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Investigation of *Selaginella bryopteris* leaf isoflavones against Japanese encephalitis Targeting NS3 Protein

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Abstract
Background: Japanese encephalitis (JE) is a clinical manifestation of encephalitis caused by the Japanese encephalitis virus (JEV). This virus induces irreversible neurological damage, hence imposing a considerable burden on public health and society. Neuroinflammation is the hallmark of JEV infection. The prolonged pro-inflammatory response is mostly due to microglial activation, ultimately leading to severe encephalitis. *Selaginella* bryopteris, often known as 'Sanjeevani,' is a medicinal plant highly esteemed in traditional medicine for its considerable therapeutic efficacy.
Aim: This study seeks to examine the effectiveness of *Selaginella bryopteris* flavonoids against NS3P to clarify their antiviral potential for Japanese encephalitis.
Method: *NS3P* was chosen as the target proteins in the current investigation. The bond was found using the Auto Dock software using a grid-based docking method. Compounds' 2D structures were generated, converted to 3D, and subsequently energetically lowered up to an arms gradient of 0.01 using the Merck Molecular Force Field (MMFF).
Result: Flavonoids of *S. bryopteris* found to be effective in JE and effectively binds to be target protein *NS3P* with binding energy -7.74 & -7.91 kcalmol^{-1} for amentoflavone & Lanaroflavone respectively.
Conclusion: The finding of the *In-Silico* molecular docking showed that both lead compound is effective binds & inhibitory action on target protein. The molecular docking of ligands like amentoflavone & Lanaroflavone with *NS3P* receptor revealed that it has exhibited the chemical interaction with the amino acids in the active pockets.

Keywords: *S. bryopteris*, molecular docking, *NS3P*, amentoflavone & Lanaroflavone

1. Introduction
A plethora of studies has shown that medicinal plants exhibit antiviral properties. The extract of Andrographis paniculata demonstrates antiviral activity against many viruses, including influenza, herpes simplex virus, and human immunodeficiency virus (HIV). The extract of Echinacea purpurea demonstrates antiviral efficacy against many viruses, including influenza, herpes simplex virus, and respiratory syncytial virus. In addition to their antiviral properties, medicinal plants offer further advantages, including immunomodulatory and anti-inflammatory activities, and are generally considered to have less side effects than conventional antiviral drugs. [1].
Japanese encephalitis (JE) is a clinical manifestation of encephalitis caused by the Japanese encephalitis virus (JEV). This virus induces irreversible neurological damage, hence imposing a considerable burden on public health and society. Neuroinflammation is the hallmark of JEV infection. The prolonged pro-inflammatory response is mostly due to microglial activation, ultimately leading to severe encephalitis. The scientific community is continually striving to understand the cellular and molecular mechanisms underlying JEV neuro-invasion and inflammatory processes. [2].
Japanese encephalitis (JE) is a serious vector-borne viral encephalitis that is widespread worldwide, especially in Asia, the Western Pacific region, and northern Australia. Over 3 billion individuals inhabit nations impacted by Japanese Encephalitis epidemics and/or endemicity. Annually, an estimated 67,900 cases of Japanese Encephalitis (JE) are projected throughout 24 nations, with merely 10,426 cases recorded in 2011.The mortality rate for Japanese Encephalitis ranges from 20% to 30%, whereas neurological or mental sequelae occur in 30% to 50% of survivors. [3-7]. Japanese encephalitis (JE) results from infection with the Japanese encephalitis virus (JEV), categorized within the JEV serogroup of the genus Flavivirus, family Flaviviridae.JEV has a single-stranded, positive-sense RNA genome around 11 kb long. The JEV virion consists of seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins: nucleocapsid or core protein (C),

non-glycosylated membrane protein (M), and glycosylated envelope protein (E).The principal vector for JEV transmission is the Cx. mosquito, specifically Cx. tritaeniorhynchus, whereas the main vertebrate amplifying hosts are pigs and wading birds.[8].

JE is called Zoonotic Disease?

JE is mostly a zoonotic disease. Pigs and birds, particularly members of the Family Ardeidae (including cattle egrets and pond herons), act as natural hosts. The virus is generally maintained in the enzootic cycle and presents as localized outbreaks under specific ecological conditions. Human infection arises from the spillover of pathogens from the zoonotic cycle. At low vector density, the virus disseminates within the ardeid bird-mosquito-ardeid bird cycle. With the commencement of the monsoon season and the heightened presence of mosquito breeding sites, including rice fields and irrigation canals, the vector population expands swiftly. The virus is spread from wild birds to peridomestic birds via vector mosquito species, subsequently affecting mammals such as cattle and pigs, and ultimately infecting people.

Epidemiological patterns

Two epidemiological patterns of Japanese Encephalitis (JE) are recognized: epidemic and endemic. Epidemic patterns predominantly noted in northern regions (Bangladesh, Bhutan, People's Republic of China, Taiwan, Japan, South Korea, North Korea, Nepal, northern Vietnam, northern India, northern Thailand, Pakistan, and Russia) demonstrate typical seasonal characteristics accompanied with intermittent outbreaks. Endemic patterns noted in southern regions (Australia, Burma, Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Papua New Guinea, Philippines, Singapore, southern Vietnam, southern Thailand, southern India, Sri Lanka, and Timor-Leste) occur sporadically throughout the year.[9].

Predominance of JE in India

JE was first recognized via a serological survey in the 1950s. The inaugural epidemic of Japanese Encephalitis was recorded in West Bengal in 1973, soon succeeded by incidents in the southern, eastern, and western states. Japanese Encephalitis (JE) was first recorded in Uttar Pradesh, the principal epidemic area for JE in northern India, in 1978. In 2005, a notable outbreak of Japanese Encephalitis occurred in Uttar Pradesh, leading to 5,700 cases and 1,315 deaths. The patients exhibited severe clinical symptoms, resulting in a 34% in-hospital mortality rate at one facility. Monitoring of hospital-based acute encephalitis syndrome (AES) in northern and northeastern India revealed that over 25% of cases were positive for Japanese Encephalitis (JE), primarily impacting youngsters. The anticipated incidence rate of JE was 15 per 100,000 in 5-9-year-olds in Tamil Nadu, a southern state in India. The infection incidence of JEV reached 70.7% among the patients.Sixty-seven laboratory tests revealed that occurrences of JE occurred throughout the year, with a heightened frequency during the wet season. A systematic strategy commenced in this JE epidemic area in 2006 with the LAV-SA 14-14-2. The Cx. vishnui subgroup, in conjunction with Cx. tritaeniorhynchus, Cx. pseudovishnui, and Anopheles subpictus, were the principal and secondary mosquito vectors in India. The minimum infection rate of JEV in mosquitoes has remained low at 0.8 annually from 1996 to 2004. [10-32].

Selaginella bryopteris, referred to as 'Sanjeevani,' is a medicinal plant widely valued in traditional medicine due to its significant therapeutic potential.

Fig 1: *Selaginella bryopteris*

The primary bioactive compounds in *Selaginella* species are bioflavonoids, which are the most prominent among them. All vascular plants intrinsically contain biflavonoids, compounds having diverse advantageous biological and pharmacological properties. [33]. The ethnic groups are utilized in the prevention and treatment of numerous ailments, including spermatorrhoea, constipation, colitis, fever, venereal diseases, urinary tract infections, epilepsy, leucorrhoea, beri-beri, and cancer. [34Its capability to treat wounds, menstrual bleeding, uterine disorders, and other internal injuries, along with its antibacterial, antifungal, antiviral, antioxidant, anticancer, wound healing, anti-inflammatory, memory-enhancing, antistress, antiprotozoal, and antihyperglycaemic activities, [35]

***In-Silico* validation of S.bryopteris leaf active compound by Molecular docking**

Selection of Lead molecules

The phenolic compounds “flavonoids” are found in good amount within the *Selaginella* in the form of biflavonoids. These secondary metabolites are keen to show potent activity *viz*., antitumor, anti-malarial, anti-allergic, anti-thrombotic, anti-inflammatory, anti-hypertensive, antibacterial, antioxidant, anti-hepatotoxic, estrogenic and antiviral [36]. They are polyphenolic compounds including flavones, flavonols, flavon-3-ols, flavonones, isoflavones and anthocyanins with low molecular weight. Flavonoids worked as vitamin C enhancer which eventually functions as antioxidants. As per literature survey S.bryopteris leaves contains Amentoflavone, 2,3-dihydroamentoflavone, 2",3"-dihydroamentoflavone, tetrahydroamentoflavone, 2,3-dihydrohinokiflavone, 2",3"-dihydrohinokiflavone, tetrahydro hinokiflavone, tetra-O-methyl-hinokiflavone, lanaroflavone, sciadopitysin and sequoiaflavone as active flavonoids [37].

Amentoflavone ($C_{30}H_{18}O_{10}$; 4′,5,7-trihydroxyflavone)-(3′→8)-(4′,5,7-trihydroxyflavone); is a biflavonoid of apigenin (3′,8″-bis-apigenin, didemethyl-ginkgetin). Amentoflavone has inhibitory effects on drug resistant variants of HSV-1 and hepatitis C Virus. Amentoflavone inhibits coxsackievirus B3 viral replication by inhibiting fatty acid synthase (FAS) activity. It reduced viral nuclear transportation through cofilin-mediated F-actin remodeling and inhibits immediate early gene expression in the HSV[38].

Lanaroflavone is C-O-C-type biflavonoid and display a large range of biological properties. including antiviral activities which potently inhibits hepatitis B virus replication.

Taking consideration of previous antiviral potential of *Amentoflavone and lanaroflavavone* both were selected as lead compound for current investigation.

Selection of Target protein

The NS3 protein of the Japanese encephalitis virus (JEV) is a multifunctional protein that possesses protease, helicase, and nucleoside 5'-triphosphatase (NTPase) capabilities. NS3 helicase/NTPase appears to be a suitable target for antiviral drugs, as its enzymatic activity is crucial for viral genome replication, transcription, and translation [39]. The JEV NS3 protein exhibits protease activity in its N-terminal domain and functions as a binding site for the cofactor protein NS2B. NS3 possesses helicase activity in its C-terminal domain, which facilitates negative supercoiling (unwinding) of dsRNA during viral RNA replication [40].

Designing of *In-Silico* molecular docking

Molecular docking is an essential tool in structural molecular biology and computer-aided drug design. The objective of ligand-protein docking is to forecast the primary binding mode(s) of a ligand with a protein possessing a known three-dimensional structure. Effective docking methodologies proficiently explore high-dimensional spaces and employ a scoring formula that accurately evaluates potential dockings. Docking facilitates virtual screening of extensive chemical libraries, ranks the outcomes, and suggests structural hypotheses regarding the mechanisms by which ligands inhibit the target, proving essential in lead optimization.

The Japanese encephalitis virus (JEV) is a flavivirus that endangers over 50% of the global population. Vaccination can avert the disease; however, no specific antiviral medication is now available for clinical treatment, and the mortality rate associated with JEV can escalate to 60%. The C-terminus of non-structural protein 3 (NS3) in flavivirus encodes helicase and has been recognized as a prospective therapeutic target.

Molecular docking studies

Ligand Preparation

2D Structure of ligands like amenthoflavone and lanaroflavone were drawn using ChemSketch [41], the two-dimensional structures of the prepared ligands were converted into their 3-D structures optimized with 3D geometry. The optimized structures were saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligands were given below:

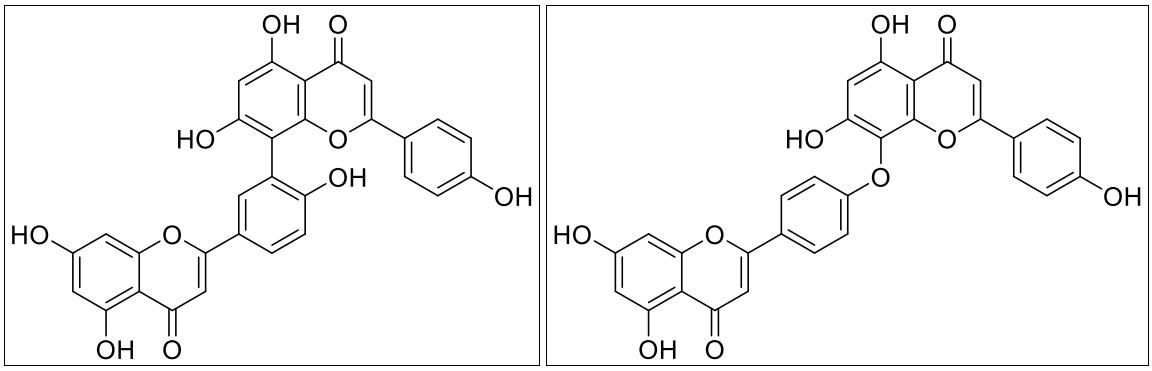


Fig 1: 2D structure of amenthoflavone and lanaroflavone

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.514 Å and No. of points considered are 40, 40 and 40 points in the x, y, and z dimensions and 7.904, -2.396 and 17.553 as x, y, z centers [42-43].

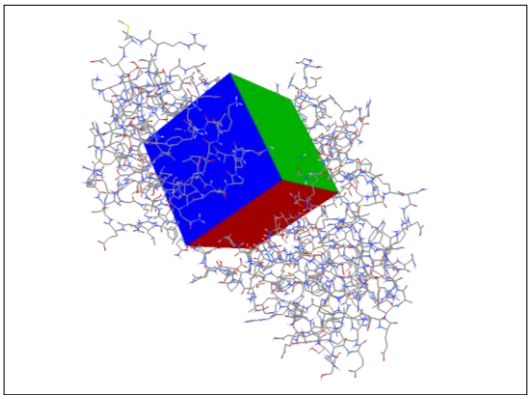


Fig 2: Grid box covering all active sites in NS3P helicase enzyme of Japanese encephalitis virus

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [44-45].

Crystal structure

The crystal structure of the protein consisting of NS3P helicase enzyme of Japanese encephalitis virus is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (2z83.pdb) registered in the Protein data bank was used [46-48].

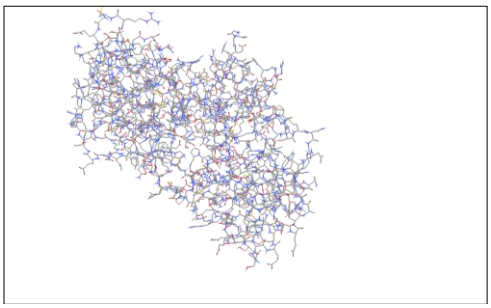


Fig 3: Crystal structure of NS3P helicase enzyme of Japanese encephalitis virus (PDB ID-2z83)

Processing of Protein

The downloaded receptor protein is having two chains, i.e. chain A, and B. Out of these two chains, chain B was selected for experimental purpose and other chains were removed from it. The bound ions were separated from the macromolecular complex by using software Chimera [49].

Molecular Docking Simulation Studies

Docking of ligands like amenthoflavone and lanaroflavone against viral NS3P helicase enzyme of Japanese encephalitis virus was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [50-51].

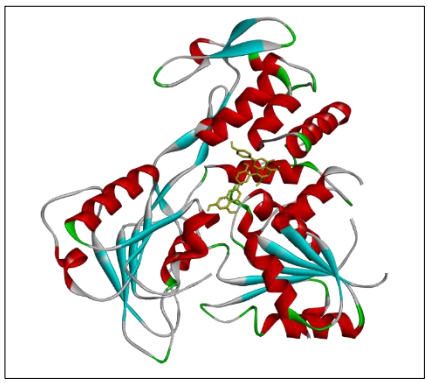


Fig 4: Binding mode of amenthoflavone within the active site of viral NS3P helicase enzyme of Japanese encephalitis virus.

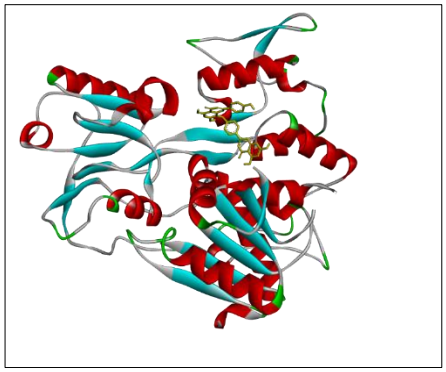


Fig 5: Binding mode of lanaroflavone within the active site of viral NS3P helicase enzyme of Japanese encephalitis virus.

Toxicity & ADME-T Studies

The ligand molecules *viz*. amenthoflavone and lanaroflavone were studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [52].

Result and Discussion

According to the literature review, the leaves of S. bryopteris contain the active flavonoids Amentoflavone, 2,3-dihydroamentoflavone, 2",3"-dihydroamentoflavone, tetrahydroamentoflavone, 2,3-dihydrohinokiflavone, 2",3"-dihydrohinokiflavone, tetrahydrohinokiflavone, tetra-O-methyl-hinokiflavone, lanaroflavone, sciadopitysin, and sequoiaflavone. Considering the prior antiviral potential of Amentoflavone and Lanaroflavone, both were chosen as lead compounds for *In-Silico* molecular docking studies.

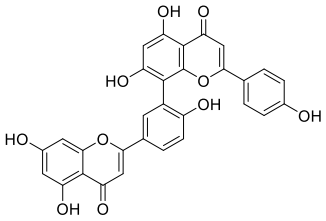
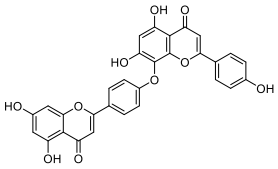
The NS3 helicase of flavivirus is categorized as a superfamily 2 helicase, commonly known as DExD (/H)-box helicase. Helicases within this family comprise three domains that facilitate NTPase and helicase functions. Domains I and II constitute a RecA-like domain that encompasses the motifs critical for RNA-binding and ATP hydrolysis. Domain 3, in conjunction with domains 1 and 2, constitutes a channel for the binding of single-stranded RNA and the unwinding of double-stranded RNA. In drug discovery, various overarching strategies have been suggested to inhibit NS3 helicase, encompassing the inhibition of NTP-binding, NTP-hydrolysis, RNA-binding, RNA-unwinding, and the linking of hydrolysis to unwinding. The NS3 protein was selected as the molecular target for the docking investigation.

The results of molecular docking of the lead molecule against various selected receptors indicated that amentoflavone and lanaroflavone have strong affinity for NS3P, with binding energies of -7.74 and -7.91 kcal mol^{-1} respectively (Table 1). The IC 50 values of amentoflavone and lanaroflavone demonstrated almost similar results. The 2D and 3D binding interactions of the lead bioactive against the designated receptor are illustrated in Figures 6-9. The drug likeness score was more or less similar i.e. 2 & 1.94 for amentoflavone and lanaroflavone respectively. The binding interaction of the selected molecule with the molecular target is demonstrated as follows:

Lead molecule	Vander waal's	Conventional hydrogen	C-H bounding	π-cation	π-Alkyl	π- π
Amentoflavone	Ala293,Met495, His 268,Leu538, Leu543,Asp542, Val601,Ala607, Thr225,Phe289, ILE 411	Glu491, Asp291, Val545, Arg226, Asp430, Arg600	-------	-----	Pro544	Pro292,
Lanaroflavone	Leu444,Arg338, Met495,Arg539, Ala293,Pro292, Val600	Arg600, Asp542, His268, Leu 538	Trp610	Asp624	Ala607, Val545, Ala603	Leu543

The pharmacokinetic profiling of the amentoflavone and lanaroflavone ligand had revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like mutagenic, reproductive effects, irritant effect, and tumorogenic properties. The pharmacokinetic and toxicity profiling results of amenthoflavone and lanaroflavone were shown in figure 10-11 & table 2-4. Theoretically, all the ligand molecules have shown encouraging docking score. All compound followed Lipinski rule and showed all most similar drug likeness score.

Table 1: Results of docking of ligands like amentoflavone and lanaroflavone against viral NS3P helicase enzyme of Japanese encephalitis virus.

S. No	Compound Name	Structure	Binding Energy (Kcal/mole)	KI	IC50
1	Amentoflavone		-7.74	13.063	0.080
2	Lanaroflavone		-7.91	a13.350	0.079

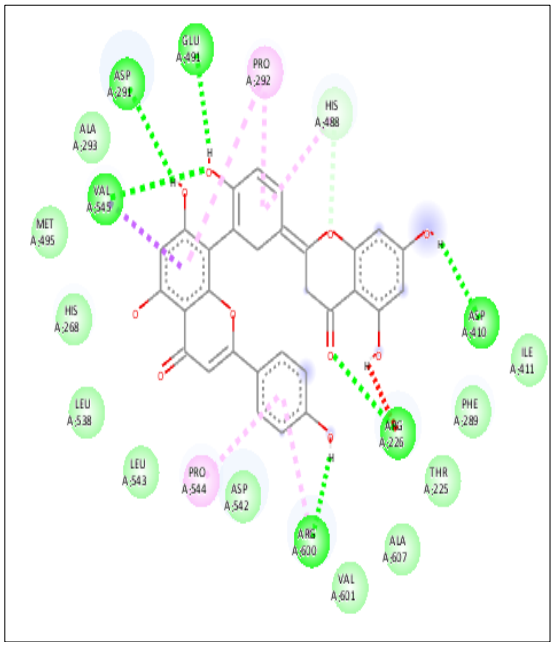


Fig 6: Two-dimensional binding mode of amentoflavone within the active site of viral NS3P helicase enzyme of Japanese encephalitis virus.

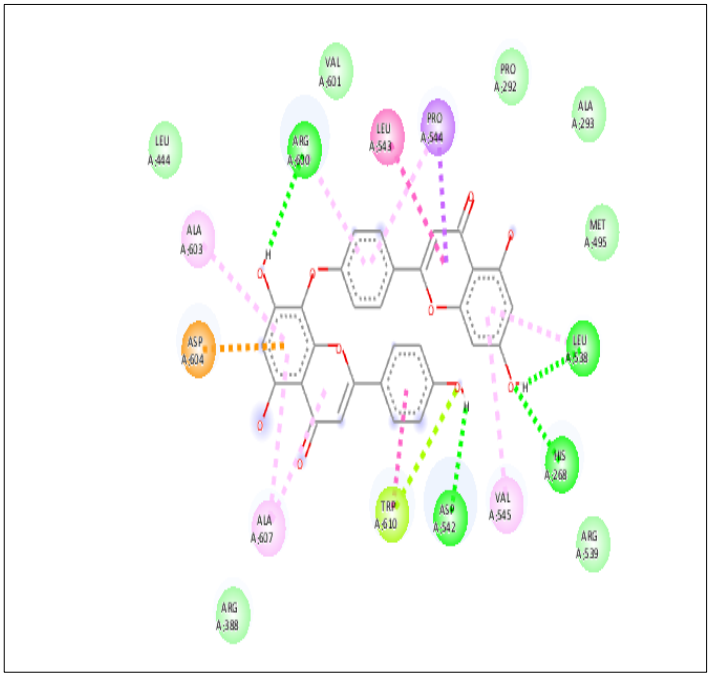


Fig 7: Two-dimensional binding mode of lanaroflavone within the active site of viral NS3P helicase enzyme of Japanese encephalitis virus.

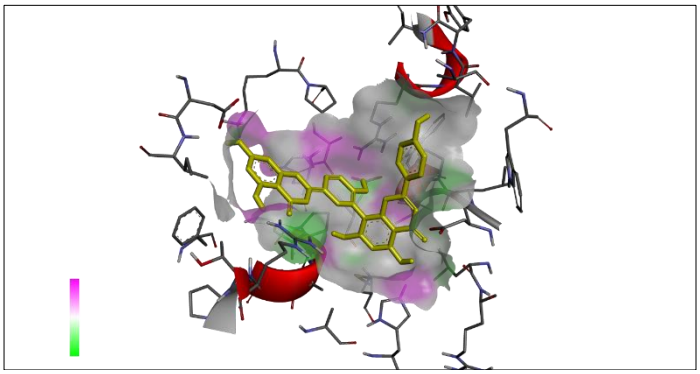


Fig 8: Three-dimensional binding conformation of amentoflavone within the active site of viral NS3P helicase enzyme of Japanese encephalitis virus.

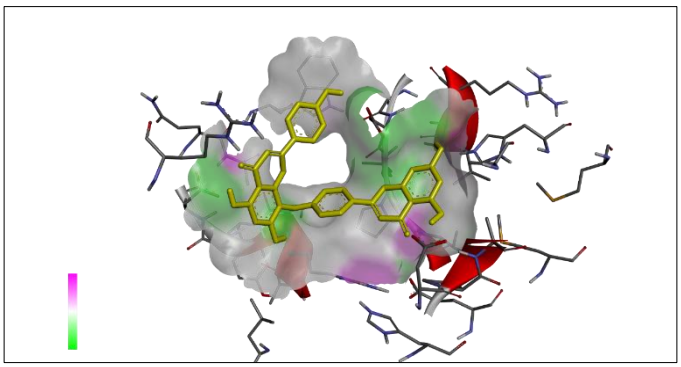
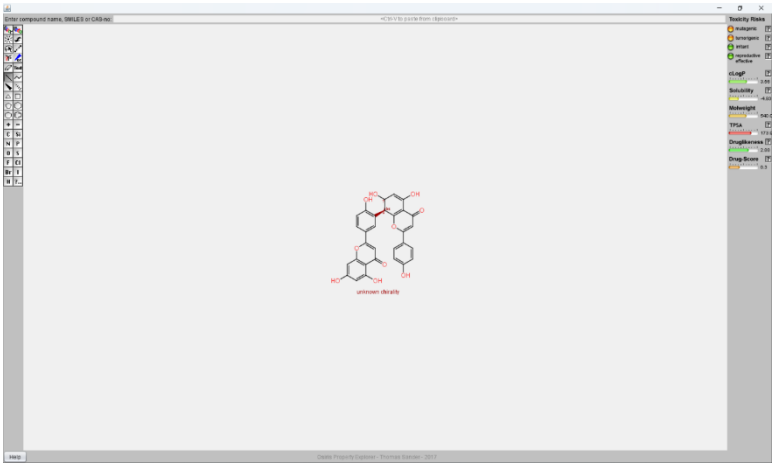


Fig 9: Three-dimensional binding conformation of lanaroflavone within the active site of viral NS3P helicase enzyme of Japanese encephalitis virus.



Figa 10: Pharmacokinetic and toxicity profiling of amentoflavone.

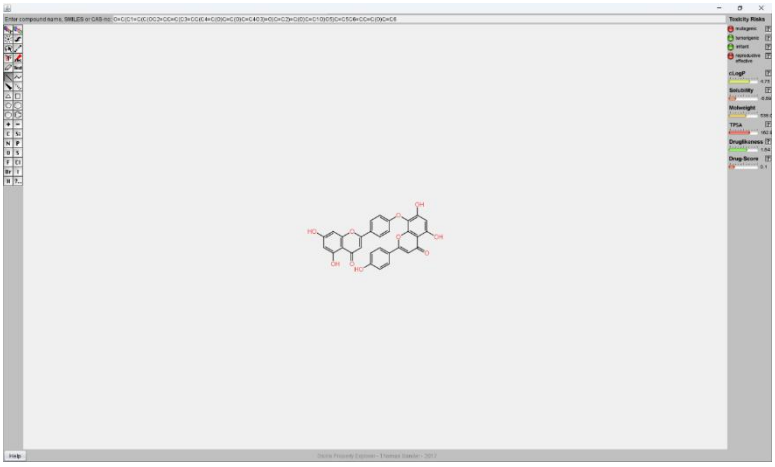


Fig 11: Pharmacokinetic and toxicity profiling of lanaroflavone

Table 2: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	Tumorigenic	Irritant	Reproductive effectivity
Amentoflavone	No	No	Yes	No
lanaroflavone	No	No	No	No

Table 3: Lipinski Properties of lead molecules

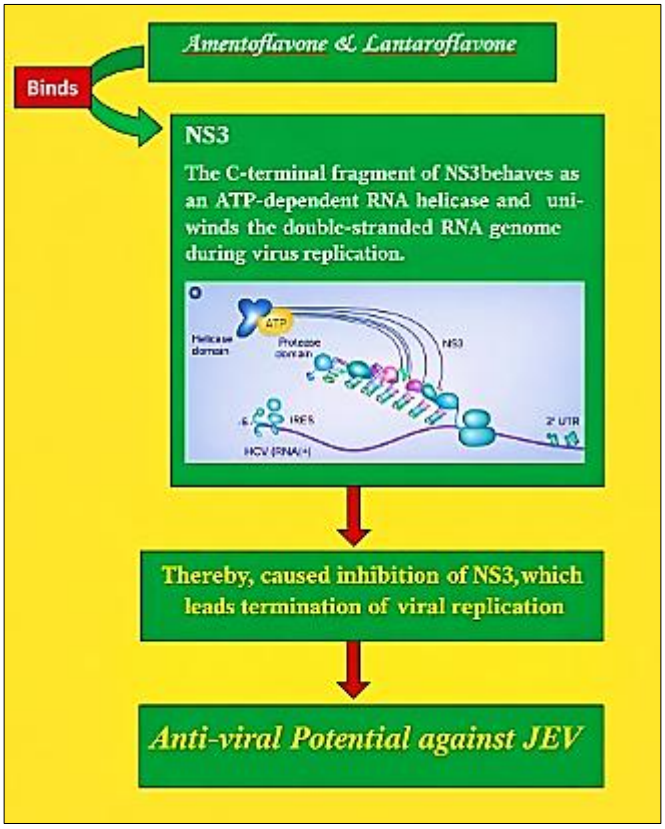
Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Amentoflavone	3	-4.03	538	173	2	0.3
Lanaroflavone	4.75	-6.09	537	102.6	1.94	0.1

Table 4: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar	H bond acceptor
Amentoflavone	Yes	6	5
Lanaroflavone	Yes	10	10

Conclusion

The literature analysis indicates that *S. bryopteris* leaves contain different isoflavone derivatives. Amentoflavone and Lanaroflavone were selected as lead molecules for molecular docking study. The molecular docking study showed that both the lead molecules had inhibitory action on NS3 protein and there by caused interrupted the viral replication of JEV. *The proposed mechanism of action of selected isoflavones against NS3 JEV showed as*



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