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In Silico Evaluation of Compounds from Antiviral Plants using Molecular Docking Analysis Targeting HSV-1 Viral Infection

M Sharanya[1]*, J Suganya[1], V Poornima[1] and Mahendran Radha[1]
[1]Department of Bioinformatics, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Chennai-600 117, Tamil Nadu, India

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Corresponding Author Email: sharanya.bioinfo@gmail.com

Abstract
Aim: Viral infections pose a difficult milieu in the present era. Herpes Simplex Virus (HSV) infects mostly the oral and genital mucosa caused by the respective HSV type 1 (HSV-1) and HSV type 2 (HSV-2). The present study aims at evaluating plants reported with antiviral activity using computational studies. **Methods:** The compounds from the medicinal plants *Hypericum mysorense*, *Cryptostegia grandiflora* and *Tagetes minuta* were retrieved from the available databases (PubChem). The 3D structure of target protein selected for the study was thymidine kinase (TK) retrieved from PDB of ID 4OQL. The docking study was carried out using Argus lab and the interactions were observed using PyMol viewer. **Results:** The compound 1,2,4-cyclopentanetrione alone had significant docking score (-6.57 Kcal/mol) among the plant compounds studied with 2 number of hydrogen bonds. The interactions were observed with the residues GLU18 and GLN158 of bond length 3.29 and 2.79Å, respectively. **Conclusion:** Plants are highly efficient in human health concerns from ancient age. Recent advancement in scientific technologies lead to the identification of principles behind the capability of curing several diseases. Future aspects of the study is to perform high-throughput virtual screening of several plant compounds and to be explored in developing a significant pharmacophore lead or an efficient drug.

Keywords
Antiviral plants, HSV-1, Thymidine kinase, Traditional medicine, Molecular Docking studies.

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INTRODUCTION
Viral infections pose a difficult milieu in the present era. Herpes Simplex Virus (HSV) infects mostly the oral and genital mucosa caused by the respective HSV type 1 (HSV-1) and HSV type 2 (HSV-2). Even the infection includes the central nervous system (CNS) with varied presentation [1]. In 2012, an estimated 3.7 billion people under the age of 50, or 67% of the population, had HSV-1 infection. Estimated prevalence of the infection was highest in Africa (87%) and lowest in the Americas (40-50%). With respect to genital HSV-1 infection, 140 million people aged 15-49-years were estimated to have genital HSV-1 infection worldwide in 2012, but prevalence varied substantially by region. Most genital HSV-1 infections are estimated to occur in the Americas,

Europe and Western Pacific, where HSV-1 continues to be acquired well into adulthood [2]. Global burden of HSV-2 infection was also found high threatening 400 million people with genital ulcer disease, HIV acquisition and transmission to neonates [3]. Although neonatal infections are rare, it is estimated 10 out of every 100,000 births globally lead to lasting neurologic disability or death [4]. Seroprevalence rate of HSV-1 and HSV-2 are found high [4]. Antiviral therapy with acyclovir (ACV) has relatively reduced the death rate however, morbidity remains high [1]. Mostly the severity of infection ranges from cold sores to brain diseases like encephalitis and distinct as lytic as well as latent phase [5]. Lytic phase produces immediate symptoms whereas the latter remains quiet. Treatment with acyclovir also faces the crisis of resistance and recently it was found, in HSV-1 the resistance to ACV was due to mutations in the gene of thymidine kinase and/or DNA polymerase [6].Using molecular docking studies, Al-Salahi [7] reported the biological antiviral activity of triazoloquinazolines against HSV- and HSV-2. The protein mostly expressed in the immediate-early genes[5] and several proteinases [7] were targeted. In the present study, thymidine kinase was chosen and docking analysis was carried out for the compounds reported in the plants *Hypericum mysorense*, *Cryptostegia grandiflora* and *Tagete sminuta*.

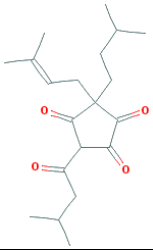
At present, traditional medicine has the very important task of healing about 75 - 80% of the world population and therefore the aim of WHO is to improve its quality and effectiveness [8]. Today in many countries modern medicine has dislodge plants with many synthetic products but we must also emphasize that almost 30% of pharmaceutical preparations are acquired directly or indirectly from plants [9]. In general, the plants are set as source of therapeutic agents based on the following criteria. They areto isolate bioactive compounds, to produce bioactive compounds through semi synthesis, to have higher activity and/or lower toxicity, to use agents as pharmacologic tools and finally to use the whole plant or part of it as a herbal remedy [10].Till today, only about 6% of the plants has been explored for their biological activity and 15% are scientifically reported the phytochemistry [11]. Even there is a belief that bioactive compounds retrieved from plants source would have lower toxicity to human [12]. The plants used here are already reported for its antiviral activity. The genus Hypericum is a well-known folklore medicine for its varied therapeutic potential and found in Western Ghats of India. Leaves are high in flavonoids and the reports represents their wound healing, bactericidal, anti-inflammatory activity. *H. mysorense* exhibited significant antiviral activity against herpes simplex virus type-I [13] and antimicrobial activity against several bacterial and fungal pathogens [14]. The antiviral activity of *Cryptostegia grandiflora* [15] and *T.* minuta [16] were also reported.

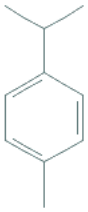
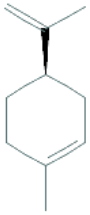
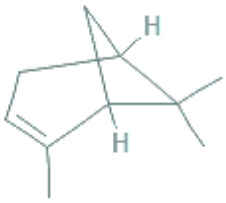
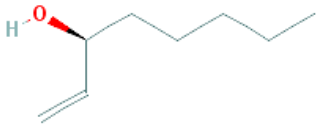
The enzyme, thymidine kinase (TK) has an essential role in DNA synthesis of HSV-1 virus. The mutation of TK gene results in reduction of viral pathogenicity. To the credit it has its own importance in the latent infection of sensory ganglion neurons [17]. Therefore, TK was chosen as the antiviral target in the present study.

METHODS AND METHODOLOGY

The 3D structure of the protein thymidine kinase (TK) was retrieved from PDB(4OQL). The structures of plant compounds were retrieved from Pubchem database. The plant compounds are 1,2,4-cyclopentanetrione, cymene, limonene, α-Pienene,1-Octen-3-ol (Table 1). The docking study was carried out using Argus lab. The interactions were observed using PyMol software.

Table 1: Structure of Plant Compounds

Compound Name	PUBCHEM ID	2D Structure
1,2,4-Cyclopentanetrione	534963	

Cymene	7463	
Limonene	440917	
Alpha-pienene	6654	
1-Octen-3-OL	2724898	

RESULTS AND DISCUSSION

The compound 1,2,4-cyclopentanetrione alone had significant docking score (-6.57 Kcal/mol) among the plant compounds studied with 2 number of hydrogen bonds. The interactions were observed with the residues GLU18 and GLN158 of bond length 3.29 and 2.79Å, respectively. The result indicated the weak interaction pattern of cymene with thymidine kinase, where the bond lengths were observed to be too long (Table 2). In recent years, molecular docking is the primary step in analyzing the interacting ability of the small molecules with the targets. In the present study, the binding efficiency of compounds from the plants *Hypericum mysorense*, *Cryptostegia grandiflora* and *Tagetes minuta* indicated only few of their reported compounds to show docking score. In addition, only two had least docking score of -6.97 and -5.52 with interactions. However, it was observed to have bond lengths beyond 2Å indicating its poor stability. Kamath and Sharma [18] had studied the interactions of anti-herpes drugs against the target thymidine kinase of PDB ID 3F0T. In future, the study has to be focused on screening vast number of compounds from various plants reported with antiviral activity, in order to identify an effective drug candidate and also to solve the existing resistance difficulty to antiviral drugs.

Table 2: Interactions of Plant Compounds With 4OQL

Compound Name	Docking score Kcal/mol	No. of Bonds	Interacting Residues	Bond Length (Å)
1,2,4-cyclopentanetrione	-6.97	2	GLU18 (O-H) GLN158 (O-H)	3.29 2.79
Cymene	-5.52	3	GLU38 (O-H) ARG163(O-H) GLY259 (O-H)	5.70 7.05 7.89
Limonene	-4.73	-	-	-
α-pinene	-4.06	-	-	-

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