Antiviral activity of natural substances against main arboviruses DENV, ZIKV and CHIKV: literature review

Atividade antiviral de substâncias naturais contra os principais arbovírus DENV, ZIKV e CHIKV: revisão da literatura

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ABSTRACT
Arboviruses have caused several epidemics worldwide, resulting in significant global health problems. Dengue virus (DENV), Zika virus (ZIKV), and Chikungunya virus (CHIKV) are endemic arboviruses throughout Brazil and have a significant impact on public health. Major gaps in protection against the most
significant emerging arboviruses remain, as no antivirals are currently available, and vaccines are only available in a few countries. A potential source of antiviral compounds can be found in natural products, of which several compounds have been documented to have antiviral activities and are expected to have good efficacy and low side effects. Polyphenols and plant extracts have been studied for their antiviral properties against arboviruses and have shown promising results. Natural products continue to play an essential role in drug production and development. This study evaluated the antiviral potential of natural substances and extracts against DENV, ZIKV, and CHIKV. Original articles published between 2018 and 2022 in Portuguese and English on the antiviral activity of natural substances against arboviruses were reviewed. A total of 70 natural substances were evaluated against DENV, ZIKV, and CHIKV, and the potential antiviral activity against these viruses was analyzed. Some of these substances have shown promise in developing new antiviral compounds. With abundant natural products to screen for new antiviral compounds, they play an important role in developing new antiviral drugs and reducing arbovirus cases.

Keywords: Antivirals, Natural Compounds, Dengue Virus, Zika Virus, Chikungunya Virus.

RESUMO
Os arbovírus têm causado várias epidemias em todo o mundo, resultando em problemas de saúde globais significativos. Os vírus da dengue (DENV), Zika (ZIKV) e Chikungunya (CHIKV) são arbovírus endêmicos em todo o Brasil e têm um impacto significativo na saúde pública. Persistem lacunas importantes na proteção contra os arbovírus emergentes mais significativos, uma vez que não existem atualmente antivirais disponíveis e as vacinas estão disponíveis apenas em alguns países. Uma fonte potencial de compostos antivirais pode ser encontrada em produtos naturais, dos quais vários compostos têm sido documentados para ter atividades antivirais e são esperados para ter boa eficácia e baixos efeitos colaterais. Polifenóis e extratos de plantas têm sido estudados por suas propriedades antivirais contra arbovírus e têm mostrado resultados promissores. Os produtos naturais continuam a desempenhar um papel essencial na produção e desenvolvimento de medicamentos. Este estudo avaliou o potencial antiviral de substâncias e extratos naturais contra DENV, ZIKV e CHIKV. Artigos originais publicados entre 2018 e 2022 em português e inglês sobre a atividade antiviral de substâncias naturais contra arbovírus foram revisados. Um total de 70 substâncias naturais foram avaliadas contra DENV, ZIKV e CHIKV, e a potencial atividade antiviral contra esses vírus foi analisada. Algumas dessas substâncias mostraram-se promissoras no desenvolvimento de novos compostos antivirais. Com produtos naturais abundantes para rastrear novos compostos antivirais, eles desempenham um papel importante no desenvolvimento de novas drogas antivirais e na redução de casos de arbovírus.

Palavras-chave: Antivírus, Compostos Naturais, Vírus Da Dengue, Vírus Zika, Vírus Chikungunya.
1 INTRODUCTION

Arboviruses have become a significant public health problem in tropical and subtropical countries in recent decades. Environmental and climatic changes have put people in constant contact with arboviruses and facilitated the expansion of vectors to new territories, causing various epidemics with great economic and social impacts in these countries [1,2].

Arboviruses are arthropod-borne viral diseases that cause morbidity and mortality worldwide [3]. These arboviruses are endemic worldwide, with dengue present in 130 countries, chikungunya in 115, Zika in 89, and yellow fever in 40 [4]. With dengue as the most significant cause of infection, it is estimated that 40% of the world is at risk of dengue virus, which is approximately 390 million infections per year [5]. According to the WHO, in the Americas alone, approximately 500 million people are at risk of contracting Dengue [6].

The main circulating arboviruses belong to the families Flaviviridae (genus Flavivirus), such as Yellow Fever virus (YFV), Dengue virus (DENV) and Zika virus (ZIKV), and Togaviridae (genus Alphavirus), such as Chikungunya virus (CHIKV) and Mayaro virus (MYAV). With the advent of ecological and environmental conditions, approximately 1,633,991 probable cases of these emerging arboviruses have been recorded in Brazil, according to data from the 54th epidemiological bulletin of arboviruses in 2023 [7,8].

Two main vectors transmit Dengue, Zika, and Chikungunya viruses which are the mosquitoes: Aedes aegypti and Aedes albopictus. Aedes aegypti is Brazil's vector of most significant epidemiological importance [9,10].

Although most arboviruses are asymptomatic, these diseases have major socioeconomic implications. They affect economically active young and adult populations, which can lead to a temporary absence of at least six days from work [11,12]. Most cases are asymptomatic or may present as an influenza-like illness [13].

Therefore, cases of arbovirus infections may be underreported or misdiagnosed as other diseases because of the similarity of symptoms. Only a small proportion of arbovirosis cases may progress to more severe forms of the
disease that can be potentially fatal and usually affect children and seniors [14,15].

An example of these more severe infections is ZIKV infection, which can have neurological implications such as Guillain-Barré syndrome in adults and pregnant patients. There may be an increased risk of giving birth to children with congenital Zika syndrome, including fetal microcephaly, brain calcification, and abnormal brain development [16,17,18,19].

These arboviruses have been circulating worldwide for several years, and until now, there has been no specific treatment for these viruses; thus, the medical recommendations are the same for DENV, ZIKV, and CHIK [20]. The treatment is symptomatic, using drugs to relieve the patient's symptoms, usually analgesics and antipyretics, rest, and good hydration. Although some vaccines have been approved in certain countries, there is still a need to develop treatments for people who cannot receive the vaccine and to care for unvaccinated, infected patients. Thus, there is a great need to develop potent and effective antivirals against these arboviruses that affect millions worldwide [21,22,23].

One potential source is natural substances, whose medicinal properties have been explored worldwide by various research groups seeking the discovery of new active substances that could be used as pharmaceuticals or as structures to optimize the development of new antiviral agents [24,25].

In vitro and in silico studies of natural products and their natural extracts have been showing significant results in the search for antivirals, as screening these products to discover new antiviral compounds offers a more cost-effective alternative in the search for antiviral drugs. However, further studies are needed before these valuable natural products can be tested as human antiviral drugs [26,27,28].

The objective of this review was to evaluate, in the main databases, studies involving natural substances with potential antiviral activity against DENV, ZIKV, and CHIKV.
2 METHODOLOGY

This study is an integrative literature review that considered the structuring through six distinct stages as proposed by Mendes, Silveira, and Galvão (2008) [29]: Identification of the topic; literature search; data collection; data analysis; interpretation of results and presentation of the literature review.

A literature search was conducted using the BVS, CAPES, PUBMED, SCIELO, and LILACS databases, using the following MeSH descriptors relating to "antivirals," "natural compounds," "dengue virus," "zika virus" and "chikungunya virus." Original articles were included without language restriction that portrayed the theme regarding the antiviral activity of natural substances against the main arboviruses: a literature review published in these databases in the last five years (2018-2022). Subsequently, after analysis, those not addressing this theme were excluded from the review.

The inclusion criteria were original full articles, in Portuguese and English, published from 2018 to 2022, addressing the antiviral activity of natural substances against arboviruses. The exclusion criteria were review articles, thesis, incomplete and unavailable studies, published outside the research period (2018-2022), and not regarding the antiviral activity of natural substances against arboviruses.

Excel ® software was used to start the data analysis, with the organization of the data obtained in the research in spreadsheets and the organization of the selected articles and other analyses.

In addition, an instrument was used for data collection (table 1), which addressed the selection of the following information: authors' names and year of publication, virus, compound, extract name, in vitro and in vivo, and antiviral activity.
3 RESULTS

The search strategy identified 917 articles. After evaluation, duplicate articles were removed, and articles that did not fit the inclusion criteria were excluded, leaving 37 articles, 31 from the Capes database and 6 from the BvS database (figure 1).

Of the 37 selected articles, 35 substances were tested against dengue virus, and 29 substances showed significant antiviral activity against DENV. For zika virus, 20 natural compounds and 6 extracts were analyzed, and all showed antiviral effects against ZIKV. When evaluating the interaction with the chikungunya virus, 18 substances were evaluated, of which 14 showed antiviral activity against CHIKV; 10 extracts and 4 natural compounds were evaluated. The selected articles are listed in table 1.
Table 1 – Characteristics of the natural compounds included in this study.

<table>
<thead>
<tr>
<th>Y/N</th>
<th>Virus</th>
<th>Compound Name / Extract</th>
<th>Antiviral activity</th>
<th>in vitro or in vivo</th>
<th>Authors and year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dengue (DENV-2)</td>
<td>- Gallic acid</td>
<td>Pre-treatment</td>
<td>in vivo</td>
<td>Trujillo-corrêa et al. 2019</td>
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<tr>
<td></td>
<td></td>
<td>- Quercetin</td>
<td>Post-treatment</td>
<td></td>
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<td></td>
<td></td>
<td>- Catechin</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td></td>
<td>- α-mangostin</td>
<td>Pre-treatment</td>
<td>in vitro</td>
<td>Panda et al. 2021</td>
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<td></td>
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<td></td>
<td>Virucidal</td>
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<td></td>
<td></td>
<td></td>
<td>Post-treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>- Curcumin</td>
<td>Co-treatment</td>
<td>in vitro</td>
<td>Halim et al. 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 6-gingerol</td>
<td></td>
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<tr>
<td>4</td>
<td>Dengue (DENV-2)</td>
<td>- Cordicepine</td>
<td>Pre-infection</td>
<td>in silico</td>
<td>Panya et al. 2021</td>
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<td></td>
<td></td>
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<td>co-infection</td>
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<td></td>
<td>Post-infection</td>
<td></td>
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<tr>
<td>5</td>
<td></td>
<td>- Voacangine 7-hydroxyindolenine</td>
<td>Pre-treatment</td>
<td>in vitro</td>
<td>Monsalve-escudero et al. 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Rupicoline</td>
<td>Viricidal</td>
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<td></td>
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<td></td>
<td>Post-treatment</td>
<td></td>
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<tr>
<td>6</td>
<td></td>
<td>- Curcuminoid</td>
<td>Pre-treatment</td>
<td>in vitro</td>
<td>Balasubramanian et al. 2019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>co-treatment</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td></td>
<td>Extracts</td>
<td>Not Informed</td>
<td>in vitro</td>
<td>Rosmalena et al., 2019</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Acorus calamus</td>
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<td></td>
<td></td>
<td>- Cymbopogon citratus</td>
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<td></td>
<td></td>
<td>- Myristica Fatua</td>
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<tr>
<td>8</td>
<td>Dengue (DENV-1, 2)</td>
<td>Extracts</td>
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<td>in vitro</td>
<td>Silva-Trujillo et al., 2022</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lippia organoides Kunth</td>
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<td>- Lippia alba</td>
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<td></td>
<td></td>
<td>- Turnera diffusa Wildenow</td>
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<td></td>
<td></td>
<td>- Piper aduncum L.</td>
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<td></td>
<td></td>
<td>- Ocimum basilicum L.</td>
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<td></td>
<td></td>
<td>- Varronia curassavica Jacq.</td>
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<tr>
<td>9</td>
<td>Dengue (DENV-2)</td>
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<td>Not informed</td>
<td>Not informed</td>
<td>Paemanee; Hitakaru; Roytrakul; Smith, 2018</td>
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<tr>
<td></td>
<td></td>
<td>- α-tocopherol</td>
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<td></td>
<td></td>
<td>- Folic acid</td>
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<td></td>
<td></td>
<td>- Acetyl-L-carntine</td>
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<td></td>
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<td>- Resveratrol</td>
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<tr>
<td>10</td>
<td></td>
<td>- Curcumin</td>
<td>Co-treatment</td>
<td>in vitro</td>
<td>Kim; Choi; Kim, 2021</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Post-treatment</td>
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<td>Virucidal</td>
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<td>Silva et al. 2020</td>
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<td>12</td>
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<td></td>
<td>- Baicalin</td>
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<td>Sadeer et al., 2021</td>
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<td>- Bruguiera gymnorrhiza</td>
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<td>14</td>
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<td>- Eucaliprobusone G</td>
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<td>in vitro</td>
<td>Yao et al. 2021</td>
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<td>Treatment</td>
<td>Mode(s)</td>
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<tr>
<td>15</td>
<td>- Aphloia theiformis</td>
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<td>in vitro</td>
<td>[43] Clain et al., 2018</td>
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<tr>
<td>16</td>
<td>- Ellagic acid</td>
<td>Not informed</td>
<td>in vitro</td>
<td>[44] Acquadro et al., 2020</td>
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<tr>
<td>17</td>
<td>- Quercetin&lt;br&gt;- Rutin&lt;br&gt;- Pedalitin</td>
<td>Post-treatment</td>
<td>in vitro</td>
<td>[45] LIMA et al., 2021</td>
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<td>18</td>
<td>- Gossypol&lt;br&gt;- Curcumin&lt;br&gt;- Digitonin</td>
<td>Pre-treatment</td>
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<td>[46] GAO et al., 2019</td>
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<td>19</td>
<td>- Theaflavin</td>
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<td>in vitro</td>
<td>[47] WEIBAO et al., 2021</td>
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<td>20</td>
<td>- Silvestrol</td>
<td>Not informed</td>
<td>in vitro</td>
<td>[48] ELGNER et al., 2018</td>
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<tr>
<td>21</td>
<td>- Isoquercitrin</td>
<td>Post-treatment</td>
<td>in vitro</td>
<td>[49] GAUDRY et al., 2018</td>
<td></td>
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<td>22</td>
<td>- Naringenine</td>
<td>Post-treated&lt;br&gt;Post-infection&lt;br&gt;Virucidal</td>
<td>in vitro</td>
<td>[50] CATANEO et al., 2019</td>
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<tr>
<td>23</td>
<td>- Emodin&lt;br&gt;- Berberine</td>
<td>pretreatment&lt;br&gt;virucidal</td>
<td>in vitro</td>
<td>[51] BATISTA et al., 2019</td>
<td></td>
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<tr>
<td>24</td>
<td>- 6-gingerol</td>
<td>Pre-treatment&lt;br&gt;virucidal&lt;br&gt;Post-treatment</td>
<td>in vitro</td>
<td>[52] HAYATI et al., 2021</td>
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<td>25</td>
<td>- Oroxylum indicum</td>
<td>virucides&lt;br&gt;pretreatment&lt;br&gt;post-treatment</td>
<td>in vitro</td>
<td>[53] MOHAMAT; SHUEB; MAT, 2018</td>
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<td>26</td>
<td>- Picrorhiza kurroa&lt;br&gt;- Ocimum tenuiflorum&lt;br&gt;- Terminalia chebula&lt;br&gt;- Commiphora wightii&lt;br&gt;- Cedrus deodara</td>
<td>Not Informed</td>
<td>in vitro</td>
<td>[54] RAGHAVENDHAR; TRIPATI; RAY; PATEL, 2019</td>
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<td>27</td>
<td>- Caulerpa racemosa</td>
<td>Post-treatment</td>
<td>in vitro</td>
<td>[55] ESTEVES et al., 2019</td>
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<tr>
<td>28</td>
<td>- α-mangostin</td>
<td>Pre-treatment&lt;br&gt;Post-treatment&lt;br&gt;Co-treatment</td>
<td>in vitro</td>
<td>[56] PATIL et al., 2021</td>
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<td>29</td>
<td>- Thymoquinone</td>
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<td>in vitro</td>
<td>[57] KUMAR; NEHUL; SINGH, 2021</td>
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<td>- Andrographis paniculata&lt;br&gt;- Phyllanthus niruri&lt;br&gt;- Tinospora cordifolia</td>
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<td>in vitro</td>
<td>[58] SHARMA et al., 2018</td>
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<tr>
<td>31</td>
<td>- Plumeria alba&lt;br&gt;- Vitex negundo</td>
<td>Pre-treatment&lt;br&gt;Post-treatment</td>
<td>in vitro</td>
<td>[59] ALAGARASU et al., 2022</td>
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</tr>
</tbody>
</table>
### Table 2 – List of natural compounds that showed antiviral properties against DENV.

<table>
<thead>
<tr>
<th>Source</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Virucidal</th>
<th>Not informed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancitrocladus heyeanus</td>
<td>- Gallic acid</td>
<td>- Gallic acid</td>
<td>- α-mangostin</td>
<td>- Acorus calamus</td>
</tr>
<tr>
<td>- Bacopa monnieri</td>
<td>- Quercetin</td>
<td>- Curcumin</td>
<td>- 6-gingerol</td>
<td>- Cymbopogon citratus</td>
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<td>- Cucurbita maxima</td>
<td>- Catechin</td>
<td>- Cordicepine</td>
<td>- Cordicepine</td>
<td>- Myristica fatua</td>
</tr>
<tr>
<td>- Hedyotis diffusa</td>
<td>- α-mangostin</td>
<td>- Voacangine - 7-hydroxyindolenine</td>
<td>- Plumeria alba</td>
<td>- Lippia organoides Kunth</td>
</tr>
<tr>
<td>- Artemisia capilaris</td>
<td>- Cordicepine</td>
<td>- Rupicoline</td>
<td>- Vitex negundo</td>
<td>- Lippia alba</td>
</tr>
<tr>
<td>- Gossypol</td>
<td>- Voacangine</td>
<td>- Plumeria alba</td>
<td>- Ancistrocladus heyeanus</td>
<td>- Turner diffusa Willdenow</td>
</tr>
<tr>
<td>Elaeocarpus grandiflorus</td>
<td>- Bacopa monnieri</td>
<td>- Vitex negundo</td>
<td>- Bacopa monnieri</td>
<td>- Piper aduncum L.</td>
</tr>
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<td>- Cucurbita maxima</td>
<td>- Cucurbita maxima</td>
<td>- Hedyotis diffusa</td>
<td>- Cucurbita maxima</td>
<td>- Ocimum basilicum L.</td>
</tr>
<tr>
<td>- Artemisia capilaris</td>
<td>- Gossypol</td>
<td></td>
<td></td>
<td>- Melatonin</td>
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<td>- Gossypol</td>
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<td></td>
<td>- α-tocopherol</td>
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<td>- folic acid</td>
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<td>- Acetyl-L-carnitine</td>
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<td></td>
<td>- Resveratrol</td>
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<td>- Hyppeastrum</td>
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<td>- Fridericia chica</td>
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<td></td>
<td>- Phyllanthus phillyreifolius</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- Psiloxylon mauritianum</td>
</tr>
</tbody>
</table>

Source: Authors (2023).
Table 1 shows the references for the respective compounds that showed antiviral activity against DENV.

The natural substances tested against DENV in the articles (table 2) included in the present study were: Gallic acid, Quercetin, Catechin, α-mangostin, Cordicepin, Voacangine 7-hydroxyindolenine, Rupicolin, Gossypol, Curcuminoid, Plumeria alba, Vitex negundo, Ancistrocladus heyeanus, Bacopa monnieri, Cucurbita maxima inhibited DENV in the pre-treatment. The substances that showed virucidal effect were α-mangostin, Voacangine 7-hydroxyindolenine, Rupicolin, Curcuminoid, Curcumin, Gossypol, 6-gingerol, Plumeria alba, Vitex negundo, Ancistrocladus heyeanus, Bacopa monnieri, Cucurbita maxima. The substances that showed antiviral activity at post-treatment were α-mangostin, Cordicepin, Voacangine 7-hydroxyindolenine, Rupicoline, Plumeria alba, Vitex negundo, Ancistrocladus heyeanus, Bacopa monnieri, Cucurbita maxima. These have shown potential for the development of new antiviral drugs against DENV [28,39,30,31,32,33].

Of the compounds tested, the extracts of Acorus calamo, Cymbopogon citratus, Myristica fatua [34], Lippia origanoides Kunth, Lippia alba, Turnera diffusa Willdenow, Piper aduncum, Ocimum basilicum, Varronia curassavica, and the substances α-tocopherol, folic acid, Acetyl- L -carnitine, resveratrol showed antiviral effect against DENV (Table 2). However, further analyses are needed to identify the active compounds responsible for the antiviral activity of the plant extract and investigate its potential as an antiviral agent [35, 36].

Halim et al. (2021) [32] showed that the active compounds of turmeric possess antiviral activity against DENV. Furthermore, the active compound of this substance had an anti-DENV effect, as at all concentrations tested in A549 cells against all four dengue serotypes, they demonstrated significant inhibitory activity against all DENV serotypes.

Trujillo-Correa et al. (2019) [30] evaluated the anti-Dengue activity of 3 compounds derived from Psidium guajava (guava tree) using two strategies: pre- and post-treatment in Vero cells. Quercetin was the most effective compound (EC50 = 19.2 μg/mL), reaching 90% viral inhibition against DENV.
Paemanee et al. (2018) [38] demonstrated that treatment with resveratrol on DENV-2 infected HEK293T cells showed significant cytotoxicity (EC$_{50}$ = 24.37 μM), leading to a significant reduction in the level of infection.

GAO et al. (2022) [66] demonstrated that the gossypol derivative ST087010 exhibited effective inhibitory activity on infections of all these virus strains. The data showed broad-spectrum activity of this compound against ZIKV and DENV-1-4 infections.

3.2 ZIKA

Table 3 – List of natural compounds that showed antiviral properties against ZIKV.

<table>
<thead>
<tr>
<th>ZIKV</th>
<th>Pre-treatment</th>
<th>post-treatment</th>
<th>virucidal</th>
<th>Not informed</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Gossypol</td>
<td>- Curcumin</td>
<td>- Curcumin</td>
<td>- Curcumin</td>
<td>- Bruguiera gymnorrhiza</td>
</tr>
<tr>
<td>- Curcumin</td>
<td>- Baicalein</td>
<td>- Silymarin</td>
<td>- Eucaliprobusone G</td>
<td>- Aphloia theiformis</td>
</tr>
<tr>
<td>- Digitonin</td>
<td>- Bai calina</td>
<td>- Naringenine</td>
<td>- Ellagic acid</td>
<td>- Silvestrol</td>
</tr>
<tr>
<td>- Conessina</td>
<td>- Baicalin</td>
<td>- Emodin</td>
<td>- Berberine</td>
<td>- Hyppeastrum</td>
</tr>
<tr>
<td>- Isoquercitrin</td>
<td>- Quercetin</td>
<td>- Berberine</td>
<td></td>
<td>- Fridericia chica</td>
</tr>
<tr>
<td>- Naringenine</td>
<td>- Rutin</td>
<td>- Ellagic acid</td>
<td></td>
<td>- Phyllanthus phillyreifolius</td>
</tr>
<tr>
<td>- Emodin</td>
<td>- Pedalitin</td>
<td>- Naringenine</td>
<td></td>
<td>- Psiloxylon mauritianum</td>
</tr>
<tr>
<td>- Berberine</td>
<td>- Theaflavin</td>
<td>- Hedyotis diffusa</td>
<td>- Artemisia capillaris</td>
<td></td>
</tr>
<tr>
<td>- Hedyotis diffusa</td>
<td>- Isoquercitrin</td>
<td>- Gossypol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Artemisia capillaris</td>
<td>- Naringenine</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 1 shows the references for the respective compounds that showed antiviral activity against ZIKV.

The results obtained on ZIKV (table 3) showed the antiviral potential of the following natural substances in the pre-treatment: *Baicalein*, *Bai calina*, *Curcumin*, *Gossypol*, *Digitonin*, *Theaflavin*, *Isoquercitrin*, *Naringenine*, *Hedyotis diffusa*, *Artemisia capillaris*, *Emodin*, *Berberine*, *Conessin*. In the virucidal action, the substances that showed antiviral activity were: *Curcumin*, *Gossypol*, *Silymarin*, *Baicalin*, *Ellagic acid*, *Naringenin*, *Hedyotis diffusa*, *Artemisia capillaris*. The substances that showed antiviral activity in the post-treatment were: *Curcumin*, *Baicalein*, *Baicalin*, *Quercetin*, *Pedalitin*, *Rutin*, *Isoquercitrin*, *Naringenin*, *Hedyotis diffusa*, *Artemisia capillaris* [37,38,39,44,45,46,48,49,50].
The tested substances, Eucaliprobusone G, Digitonin, and Silvestrol, and the extracts Bruguiera gymnorhiza, Aphloia theiformis, Hippeastrum, Fridericia chica, Phyllanthus phillyreifolius, Psiloxylon mauritianum showed antiviral activity against ZIKV (table 3) [40,41,42,43,47].

Of the compounds analyzed for antiviral activity against ZIKV, the substances that showed the best antiviral activity were curcumins, baicalein, baicalin, naringenin, pedalitin, and the extracts of Hedyotis diffusa and Artemisia capillaris. These compounds showed virucidal activity both pre-treatment and post-treatment, demonstrating that they can be strong candidates for producing new antiviral therapies.

According to the study of Oo et al. (2018) [41], substances baicalein and baicalin showed anti-ZIKV effects in Vero cells, where baicalein showed the lowest EC$_{50}$ value (0.004 µM) in the post-treatment. Baicalin showed the lowest EC$_{50}$ value (14 µM) when introduced in the pre-treatment. Both compounds demonstrated a virucidal effect against ZIKV.

Cataneo et al., 2019 [51] demonstrated that NAR was able to inhibit ZIKV infection in A549 cells having a value of IC$_{50}$ =58.79 and IC$_{90}$ =154.3 µM acting in the late phase of the viral life cycle, acting as a non-competitive inhibitor of the NS2B-NS3 protease.

Lima et al. (2021) [46] evaluated the flavonoids quercetin, rutin, and pedalitin, which were isolated and purified from Pterogyne nitens, a Brazilian medicinal plant. Of the 3 flavonoids studied, pedalitin was presented as a potent inhibitor of the NS2B-NS3 protease of ZIKV with an IC$_{50}$ of 3.5 µM in biophysical and enzymatic assays, showing that this substance acts as a non-competitive inhibitor in kinetic assays.

Mao et al. (2022) [63] demonstrated that the extract of the plants Hedyotis diffusa (HD) and Artemisia capillaris (AC) had inhibitory activity on viral replication of ZIKV and also DENV in Vero cells, which suggest that HD and AC possess bioactive compounds that are promising antiviral candidates against these viruses.
3.3. CHIKUNGUNYA

Table 4 – List of natural compounds that showed antiviral properties against CHIKV.

<table>
<thead>
<tr>
<th>CHIKUNGUNYA</th>
<th>Pre-treatment</th>
<th>post-treatment</th>
<th>virucidal</th>
<th>Not informed</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 6-gingerol</td>
<td>- Oroxylum indicum</td>
<td>- Oroxylum indicum</td>
<td>- 6-gingerol</td>
<td>- Picrorhiza kurroa</td>
</tr>
<tr>
<td>- Oroxylum indicum</td>
<td>- Caulerpa racemosa</td>
<td>- Oroxylum indicum</td>
<td>- Oroxylum indicum</td>
<td>- Ocimum tenuiflorum</td>
</tr>
<tr>
<td>- α-mangostin</td>
<td>- Plumeria alba</td>
<td>- α-mangostin</td>
<td>- α-mangostin</td>
<td>- Terminalia chebula</td>
</tr>
<tr>
<td>- Plumeria alba</td>
<td>- Vitex negundo</td>
<td>- Plumeria alba</td>
<td>- Plumeria alba</td>
<td>- Commiphora wightii</td>
</tr>
<tr>
<td>- Ancistrocladus heyeanus</td>
<td>- Bacopa monnieri</td>
<td>- Vitex negundo</td>
<td>- Vitex negundo</td>
<td>- Cedrus deodara</td>
</tr>
<tr>
<td>- Bacopa monnieri</td>
<td>- Cucurbita maxima</td>
<td>- Ancistrocladus heyeanus</td>
<td>- Ancistrocladus heyeanus</td>
<td>- Thymoquinone</td>
</tr>
<tr>
<td>- Cucurbita maxima</td>
<td>- 6-gingerol</td>
<td>- Bacopa monnieri</td>
<td>- Bacopa monnieri</td>
<td>- Andrographis paniculata</td>
</tr>
<tr>
<td>- 6-gingerol</td>
<td>- Oroxylum indicum</td>
<td>- Cucurbita maxima</td>
<td>- Cucurbita maxima</td>
<td>- Phyllanthus niruri</td>
</tr>
<tr>
<td>- Plumeria alba</td>
<td>- Vitex negundo</td>
<td>- Bacopa monnieri</td>
<td>- Bacopa monnieri</td>
<td>- Tinospora cordifolia</td>
</tr>
</tbody>
</table>

Source: Authors, 2023.

Table 1 shows the references for the respective compounds that showed antiviral activity against CHIKV.

The results obtained for CHIKV (table 4) showed the antiviral potential of the following natural substances in the pre-treatment: 6-gingerol, α-mangostin, *Oroxylum indicum*, *Plumeria alba*, *Vitex negundo*, *Ancistrocladus heyeanus*, *Bacopa monnieri*, and *Cucurbita maxima*. In the virucidal, the substances that had antiviral activity were: mangostin, *Oroxylum indicum*, *Plumeria alba*, *Vitex negundo*, *Ancistrocladus heyeanus*, *Bacopa monnieri*, and *Cucurbita maxima*. Of the tested substances that showed antiviral activity at post-treatment were: 6-gingerol, α-mangostin, *Oroxylum indicum*, *Caulerpa racemosa*, *Plumeria alba*, *Vitex negundo*, *Ancistrocladus heyeanus*, *Bacopa monnieri* and *Cucurbita maxima* [51,52,54,55,58,61,64].

The tested substances, Thymoquinone and the extracts *Picrorhiza kurroa*, *Ocimum tenuiflorum*, *Terminalia chebula*, *Commiphora wightii*, *Cedrus deodara*, *Andrographis paniculata*, *Phyllanthus niruri*, *Tinospora cordifolia*, showed antiviral activity against CHIKV (Table 4) [53,56,57,59,60,62,63].

The study by Patil *et al.* (2021) [57] evaluated α-mangostin in Vero E6 cells and demonstrated that 8 µM of α-Mangostin completely inhibited CHIKV infection in the co-treatment condition. CHIKV replication was also inhibited in virus-
infected mice. This first in vivo study demonstrates that α-mangostin effectively reduces viral replication in serum and muscle.

Mohamat et al. (2018) [54] demonstrated that the aqueous extract of the plant Oroxyllum indicum in Vero cells have some comparatively higher anti-CHIKV activity than the methanol extract in this study. The antiviral activity of O. indicum may be partly attributed to the presence of the compound Baicalein in the extracts. However, the anti-Chikungunya activity showed a low to moderate effect, suggesting that O. indicum extracts have the potential for effective therapy against CHIKV infection.

Research by Hayati et al. (2021) [53] evaluated the substance [6]-gingerol in the HepG2 cell line, which demonstrated the antiviral activity of this substance both post-treatment and virucidal, where post-treatment (CI50 was 0.038 mM and 0.031 mM) and virucidal (CI50 of 0.24 mM), indicating that [6]-gingerol inhibits CHIKV infection by suppressing viral replication.

The studies by Alagarasu et al. (2022) [60] reported the antiviral activity against CHIKV and DENV of 5 extracts (Plumeria alba, Ancistrocladus heyneanus, Bacopa monnieri, Curcubita maxima, and Vitex negundo) in Vero CCL-81 cells. These extracts can be further characterized to identify effective phytochemicals against dengue and chikungunya.

4 DISCUSSION

To date, there are no approved therapeutic drugs against DENV, ZIKV, and CHIKV infections [67]. Treatments mainly target the symptoms of infection [68]. Research on antiviral drugs for the treatment of arbovirus infections is growing rapidly, with many drug candidates emerging from natural product screening and drug reuse studies [69,70].

Over the years, polyphenols, which are natural compounds found in fruits, juices, vegetables, wine, and teas, have gained increasing scientific interest as they demonstrate favorable physicochemical properties and lower toxicity, exhibiting a wide range of pharmacological activities, such as antiviral, antibacterial, antioxidant, anti-inflammatory and anticancer effects [71,72].
As per the literature, in the studies conducted by Akhtar et al. (2021), He et al. (2020), Lee et al. (2018), Pridgeon, Klesius and Yildirim-Aksoy (2013), Ruan et al., (2021) [73,74,75,76,77], the natural substances quercetin, curcumin, 6-gingerol, resveratrol, and gossypol showed activity against various microorganisms, corroborating that these substances have multi-biological activity.

Curcumin is a component of turmeric, which is one of the major phytochemicals in Curcuma longa L., commonly known as saffron, and is a strong candidate for the production of new drugs against different pathogens [78]. This polyphenolic compound has gained much attention worldwide due to its various biological activities [79]. The study by Moghadamtousi et al. (2014) [80] showed that curcumin is a component of turmeric and proved in vivo an in vitro study that this compound and its derivatives possess antibacterial, antifungal, and antiviral properties.

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is an important bioflavonoid present in abundance in various foods, mainly in vegetables and fruits, such as cabbage, onions, berries, apples, red grapes, broccoli, and cherries, as well as tea and red wine [81,82,83]. It is one of the most abundant representatives of the flavonoid subclass, with documented multi-biological activities, is widely used in traditional medicine, and has several health benefits [84,85]. In addition to having antiviral effects, Chiang, Tsai, and Wang (2023) [86] found that quercetin, as a natural product, has the potential for neuroprotection and neuroinflammation in various neurological disorders, thus corroborating that quercetin can be a potent therapeutic agent for the treatment of various pathologies.

Resveratrol (3,5,4’-trihydroxy-trans-stilbene) is a natural phytoalexin produced by plants and is an integral part of the plant's intrinsic immune reaction against infectious diseases [87,88,89]. This substance is found in plants, fruits, and derivatives, such as grapes, peanuts, wine, blueberries, blueberries, dark chocolate and tea. [90]. Resveratrol exerts multiple biological activities [91,92], including anti-inflammatory effects [93], cardioprotective activities [94], and
anticancer potential [95]. This substance also shows antiviral activity against several viruses, such as Influenza A [96] and HIV [97].

Gossypol [(2,2'-binaphthalene)-8,8'-dicarboxaldehyde,1,1',6,6',7,7'-hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl] is a fat-soluble polyphenolic compound isolated from the seeds of Gossypium (cotton) [98,99]. Gossypol is widely reported in the literature for its anti-fertility [100,101], antioxidant [102], anticancer [103,104], antiviral [105], antimicrobial [106], and antifungal properties [107].

As described by Gao et al., 2022 and Gao et al., (2019) [47,66], Gossypol Kim; Choi; Kim., (2021) [39] curcumin showed high anti-DENV activity. Moreover, these substances exhibited antiviral activity against ZIKV, thus corroborating that these substances and their analogs present themselves as strong candidates for the development of antiviral therapy against these arboviruses.

Baicalein and baicalin are polyphenolic compounds belonging to the flavone family that is isolated from the plants Scutellaria baicalensis and Scutellaria lateriflora [108,109]. Studies have shown that baicalein exerts antiviral activity against DENV-2 in Vero cells through different mechanisms [110]. In addition, the anti-dengue activity of an extract of the roots of Scutellaria baicalensis, the main natural source of baicalein and baicalin against the in vitro replication of Dengue virus [111], has previously been reported, thus confirming that these substances have antiviral potential against flaviviruses.

Naringenin (2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is one of the most important naturally occurring flavonoids, predominantly found in vegetables, fruits, herbs, and nut foods, widely consumed by humans [112]. The flavonoid naringenin has been a widely described compound in the literature because of its anti-inflammatory activity. Moreover, in traditional medicine, this substance is of great interest because it acts as an inflammatory mediator in various diseases [113]. Thus, in cardiovascular diseases, this compound has been well-studied because of its vasoactive properties. Flavonoids of the citrus genus induce vasodilation via endothelial nitric oxide (NO) production [114].
Pedalitin also exhibits antiviral activity against another virus, as Shimizu and colleagues (2017) [115] reported that pedalitin exhibits antiviral activities against hepatitis C virus (HCV) in Huh-7.5 cell lines, where it decreased HCV infectivity in a dose-dependent manner.

_Hedyotis diffusa_ (HD) and _Artemisia capillaris_ (AC) are broad-spectrum medicinal herbs with diverse pharmacological properties that are widely distributed in China [116]. Current studies of these herbs in traditional medicine aim to find molecular, cytological, and pharmacological evidence to support the use of traditional medicinal herbs, to confirm that, in nature, they have active ingredients, and to explore the roles of these compounds in the treatment of various diseases [117,118]. There are several reports in the literature on the effects of these herbs against liver diseases, especially against viral hepatitis viruses [119,120].

α-mangostin is a major bioactive compound purified from the pericarp of the mangosteen fruit _Garcinia mangostana_ Linn [121,122]. α-mangostin (α-MG), has been used in traditional medicine for various conditions, including anti-inflammatory activity [123], exerting intestinal epithelial barrier protective activities via a dual mechanism involving AhR and Nrf2 pathways [124], analgesic activity [125], suppressing hepatitis C virus replication [126] and inhibiting DENV production [127].

6-Gingerol is one of the major pharmacologically active phenolic compounds found in ginger rhizomes and exhibits a variety of pleiotropic pharmacological functions, including anti-inflammatory [128,129,130], anticancer [131], and immunomodulatory effects [132]. In addition, 6-gingerol can decrease fasting plasma glucose, LDH cholesterol, TG, aspartate aminotransferase, and alanine aminotransferase in a rat model of non-alcoholic fatty liver disease [133].

_Oroxylum indicum_ (O. indicum) is a small to medium-sized tree belonging to the family Bignoniaceae, commonly called Indian trumpet, found in tropical countries. It is a plant traditionally used in Ayurvedic and folk medicine [134,135]. O. indicum possesses a wide variety of bioactive phytochemicals, including alkaloids, flavonoids, cardiac glycosides, phenols, and other bioactive
compounds, which may help accelerate the discovery of new nature-based LDHA inhibitors. Different parts of the tree have also been used in folk medicine to treat diseases, such as urinary tract infections, bronchitis, diarrhea, cancer, and liver diseases [136,137,138,139].

5 CONCLUSION

The spread of arboviruses in recent years has demonstrated the need to develop effective antivirals to treat these diseases and overcome the current lack of antivirals against these arboviruses. With the abundance of natural products worldwide, it is highly optimistic that natural products will continue to play a significant role in contributing to the development of antiviral drugs.

Our results showed the antiviral activity of several plant-derived compounds against infection by viruses, DENV, ZIKV and CHIKV, that are endemic to many tropical and subtropical regions, including Brazil. Finally, more extensive studies, both in vitro and in vivo, are needed to further evaluate the potential of natural compounds as antivirals for arboviruses.
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