue virus (DENV), Chikungunya virus (CHIKV), Zika virus (ZIKV), and Yellow Fever virus (YFV), or with insecticidal action against *A. aegypti*. The inclusion criteria comprised systematic reviews, *in vitro* and *in vivo* experimental studies, and molecular analyses addressing the mechanisms of action of phytotherapeutic agents.

3. Results and Discussion

3.1 Pathophysiology of DENV Infection

DENV contains a single-stranded, positive-sense RNA genome encoding a single polyprotein that is cleaved into multiple structural and nonstructural proteins. Structural proteins are essential for viral nucleocapsid and envelope formation, whereas nonstructural proteins play crucial roles in viral replication and immune evasion. Cellular receptors mediating viral entry include DC-SIGN, heparan sulfate, mannose receptor, among others. Viral particles bind to these receptors and enter host cells through clathrin-mediated endocytosis. Once in the cytoplasm, the viral genome is released and replicated, leading to the assembly of new virions, which are subsequently released from the host cell (Khan et al., 2023).

3.2 Pathophysiology of CHIKV Infection

Although CHIKV infection has a low mortality rate, symptoms such as fever and arthralgia may compromise quality of life for prolonged periods. CHIKV infection is divided into acute and chronic phases. During the acute phase, viral replication is intense, resulting in viremia and activation of the innate immune response. In the chronic phase, persistent joint inflammation may occur, with viral maintenance in macrophages. The adaptive immune response is prominent during CHIKV infection, with production of IgM and IgG antibodies (Burt et al., 2017; Kumar et al., 2021).

3.3 Pathophysiology of ZIKV Infection

ZIKV antagonizes the type I interferon (IFN-I) immune response through the NS5 protein, which induces degradation of STAT2, a key factor in antiviral defense. Experimental studies in immunocompromised murine models have demonstrated that ZIKV can accumulate in several organs, including the brain, spleen, and spinal cord, causing adverse clinical manifestations such as paralysis and, in congenital cases, microcephaly. Fetal susceptibility to infection is particularly pronounced during the first and second trimesters of pregnancy, which carries serious implications for public health (Miner & Diamond, 2017).

3.4 Pathophysiology of YFV Infection

In the urban transmission cycle, YFV is spread directly between humans and mosquitoes, without the need for nonhuman amplifying hosts, as infected humans act as disseminators of the virus (Monath, 2001; Vasconcelos, 2003). Viremia in infected individuals can sustain transmission until the susceptible population is reduced or mass vaccination is implemented.

In the sylvatic cycle, transmission occurs mainly through *Haemagogus* mosquitoes, which feed on primates and exhibit daytime activity, coinciding with human outdoor exposure. *H. janthinomys* has emerged as the primary vector of sylvatic yellow fever in Brazil, due to its high infection rates that facilitate viral dissemination (Monath, 2001; Vasconcelos, 2003).

Hamsters (*Mesocricetus auratus*) have been used as an alternative model to study YFV viscerotropism due to their cost-effectiveness and ease of handling. In experimental infections, YFV is detectable in the bloodstream approximately 48 hours post-infection, with viral titers increasing rapidly up to 96 hours. Initial liver lesions in these animals include nuclear enlargement and chromatin margination, predominantly in midzonal hepatocytes, yielding necrotic patterns like those observed in humans and nonhuman primates (Monath, 2001).

In rhesus macaques (*Macaca mulatta*), YFV infects Kupffer cells and hepatocytes, initially causing acidophilic degeneration followed by hyaline necrosis approximately three days post-inoculation. Hepatic lesions are characterized by coagulative hyaline necrosis with minimal inflammatory infiltrate, particularly in regions with prominent apoptosis. The virus initially appears in the liver within 24 hours and later in the kidneys, spleen, bone marrow, lymph nodes, and heart. The characteristic hepatic pattern, including Councilman–Rocha Lima bodies and midzonal necrosis, becomes evident 24-48 hours before death (Monath, 2001).

Following inoculation by a vector, the virus reaches regional lymph nodes within hours and becomes temporarily undetectable in the bloodstream during the first 24 hours. Viral replication within lymphoid cells and macrophages precedes reappearance in circulation, initiating the viremic period, which lasts from several hours to five to seven days depending on clinical severity. This period coincides with the onset of prodromal symptoms and renders human blood infectious for naïve vectors (Monath, 2001).

Histopathological findings in humans closely resemble those in nonhuman primates, predominantly characterized by midzonal necrosis. Degenerative lesions include Councilman-Rocha Lima bodies, representing apoptotic hepatocytes, accompanied by mild mononuclear inflammatory infiltrates (Monath, 2001).

3.5 Antiviral Effects of Medicinal Plant-Derived Products

3.5.1 Interference of Natural Compounds in the DENV Replication Cycle

Bioprospecting of natural compounds has revealed multiple phytochemicals capable of inhibiting DENV through either direct antiviral effects or modulation of host cellular processes required for replication. Essential oils from Colombian plant species have exhibited in vitro antiviral activity, with compounds such as carvacrol and thymol reducing viral replication by inhibiting entry or fusion (Silva-Trujillo et al., 2022). Their lipophilic properties enable interactions with the lipid envelope of flaviviruses, destabilizing the viral membrane and altering glycoprotein conformation essential for receptor binding and fusion (Lee, Wu & Poh, 2023).

Additionally, plant extracts have shown inhibitory effects in post-entry stages, including impairment of RNA synthesis and virion assembly, suggesting modulation of nonstructural proteins, replication complexes, or intracellular membrane remodeling (de Castro Barbosa et al., 2022). Phenolics and alkaloids also modulate oxidative stress and inflammatory responses, rendering host cells less permissive to viral replication (Loaiza-Cano et al., 2021). Essential oils from *Lippia alba* and *Lippia origanoides* also demonstrated direct virucidal action when applied prior to infection (Ocazone et al., 2010). Collectively, botanical compounds exert combined mechanisms: (i) direct virucidal action; (ii) inhibition of viral replication stages; and (iii) host-cell response modulation, supporting their potential as prototypes for DENV antiviral therapy.

3.5.2 Antiviral Mechanisms of Phytochemicals Against CHIKV

Natural products have gained increasing attention as candidates for CHIKV treatment due to their ability to neutralize free viral particles, interfere with critical replication steps, and modulate host cellular pathways. Extract screening has shown that plant fractions of different polarities (hexane, chloroform, ethanol) maintain cell viability above 70% in Vero cells while significantly reducing viral load, suggesting virion inactivation or entry inhibition (Chan, Khoo & Sekaran, 2021).

Furthermore, withaferin A, an alkaloid from *Withania somnifera*, was shown to inhibit CHIKV nsP2 protease, a key enzyme for polyprotein processing and viral replication (Sharma et al., 2024). Other bioactive classes such as flavonoids, coumarins, and phenolics modulate oxidative stress and inflammation, creating a less favorable intracellular environment for viral propagation (Kumar et al., 2021). These multiple mechanisms, virucidal action, replication blockade, and host-cell modulation, highlight phytochemicals as promising candidates for innovative CHIKV antiviral development.

3.5.3 Andrographolide Analogs Against ZIKV

Andrographolide is a diterpenoid isolated from *Andrographis paniculata*, widely used for its anti-inflammatory, antiviral, immunomodulatory, and antioxidant properties. Despite its therapeutic relevance, it presents low solubility and bioavailability. Conversely, zinc-andrographolide derivatives (ZADs) exhibit improved absorption, enhanced therapeutic activity, reduced toxicity, and increased metabolic stability (Li et al., 2020).

ZAD-1 treatment in ZIKV-infected cells reduced HSPA1A expression and enhanced PGK1 levels, while modulating transketolase (TKT) and the Ran GTP-binding nuclear protein, suggesting interference in key cellular pathways critical for ZIKV replication (Frederico et al., 2017; Saleh & Kamisah, 2020; Cruz-Arreola et al., 2022). These compounds also regulate autophagy, oxidative stress responses, mitochondrial function, HO-1 pathway, NF- κ B signaling, and GRP78 (Haddad et al., 2019; Acquadro et al., 2020; Kumar et al., 2021). Taken together, these findings support the suitability of 14-aryloxy-andrographolide analogs for future development as anti-ZIKV treatments (Kumar et al., 2021; Acquadro et al., 2020; Cruz-Arreola et al., 2022).

3.5.4 Phytocompounds with Potential Against YFV

Various botanical extracts and essential oils demonstrate antiviral activity against YFV. Essential oils from *L. alba* and *L. origanoides* are rich in monoterpenes and phenylpropanoids such as citral, limonene, carvacrol, and thymol, which exhibit strong virucidal activity before host-cell entry by disrupting the viral envelope and impairing glycoprotein-mediated attachment and fusion (Meneses et al., 2009).

Beyond direct virion destabilization, these compounds interfere with intracellular replication processes, including nonstructural protein activity, assembly of replication complexes, and endoplasmic reticulum membrane organization (Gómez et al., 2013). Secondary metabolites such as steroidal saponins from *Solanum sisymbriifolium* alter membrane permeability, potentially preventing fusion and budding of new virions (Figueiredo et al., 2021). Alkaloid-rich extracts from *Hippeastrum puniceum* may combine direct virion damage with modulation of cellular signaling, translation, and apoptotic pathways. The multifactorial actions, virucidal, replication-blocking, and host-response modulatory, position these phytochemicals as valuable leads for YFV antiviral discovery and complementary therapeutic strategies.

4. Final Considerations

The current scenario of arboviral diseases highlights the growing need for effective therapeutic strategies that complement existing preventive measures, such as vector control and vaccination. The findings presented in this review demonstrate that plant-derived compounds exhibit relevant mechanisms of action against different arboviruses, showing potential to reduce viral load, prevent infection, and modulate host immune responses.

Although most available evidence is still based on pre-clinical studies, phytochemicals emerge as important sources for the development of safe and cost-effective antiviral agents. Therefore, investments in translational research, extract standardization, clinical testing, and molecular elucidation of their effects are essential to enable future integration of these compounds into effective therapeutic strategies against mosquito-borne arboviral infections.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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