Quinacrine and Berberine as Antiviral Agents against Dengue and Zika Fever: In Silico Approach

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Abstract

Dengue and Zika fever are mosquito-borne viral diseases that have rapidly spread all over the world. Currently there are no specific drugs for DENV and ZIKV infection. The recent outbreak of these viruses realized that there are major health risks, demands an enhanced surveillance and a need to develop novel drugs against them. Non-structural proteins NS5 and NS3 are essential for the replication of the flavivirus RNA genome. Therefore its inhibition could be considered as a useful strategy for treatment of DENV and ZIKV infection. Quinacrine and Berberine had been docked with NS5-methyltransferase of Dengue virus and NS3 protein of ZIKV using Auto dock 4.2 tools. Quinacrine and Berberine showed binding affinity -6.83 kcal/mol and -6.22 kcal/mol with NS5-methyltransferase and -7.32 kcal/mol and -8.03 kcal/mol with NS3 protease of ZIKV, respectively. Observations discussion in review will be useful in designing single drug against both virus infections.

Keywords: NS5 protease; NS5-methyltransferase; Antiviral drugs; Dengue virus; Zika virus

Introduction

Dengue is the most prevalent mosquito-borne virus, with nearly 400 million annual cases worldwide [1]. Dengue fever and dengue hemorrhagic fever are the quickly spreading mosquito-borne diseases in the universe today, for an watched 30-fold expand from claiming accounted cases in the most recent 50 years a long time [2]. The WHO estimates that, globally, 2.5 billion people are at risk, and annually, 50-100 million people become infected, of which approximately 0.5 million require hospitalization [3] and 22,000 deaths occur each year in areas where it is endemic [4].

The dengue disease has four viral serotypes (DENV-1, DENV-2, DENV-3, and DENV-4), and its spectrum ranges from asymptomatic infection to dengue fever, Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS), and may lead the patient to death [5]. All four serotypes of dengue virus are transmitted to humans by the Aedes aegypti and Aedes albopictus mosquitoes [6]. The positive-sense flavivirus RNA genome of 11kb forms a single open reading frame that is translated into an ~370kDa poly protein precursor containing the structural proteins and seven non-structural proteins known as NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. NS5 is about 900 amino acids long, largest (104kDa) and the most conserved protein in DENV. The positive-sense flavivirus RNA genome of 11kb forms a single open reading frame that is translated into an ~370kDa poly protein precursor containing the structural proteins and seven non-structural proteins known as NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. NS5 is about 900 amino acids long, largest (104kDa) and the most conserved protein in DENV. It is also a bi-functional enzyme with a methyl transferase domain (M Tase; residues 1-296) at its N-terminal end and a RNA-dependent RNA polymerase (RdRp; residues 320-900) [7] C-terminal end [8]. Its enzymatic activities form attractive target for antiviral development [9-11]. In this article, we comprises molecular docking of four antiviral drugs such as Quinacrine, Amodiaquine, Berberine and Pro-chlorperazine against NS5-methyltransferase of dengue virus using in silico approach.

While zika virus is a mosquito-borne flavivirus that was initially recognized in Uganda, Africa [12] in 1947 in monkeys through a method that observed yellow fever. It was later distinguished in people in 1952 in Uganda and the United Republic of Tanzania. Congenital ZIKV syndrome includes microcephaly, spasticity, craniofacial disproportion, irritability, seizures and other brainstem dysfunctions [13] has caused a public health emergency of international concern [14]. Brazil without immunity in the population saw large numbers infected immediately as the virus was amplified in the population, resulting in thousands of pregnant women infected at once. The Brazilian ZIKV strain has been shown to cause birth defects in experimental models by targeting cortical progenitor cells, inducing cell death and impairing neurodevelopment [15]. Initially the Brazilian Ministry of Health advised reporting diagnosed cases of Zika as dengue, since the symptoms were in most of the cases similar to a mild case of the latter.

The first baby in the USA born with ZIKV occurred on January 16th, 2016 [16]. Amodiaquine [17], prochlorperazine [18], quinacrine [19], and Berberine [19] are promising drugs approved by Food and Drug Administration against dengue virus which also belong to Flaviviridae family [20]. The WHO Director-General declared on February 1st, 2016 that the cluster of microcephaly cas-
Amongst these four drugs, Berberine has shown lowest binding activity of NS3 is necessary for viral replication and its prohibition (NS3) protein of ZIKV using Auto dock 4.2 tools. The protease activity was shown in Table 2 which revealed that Berberine by Auto Dock 4.2 program. The docking result of these drugs with NS5-methyltransferase fold composed of four helices surrounding a central 7-stranded β-sheet [8,26] is shown in Figure 1 and Table 1. The active site, containing a catalytic K61-D146-K180-E216 (KDKE) motif, is positioned in the center of the β-sheet.

The docking result of these drugs with NS5-methyltransferase was shown in Table 1 which revealed that Quinacrine be a novel inhibitor for NS5-protein. Zika virus infection in humans is usually mild or asymptomatic. However, some babies born to women infected with Zika virus have severe neurological sequelae. An unusual cluster of cases of congenital microcephaly and other neurological disorders in the WHO Region of the Americas, led to the declaration of a public health emergency of international concern by the World Health Organization. In docking studies of known antiviral drugs against other members of the flaviviridae family like Hepatitis C, Infection with one of four dengue virus serotypes (DENV1-4) can lead to febrile illness and flu-like symptoms, or can progress to the more severe dengue hemorrhagic fever or dengue shock syndrome. Development of the more severe hemorrhagic fever is more likely if recovery from infection by one dengue serotype is followed by subsequent infection by a second serotype. Individual MTase and RdRp domains in full-length NS5 have conserved protein folds. The MTase (residues 1-262) adopts the SAM-dependent methyltransferase fold composed of four helices surrounding a central 7-stranded β-sheet [8,26] is shown in Figure 1 and Table 1. The active site, containing a catalytic K61-D146-K180-E216 (KDKE) motif, is positioned in the center of the β-sheet.

Discussion

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Zika virus (ZIKV) is a mosquito borne pathogen currently causing large epidemics in Brazil. Its infection can cause microcephaly, a serious birth defect during pregnancy. The recent outbreak of ZIKV in February 2016 in Brazil realized it as a major health risk, led to the declaration of a public health emergency of international concern by the World Health Organization. In docking studies of known antiviral drugs against other members of the flaviviridae family like Hepatitis C, Infection with one of four dengue virus serotypes (DENV1-4) can lead to febrile illness and flu-like symptoms, or can progress to the more severe dengue hemorrhagic fever or dengue shock syndrome. Development of the more severe hemorrhagic fever is more likely if recovery from infection by one dengue serotype is followed by subsequent infection by a second serotype. Individual MTase and RdRp domains in full-length NS5 have conserved protein folds. The MTase (residues 1-262) adopts the SAM-dependent methyltransferase fold composed of four helices surrounding a central 7-stranded β-sheet [8,26] is shown in Figure 1 and Table 1. The active site, containing a catalytic K61-D146-K180-E216 (KDKE) motif, is positioned in the center of the β-sheet.

Figure 1: Overall fold of the DENV NS5 monomer [26].

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Table 1: Docking results of known antiviral drugs with NS5-methyltransferase of dengue virus.

<table>
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<tr>
<th>Compound Name</th>
<th>PubChem CID</th>
<th>BE</th>
<th>IME</th>
<th>IE</th>
<th>TorE</th>
<th>VdwE</th>
<th>EE</th>
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<td>-7.86</td>
<td>-1.02</td>
<td>1.19</td>
<td>-6.93</td>
<td>-0.94</td>
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</table>

BE: Binding Energy; IME: Intermolecular Energy; IE: Internal Energy; TorE: Torsional; Energy; VdwE: vdW + Hbond + desolv Energy; EE: Electrostatic energy.

Table 2: Docking results of known antiviral drugs with NS3-Protein of Zika Virus.

<table>
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<tr>
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</table>

BE: Binding Energy; IME: Intermolecular Energy; IE: Internal Energy; TorE: Torsional; Energy; VdwE: vdW + Hbond + desolv Energy; EE: Electrostatic energy.

Conclusion

The results obtained are useful in understanding the inhibitory mode of Quinacrine, Amodiaquine, Berberine and Prochlorperazine with catalytic site of NS5-methyltransferase and NS3-protein of dengue and zika virus respectively accurately predicting the activities of drugs on the basis of docking score of both. Here, we concluded that Quinacrine and Berberine are novel inhibitor for NS5-protein and of dengue and zika virus to prevent the dengue fever and zika fever respectively.

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References


