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Exploring the Therapeutical Potential of *Pongamia Pinnata* for Herpes Simplex Virus Type 1 (HSV-1)

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Abstract

Objective: *Pongamia pinnata (L.), commonly known as Indian beech or pongam tree, is a tropical plant renowned for its medicinal properties in traditional medicine systems. Extracts derived from various parts of Pongamia pinnata have demonstrated antimicrobial, anti-inflammatory, and immunomodulatory activities. Such attributes make it a compelling candidate for exploring its therapeutic potential against HSV infections. Thymidine kinase is the target protein mostly used in the treatment of HSV1 infections. In this study the various phytocompounds present in the Pongamia pinnata are chosen to investigate their pharmacological characteristics and therapeutic aspects against the targeted protein thymidine kinase in the treatment of HSV1 infection.* ***Method:*** *In this study, the phytoconstituents of Pongamia pinnata were derived from IMPPAT database and structures were downloaded by using PubChem database. Pharmacological analysis of phytocompounds were done by using the SwissADME, ADMETLAB 2.0 tools. The protein structure is downloaded from RCSB-PDB and validated using PDBsum generate and BIOVIA Discovery Studio Software. By using the PyRx, virtual screening tool the docking was performed and results were investigated to calculate the binding affinity between targeted protein and phytocompounds (ligands).* ***Result:*** *The 3 phytocompounds of Pongamia pinnata, ovalichromene B, pongachromene and isopongachromene are discovered to show the high binding affinity with targeted protein thymidine kinase.* ***Conclusion:*** *The phytoconstituents of Pongamia pinnata have potential to be used in the treatment of herpes simplex virus 1 infection. However, further in vitro analysis is required to support this finding.*

Keywords: *Pongamia pinnata (L.)*, herpes simplex virus (HSV), thymidine kinase, phytocompounds, pharmacological analysis, toxicity analysis, molecular docking

INTRODUCTION

Herpes simplex virus (HSV), which includes HSV-1 and HSV-2, is a widespread viral infection that leads to oral and genital herpes. These viruses, also referred to as human alpha herpesvirus 1 and human alpha herpesvirus 2, belong to the human *Herpesviridae* family, which encompasses viruses responsible for infecting many humans. Many individuals infected with herpes do not show symptoms or experience only mild ones. When symptoms do occur, they may involve painful blisters or ulcers that recur over time. Initial infections may cause symptoms, such as fever, body aches, and swollen lymph nodes. Oral herpes typically presents as cold sores or open sores around the mouth or lips, while genital herpes can result in bumps, blisters, or ulcers in the genital or anal regions [1].

Herpes simplex virus (HSV) infections pose a major global health challenge, impacting millions of people each year. Although antiviral treatments have improved, there is still a strong demand for new, more effective therapies. Natural products, derived from a wide variety of plant species, have

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historically been a valuable source for discovering therapeutic compounds with potential for treating such infections [2, 3].

Pongamia pinnata, commonly known as Karanj in Hindi and Indian beach in English, is a versatile leguminous tree native to the Indian subcontinent and Southeast Asia. It is a non-edible oil-producing tree with significant potential for seed yield. Known for its resilience, this drought-resistant, nitrogen-fixing tree can endure waterlogging, and mild frost, and has a high tolerance to salinity. Traditionally, various parts of the plant have been used in medicine to treat a wide range of diseases and injuries. The oil extracted from its seeds is particularly valued for treating conditions like ulcers, rheumatism, leucoderma, and scabies. The plant contains numerous bioactive compounds, including alkaloids, tannins, steroids, glycosides, flavonoids, and fixed oils. Its extracts have demonstrated a range of beneficial properties, such as anti-diarrheal, antifungal, anti-plasmodial, anti-ulcer, anti-inflammatory, analgesic, anti-hyperglycemic, anti-lipoxidative, antioxidant, and anti-hyperammonic effects [4].

Thymidine kinase from herpesvirus is a type of thymidine kinase enzyme that facilitates the transfer of a phosphate group from ATP to thymidine, resulting in the formation of thymidine monophosphate. This compound acts as a substrate for viral DNA replication. When HSV-1 infects a cell, it takes over the cell's machinery to replicate its own genetic material. One critical step in this replication process involves the virus incorporating thymidine (a nucleoside) into its DNA. Thymidine kinase is an enzyme produced by HSV-1. Its main function is to phosphorylate thymidine, converting it into its monophosphate form, which is then further phosphorylated by cellular enzymes into its triphosphate form. This triphosphate form can be incorporated into the viral DNA during replication. Antiviral medications like acyclovir, valacyclovir, and famciclovir are frequently prescribed to treat HSV-1 infections. These drugs are nucleoside analogs, which means they resemble the structure of natural nucleosides [5, 6].

When these drugs are administered, the virus's TK enzyme mistakenly incorporates them into the viral DNA during replication. Once incorporated into the viral DNA, these nucleoside analogs inhibit further DNA synthesis, ultimately halting viral replication. However, these drugs require activation by the viral TK enzyme to become effective. The presence of thymidine kinase in herpesvirus-infected cells is utilized to activate various antiviral drugs, allowing the treatment to be directed specifically at the infected cells [7].

In this study, we aimed to identify the potential of phytocompounds present in the plant *Pongamia pinnata* in the treatment of HSV1 viral infection by concluding its pharmacological properties and demonstrating the binding affinity between the suitable phytoconstituents and targeted protein [8].

METHODOLOGY

Retrieval of Ligands

The phytoconstituents present in the medicinal plant *Pongamia pinnata* were retrieved from IMPPAT database (Indian Medicinal Plants, Phytochemistry and Therapeutics) (https://cb.imsc.res.in/imppat/) [9]. The total 79 phytocompounds were present in whole plant. By using PubChem database (https://pubchem.ncbi.nlm.nih.gov/) the canonical SMILES, PubChem CID, and two-dimensional (2D) models of these compounds in SDF format were retrieved [10]. The SwissADME analysis (http://www.swissadme.ch) was used to assess the ligands pharmacological characteristics [11]. Various physicochemical qualities are evaluated like size, flexibility, lipophilicity, polarity, insolubility, and instauration. The best ligands are then chosen using the LIPINSKI rule. For the evaluation of toxicity parameters of ligands ADMETLAB 2.0 (https://admetmesh.scbdd.com), was employed [12]. Finally, a total of 55 phytocompounds are screened based on criteria of High GI absorption, Lipinski rule and non-aggregator.

Retrieval of Proteins

The crystal structure of thymidine kinase protein from herpes simplex virus type I (PDB ID – 1KI2) was downloaded from the RCSB-PDB database in PDB format (https://www.rcsb.org/structure/1KI2).

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The resolution of the protein downloaded is 2.20 Å and the x-ray diffraction method is used for retrieval of the protein [13].

Purification of Protein Structure

The protein structure was purified before docking by using the BIOVIA Discovery Studio software. The heteroatoms, ligand group were removed and water molecules, polar hydrogens were added during the purification process (https://www.3ds.com/products/biovia/discovery-studio) [14].

Molecular Docking

Molecular docking is a computational technique used to predict the binding affinity between ligand compounds and target proteins. In this study, we utilized PyRx software as the molecular docking tool. The ligands were docked with targeted protein independently using PyRx software. Purified proteins were uploaded into PyRx as a macromolecule and plant phytocompounds were added as ligands. Ligands were converted from SDF to PDB format by using the Openbabel software (https://sourceforge.net/projects/openbabel/). Protein and ligand files are converted into Pdbqt file format. The following grids were generated for protein, 1KI2 (Center X:42.5731 Y:76.0400 Z:52.7150, Dimensions (Angstrom) X:54.9258 Y:57.3309 Z:50.7242). All the screened ligands were docked with the target protein and the corresponding docking interactions were evaluated based on the binding affinity. 9 different conformational changes were taken by the ligand to attain the best binding scores [15–17]. The docking conformation with a zero RMSD (root mean square deviation) value was considered the optimal one, as it exhibited the lowest binding scores compared to all other conformations [7].

The top six conformations with the least binding affinity were selected as the best protein-ligand complex. The docked ligand structures were extracted as PDB files, and the interaction was visualized in DS BIOVIA Discovery Studio [18].

Visualization

By using DS BIOVIA Discovery Studio Visualizer, the interaction of the targeted protein with ligands was checked and the conformations showing the highest binding scores were downloaded. The 2D and 3D structure models of interactions were produced.

RESULT

Protein Structure Analysis

The Ramachandran plot is used to see the energetically permissible areas where amino acid torsions are angled against one another in a protein structure. The Ramachandran plot of thymidine kinase protein (Figure 1) is created by using PROCHECK. As per the Ramachandran plot statistics, the purified structure of thymidine kinase has its 91.6% residues in the most favored regions, 7.5% residues were in the additional allowed regions, 0.4% residues were in the generally allowed regions and 0.4% were in the disallowed regions. Secondary structure of thymidine kinase is depicted in Figure 2.

Pharmacological Studies

The phytoconstituents from *Pongamia pinnata* were subjected to pharmacological screening based on the parameters and were listed in Table 1. The pharmacological properties of the top ligands are listed in Table 2.

The properties of the compounds following Lipinski's rule, as detailed in Table 3, were analyzed using SwissADME. Similarly, the ADME data obtained from SwissADME is summarized in Table 4, Additionally, the toxicity profile of the compounds, as analyzed, is provided in Table 5.

Molecular Docking

The binding affinity of 6 ligands towards the thymidine kinase protein is obtained by using PyRx software enlisted in Table 6.

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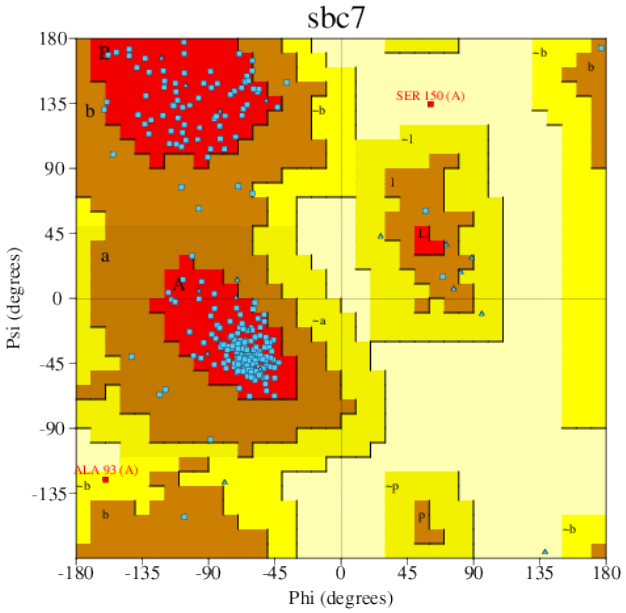

Figure 1. Ramachandran plot of thymidine kinase protein using PDBsum.

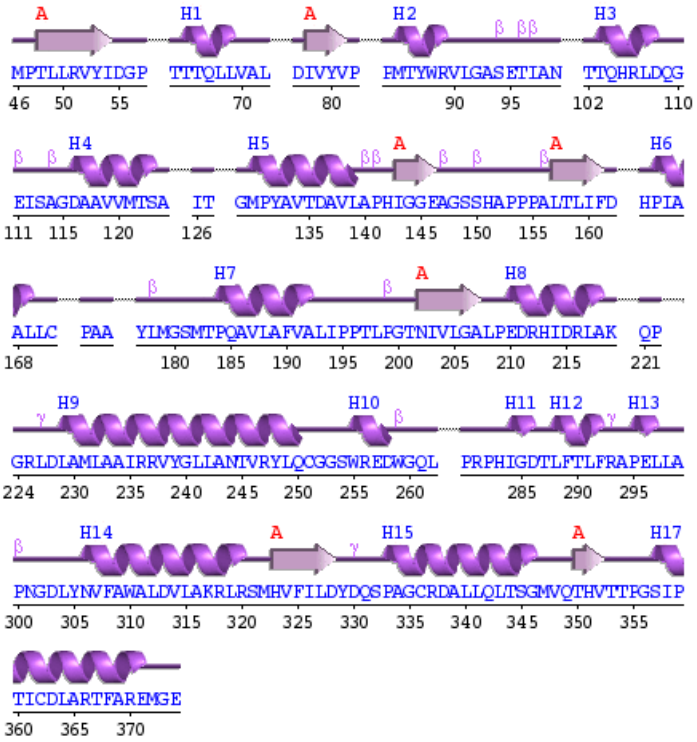

Figure 2. Secondary structure of thymidine kinase.

Table 1. Parameters for pharmacological properties.

Properties		Optimal Range
Lipophilicity	xLogP	–0.7 to +5.0
Size	MW	150–500 g/mol
Polarity	TPSA	20–130
Saturation	Sp3 hybridization	Not less than 0.25
Flexibility	Rotatable bonds	Not more than 9

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Table 2. Pharmacological properties.

Ligand	MW	Fraction Csp3	Rotatable bonds	TPSA
Pongaglabrone	306.27	0.06	1	61.81
Ovalichromene B	350.36	0.29	1	53.99
Pongachromene	378.37	0.23	2	67.13
Ponganone IV	396.43	0.35	4	63.22
3'-Methoxypongapin	366.32	0.15	3	80.27
Isopongachromene	378.37	0.23	2	67.13

Table 3. Data for the properties of the Lipinski rule obtained using SwissADME.

Ligand	MW	MLogP	H Donors	H acceptors	Molar refractivity
Pongaglabrone	306.27	1.51	0	5	83.75
Ovalichromene B	350.36	2.45	0	5	95.69
Pongachromene	378.37	1.94	0	6	104.6
Ponganone IV	396.43	1.93	0	6	109.1
3’-Methoxypongapin	366.32	0.89	0	7	96.74
Isopongachromene	378.37	1.94	0	6	104.6

Table 4. ADME data obtained using SwissADME.

Ligands	BBB	GI absorption	PGP substrate	Solubility (LOGSw-SILICOS IT)
Pongaglabrone	Yes	High	No	–6.76
Ovalichromene B	Yes	High	Yes	–5.72
Pongachromene	Yes	High	No	–6.81
Ponganone IV	Yes	High	Yes	–6.32
3’-Methoxypongapin	No	High	No	–6.97
Isopongachromene	Yes	High	No	–6.81

Table 5. Toxicity analysis.

Ligands	hERG	H-HT	DILI	Ames	ROA	Carcinogenicity	Respiratory
Pongaglabrone	0.026	0.236	0.958	0.272	0.306	0.94	0.789
Ovalichromene B	0.333	0.871	0.772	0.31	0.672	0.937	0.893
Pongachromene	0.026	0.941	0.982	0.45	0.12	0.95	0.884
Ponganone IV	0.073	0.776	0.58	0.068	0.936	0.591	0.917
3’-Methoxypongapin	0.017	0.362	0.98	0.261	0.144	0.907	0.797
Isopongachromene	0.025	0.9	0.958	0.232	0.461	0.941	0.926

Table 6. Docking affinity score of thymidine kinase protein with selected ligands.

Ligand	Binding affinity with thymidine kinase
Pongaglabrone	–8.1
Ovalichromene B	–8.5
Pongachromene	–8.5
Ponganone IV	–8.3
3’-Methoxypongapin	–8.2
Isopongachromene	–8.5

Visualization

From the 6 ligands that show high binding affinity with targeted protein, the top 3 ligands showing the least binding are selected for visualization. The 2D and 3D interaction diagrams are shown below.

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Figure 3 shows the molecular interaction between ovalichromene B with protein thymidine kinase. The ligand interacts with protein by establishing bonds with respective amino acid residues as Thr, Gln, Ala and Arg., the bond distances are shown in Figure 3.

Figure 4 shows the molecular interaction between pongachromene with protein thymidine kinase. The ligand interacts with protein by establishing bonds with respective amino acid residues, such as Pro, Thr, Ala, and the bond distances are shown in Figure 4.

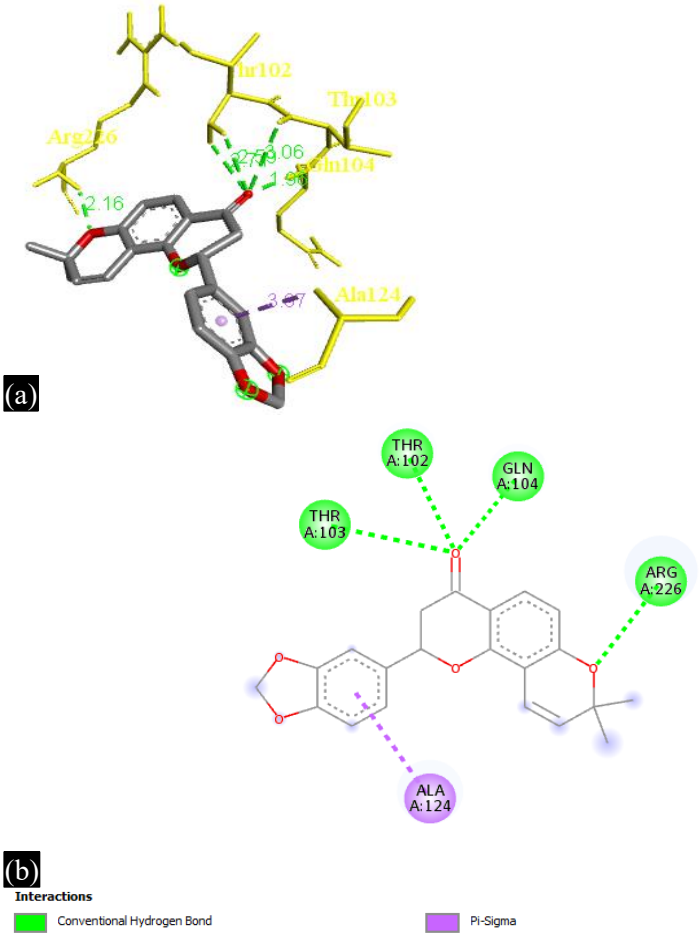
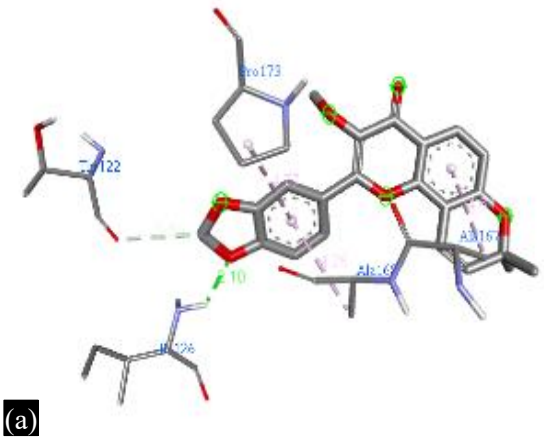


Figure 3. (a) 3D and (b) 2D diagram of Interaction between Ovalichromene B and protein Thymidine Kinase.



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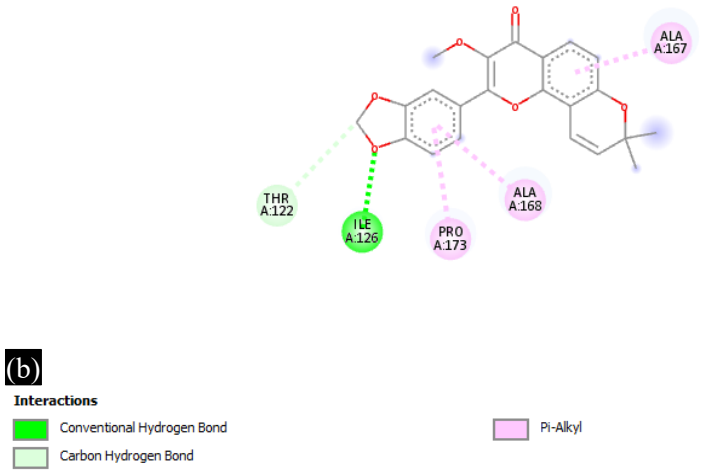

Figure 4. (a) 3D and (b) 2D diagram of Interaction between pongachromene and protein thymidine kinase.

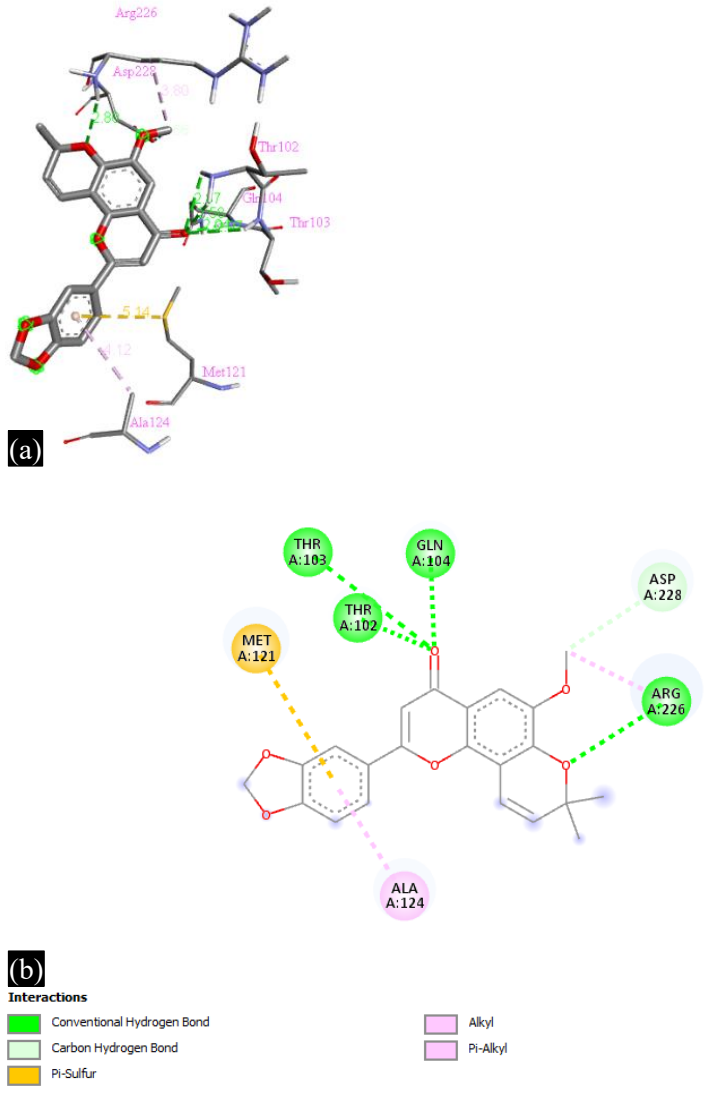

Figure 5. (a) 3D and (b) 2D diagram of Interaction between and protein isopongachromene and protein thymidine kinase.

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Figure 5 shows the molecular interaction between isopongachromene with protein thymidine kinase. The ligand interacts with protein by establishing bonds with respective amino acid residues, such as Thr, Ala, Arg, Asp, Met, and the bond distances are shown in Figure 5.

DISCUSSION

Approximately 3.7 billion people worldwide under the age of 50 (67%) are infected with herpes simplex virus type 1 (HSV-1). Most HSV infections are asymptomatic or go unrecognized, but when symptoms occur, they typically include painful blisters or ulcers that can recur. HSV-1 is primarily spread through contact with the virus present in sores, saliva, or surfaces around the mouth. Less frequently, it can be transmitted to the genital region through oral-genital contact, leading to genital herpes. The virus can also spread from oral or skin surfaces that appear normal, although the highest risk of transmission occurs when active sores are present. Individuals already infected with HSV-1 are not at risk of reinfection, but they can still acquire HSV-2. Both HSV-1 and HSV-2 are part of the Herpesviridae family, which has a distinctive structure consisting of four layers: a central double-stranded DNA core, surrounded by an icosahedral capsid, followed by a layer of tegument proteins, and an outer lipid bilayer envelope containing membrane proteins and glycoproteins.

Thymidine kinase (TK), an essential enzyme in nucleotide salvage pathways, catalyzes the conversion of thymidine (dT) to thymidylate (dTMP). TK plays a critical role in the replication cycle of herpes simplex virus type 1 (HSV-1). Upon infecting a host cell, HSV-1 must replicate its DNA to produce new viral particles, but it lacks the ability to replicate its DNA independently. Instead, HSV-1 depends on the host cell's machinery for DNA replication. The enzyme thymidine kinase, encoded by the HSV-1 genome, facilitates this process by phosphorylating external thymidine to generate thymidine monophosphate (TMP), which the virus incorporates into its DNA during replication. Since HSV-1 cannot synthesize certain nucleotides, especially thymidine, it relies on the host cell to provide these essential building blocks.

Antiviral medications like acyclovir, valacyclovir, and famciclovir are frequently used to treat HSV infections. These drugs are nucleoside analogs, which means they resemble the natural nucleosides that form the building blocks of DNA. However, they are designed to lack a 3' hydroxyl group, which is necessary for further DNA chain elongation. Once inside HSV-infected cells, these nucleoside analogs are selectively phosphorylated by the viral thymidine kinase (TK) enzyme. The absence of the 3' hydroxyl group in these analogs doesn't hinders their initial phosphorylation by TK. The phosphorylated versions of these drugs serve as substrates for the viral DNA polymerase. However, once integrated into the growing DNA chain, they lack the necessary 3' hydroxyl group for adding additional nucleotides. As a result, this causes chain termination and halts viral DNA replication. By inhibiting viral replication, these drugs help reduce the severity and duration of symptoms associated with HSV infections, such as cold sores or genital herpes lesions. They also decrease the amount of virus shed from lesions, thereby reducing the risk of transmission to others.

Several studies have explored the antiviral properties of *Pongamia pinnata* extracts against different viruses. These studies suggest that certain compounds found in *Pongamia pinnata*, such as flavonoids and other phytochemicals, may exhibit antiviral effects. In traditional medicine systems like Ayurveda, *Pongamia pinnata* is used for various purposes, including wound healing, skin conditions, and as an anti-inflammatory agent. While these traditional uses may suggest potential benefits for conditions like herpes simplex virus infections, more scientific evidence is needed to support its efficacy specifically against HSV-1.

The results of the study suggest that the phytocompounds pongaglabrone, ovalichromene B, pongachromene, ponganone IV, 3'-methoxypongapin, and isopongachromene show the best binding with targeted protein Thymidine kinase. Especially the ovalichromene B, pongachromene, isopongachromene were found to be show high binding affinity (-8.5) towards the protein molecule.

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CONCLUSIONS

According to the results of this study, the derivatives of *Pongamia pinnata* were discovered to show the best binding with the Thymidine kinase. Thus, the study suggests that these phytocompounds could be used in the treatment of HSV1 infections.

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