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MOLECULAR DOCKING STUDIES OF NOVEL HERBAL DRUG DEVA CHOORNAM ON HUMAN IMMUNE DEFICIENCY VIRUS (HIV) PDB 1HNV REVERSE TRANSCRIPTASE ENZYME

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Keywords: *HIV, HIV-1 reverse transcriptase, Siddha medicine, Deva Choornam, Molecular docking.*

Abstract

Background: Acquired Immuno Deficiency Syndrome (AIDS) is the most serious pandemic health problem that is affecting globally. The main causative organism, Human Immuno Virus (HIV) and its key enzyme HIV-1 reverse transcriptase (1HNV) is the main area of research for finding a novel drug for its management. In structure-based drug design concerned with Anti HIV Drugs, Computational methods like molecular docking (MD) is most commonly observed for binding confirmation of ligand molecules with that of target sites in 1HNV. Amino acids such as Leucine, Valine, Tyrosine, Phenylalanine, Tryptophan, Lysine are the core residue involved in mediating the RTof Human immunodeficiency virus (HIV) PDB- IHNV enzyme activity. Binding of lead compounds with this core residue may inhibit the enzyme activity. Deva Choornam (DC) is an unique Siddha herbal formulation that is well acclaimed for its Anti HIV property. The lead molecules from this formulation were interpreted for its 1HNV receptor inhibitor activity.

AIM and Objectives: MD studies of DC to find the lead molecular interaction on IHNV Receptor.

Methodology: Docking calculations were carried out using Auto Dock 4. Gasteiger partial charges were added to the ligand atoms Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (*Solis and Wets, 1981*). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking

Results and Conclusion: The compounds present in DC like such as Eugenol, Kaempferol, Atlantone, Apigenin and Pinene has maximum interactions with when compared to that of the standard Nevirapine. Hence, these compounds possess promising RTenzyme inhibition activity.

Introduction

Inspite of advancement in medical science, the search for novel drug therapies for HIV is still in progress. Acquired Immuno deficiency Syndrome (AIDS) is the leading cause of mortality either due to the primary infections or it's after effect complications. According to one source, in each year approximately 2.1 million peoples die with this pandemic and 2.5 million new cases appear chiefly because of the failure in its prevention or to improve the quality of life (QOL) of the sufferers.[1] There is greater prevalence of HIV victims in Tamil Nadu, India and around 500,000 affected cases has been reported all over the state.[2]

There are atleast 30 Anti- HIV drugs used in Allopathic system which primarily targets the HIV virus enzyme called Reverse Transcriptase (RT). RT is the key component which plays multiple role in the completion of HIV

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replication cycle within the body.[3] The drug molecule which inhibits the RT receptors and further blocking the active viral replication is considered in the the core area of HIV research. HIV-1 RT inhibitors are used both for treatment of HIV infection and for prevention of mother-to-child transmission of HIV-1. [4]Amino acids such as Leucine (LEU), Valine (VAL), Tyrosine (TYR), Phenylalanine (PHE), Tryptophan (TRY), Lysine (LYS) are the important residues which have strong influence on RT which leads to increase in viral load by multiplication of its genome. Binding of lead/ drug with these core amino acids by forming hydrogen bond will hinder the functions of this enzyme and thereby it halts the generation of cDNA from RNA preventing the virus multiplication. There are numerous studies which reports the development of RT inhibitors through computer aided designs and out of this structure based molecular docking is the key element of practice today.[3]

Siddha medicine describes the entire clinical picture of sexually transmitted diseases under the classification of 20 varieties of *megha noikal*.[5] Numerous herbal or herbomineral formulations are exclusively given for HIV and Deva Choornam (DC) is one among the herbal preparation which has been successfully practiced. Cedrusdeodara, Alpiniagalanga and Cinnamomumtamala are the main ingredients of this herbal combination.[2] The lead molecules from this formulation were interpreted for its 1HNV receptor inhibitor activity. This may help in wider acceptability of DC as an efficient Anti HIV herbal formulation.

Aim and Objectives

The primary aim of this study was to carry out Molecular Docking (MD) studies of DC to find the lead molecular interaction on IHNV Receptor.

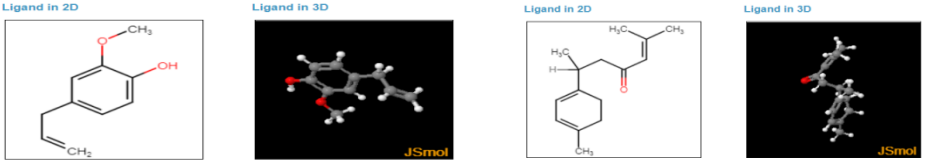
Methodology

Lead Molecules from DC

Docking calculations were carried out for the compounds retrieved such as Eugenol, A-Pinene, Atlantone, Myrcene, Luteolin, Apigenin, Kaempferol and their respective standard Nevirapine [3] against target protein model (Table. 1 & Fig A). The ligand molecular properties are illustrated in Table. 2.

Table. 1 List of Lead Molecules taken from each Herb

S.No	**Name of the Herb**	**Phytocomponents**
1.	*Cinnamomumtamala*	Eugenol A-Pinene
2.	*Cedrusdeodara*	Atlantone
		Myrcene
3.	*Alpiniaofficinarum*	Luteolin
		Apigenin
		Kaempferol



EUGENOL **ATLANTONE**

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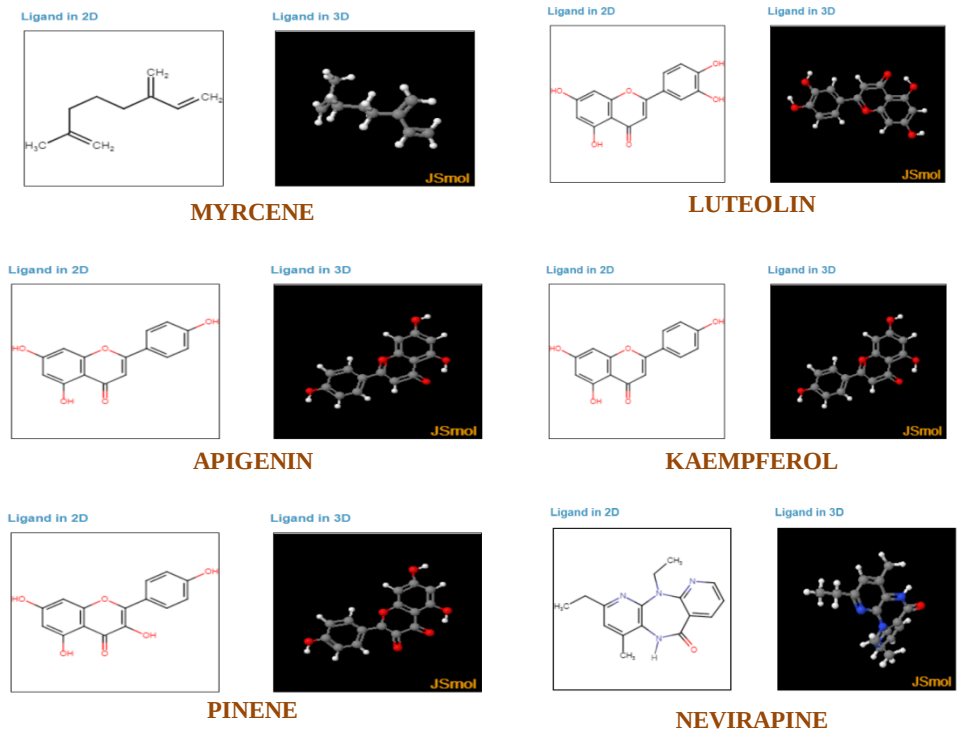

Fig: A. 2D And 3D Structure Of Lead Compounds

Table. 2 Ligand Properties of the Compounds selected for docking

Compound	Molecular Formula	Molar weight g/mol	H Bond Donor	H Bond Acceptor	Rotatable bonds	Log P
Eugenol	$C_{10}H_{12}O_2$	164.204 g/mol	1	2	3	2
Atlantone	$C_{15}H_{22}O$	218.34 g/mol	0	1	4	4.1
Myrcene	$C_{10}H_{16}$	136.238 g/mol	0	0	4	4.3
Luteolin	$C_{15}H_{10}O_6$	286.239 g/mol	4	6	1	1.4
Apigenin	$C_{15}H_{10}O_5$	2 0.24 g/mol	3	5	1	1.7
Kaempferol	$C_{15}H_{10}O_6$	286.239 g/mol	4	6	1	1.9
Pinene	$C_{10}H_{16}$	136.238 g/mol	0	0	0	2.8
Nevirapine	$C_{15}H_{14}N_4O$	266.304 g/mol	1	4	1	2

Target details and Receptor Structure

Crystalline structure of the target protein RT of Human immunodeficiency virus (HIV) PDB 1HNV was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atom were been added. Different orientation of the lead molecules with respect to the target protein was evaluated by Autodock program and the best dock pose was selected based on the interaction study analysis.

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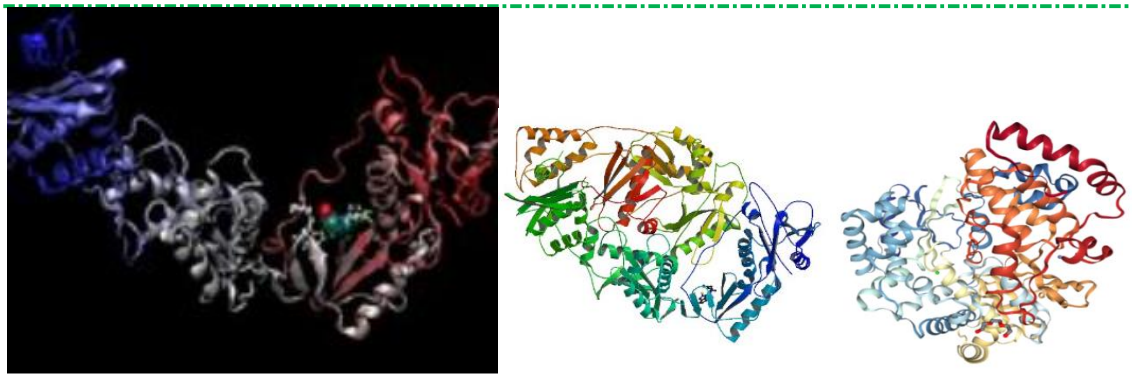

Fig B. 2. HIV- Reverse transcriptase

Tool for Study

Docking calculations were carried out using Auto Dock 4. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (*Morris, Goodsell et al., 1998*). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (*Morris, Goodsell et al., 1998*). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (*Solis and Wets, 1981*). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

Results

The compounds of DC such as Eugenol, Kaempferol, Atlantone, Apigenin and Pinene has maximum interactions with when compared to that of the standard Nevirapine. The Summary of the molecular docking studies of the lead compounds and standard Nevirapine against 1HNV and its amino acid binding interactions has been tabulated (Table. 3 & 4, Fig C)

Table. 3 Summary of the molecular docking studies of the DC lead compounds against 1HNV

Compounds	Binding Free energy Kcal/mol	Inhibition constant Ki µM (*mM)(**nM)	Total Intermolecular energy Kcal/mol	Total Interaction Surface
Eugenol	-4.76	321.67	-5.28	508.14
Atlantone	-7.34	4.17	-8.31	670.58
Myrcene	-4.7	357.74	-6.08	493.59
Luteolin	-5.63	74.97	-5.88	685.72
Apigenin	-5.54	86.69	-6.06	653.35
Kaempferol	-6.16	30.72	-6.17	687.82
Pinene	-6.08	35.03	-6.08	420.12
Nevirapine	-7.76	2.06	-8.29	727.52

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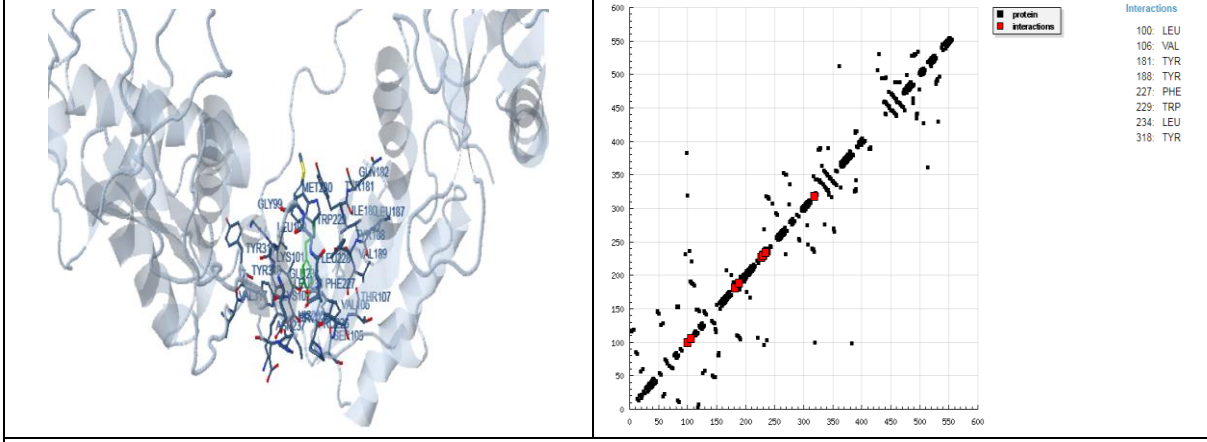
Table. 4. Amino acid Residue Interaction of Lead and Standard against RT of HIV -PDB- IHNV

No of Interactions	Lead / Standard	Amino Acid Residue- Binding								
5	Eugenol	100 LEU	106 VAL	181 TYR	188 TYR	227 PHE	229 TRP	234 LEU	318 TYR	
4	Atlantone	100 LEU	181 TYR	188 TYR	227 PHE	234 LEU	318 TYR			
3	Myrcene	100 LEU	103 LYS	106 VAL	188 TYR	227 PHE	234 LEU	318 TYR		
2	Luteolin	100 LEU	103 LYS	179 VAL	181 TYR	188 TYR	234 LEU	318 TYR		
3	Apigenin	95 PRO	100 LEU	181 TYR	188 TYR	229 TRP	234 LEU			
4	Kaempferol	101 LYS	103 LYS	106 VAL	179 VAL	181 TYR	188 TYR	227 PHE	234 LEU	318 TYR
3	Pinene	95 PRO	100 LEU	181 TYR	188 TYR	229 TRP	234 LEU			
5	Nevirapine	101 LYS	103 LYS	181 TYR	188 TYR	227 PHE	229 TRP	234 LEU	318 TYR	

LEU= Leucine VAL = Valine TYR = Tyrosine PHE = Phenylalanine TRP = Tryptophan LYS = Lysine



Eugenol With RT

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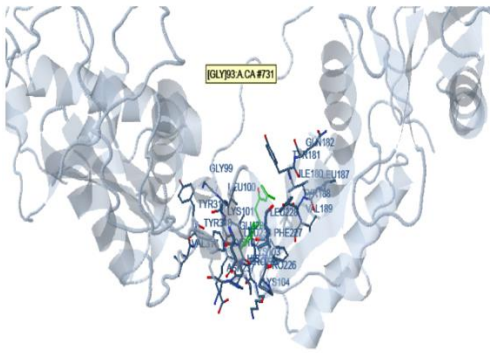
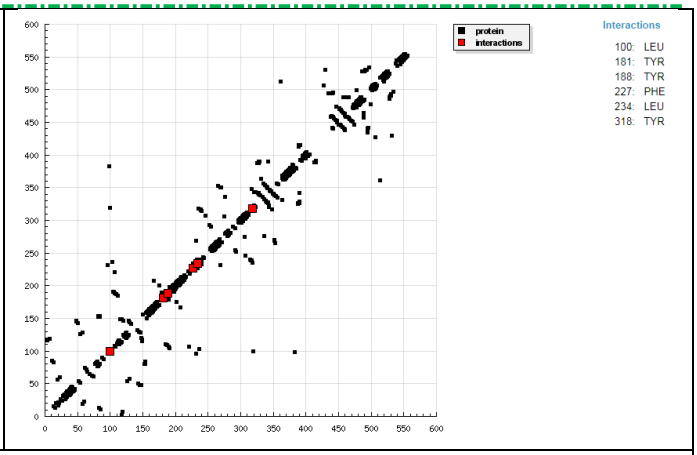
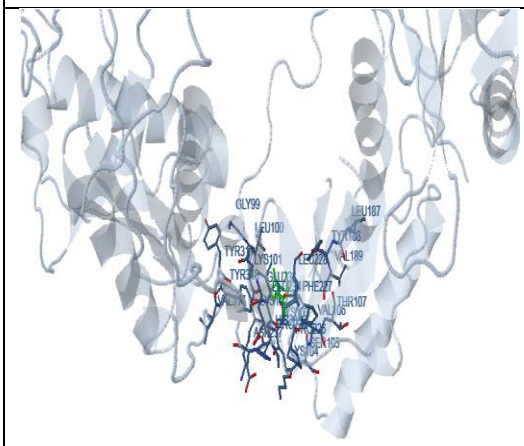
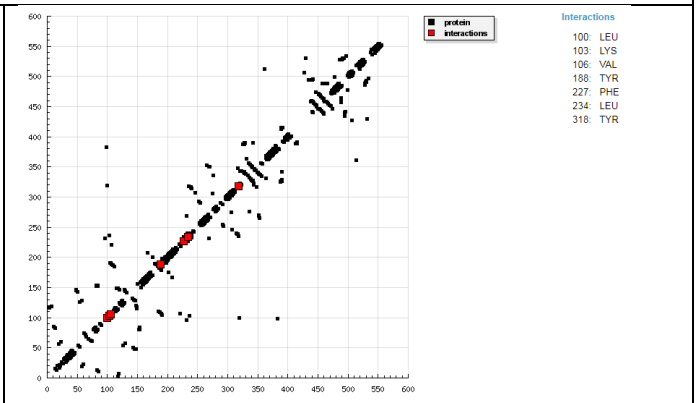


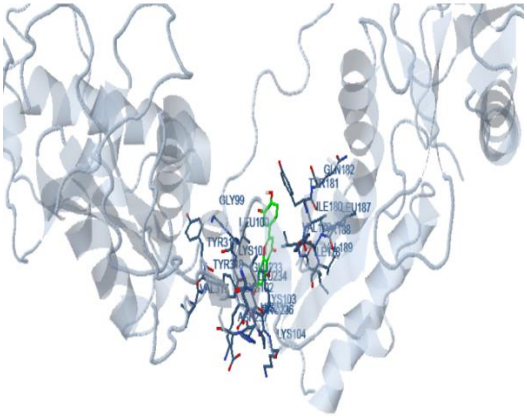


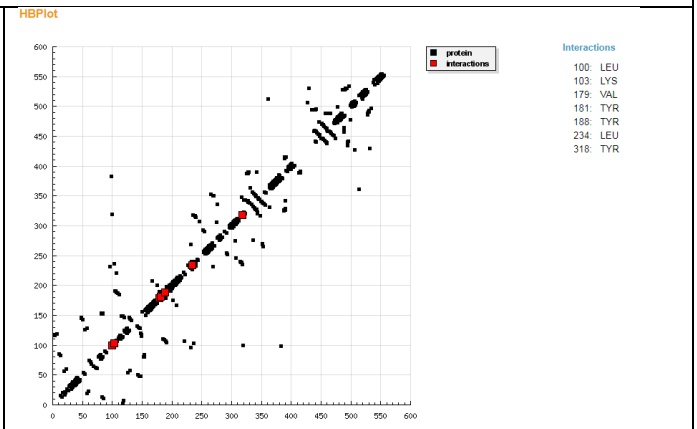
Atlantone with RT





Myrcene With RT





Luteolin With RT

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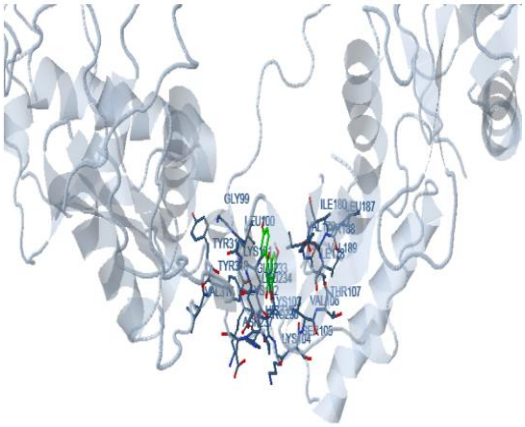
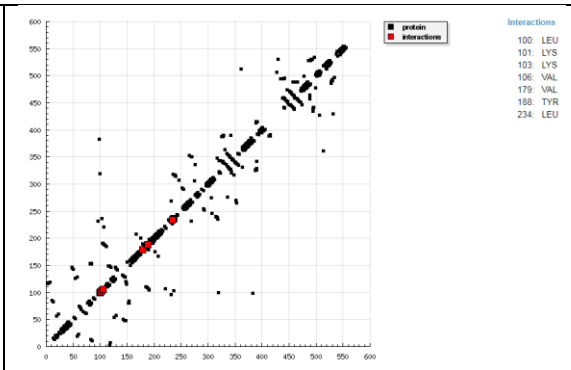
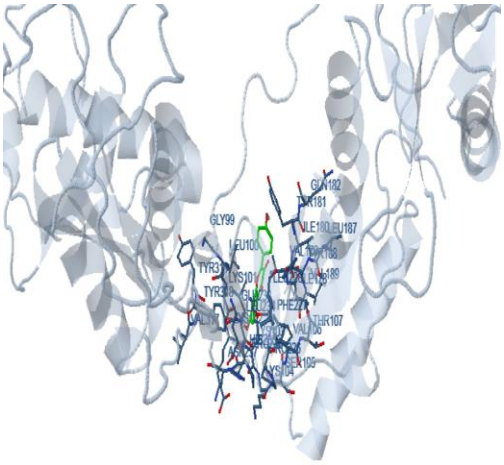
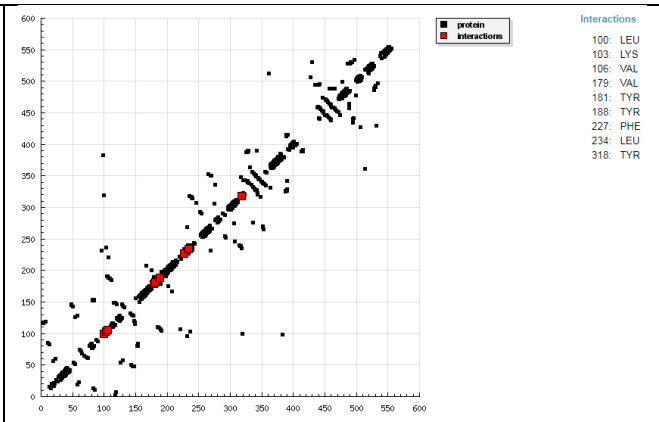


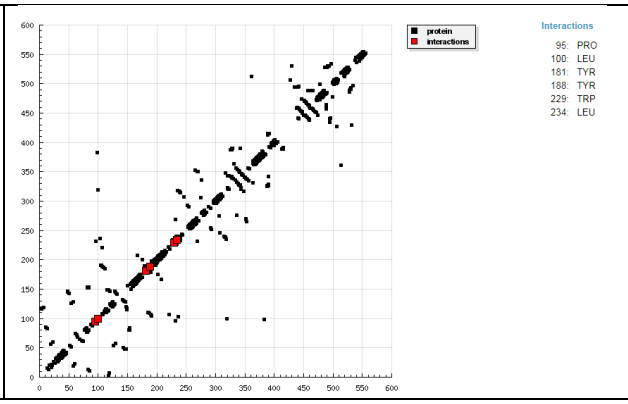


Apigenin With RT





Kaempferol With RT



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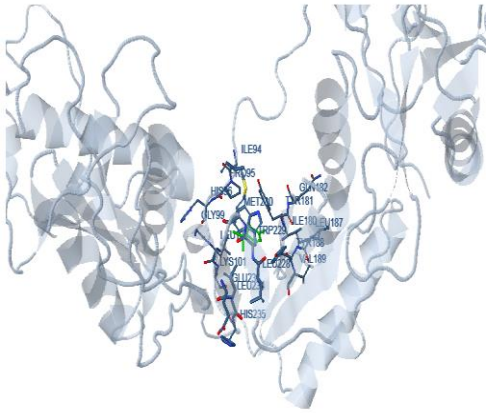
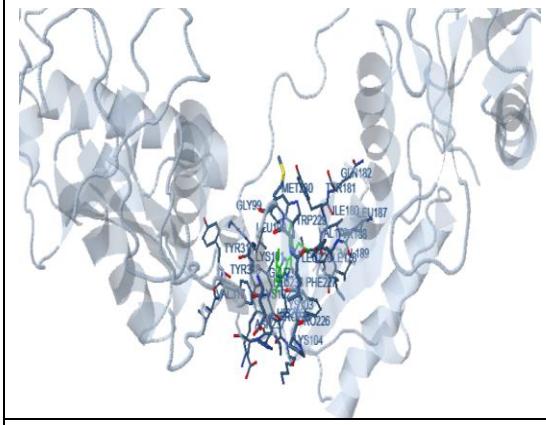
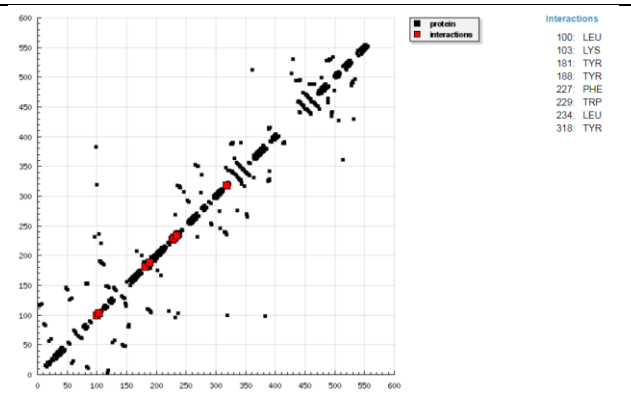


Pinene with RT





Nevirapine with RT

Fig. C. Amino acid interactions of Lead molecules of DC and standard

Discussion

Molecular docking is one of the most frequently used computational methods for drug design. Its prediction ability in confirming the interaction of molecule ligands with that of target binding site is reliable with considerable accuracy. They also perform predictions on binding energetics and ranks the docked compounds depending on the binding affinities of ligand molecules with receptor complexes.[6-8]

Deva Choornam is a clinically acclaimed herbal formulation indicated for the management of HIV. [9] The lead compounds of Deva Choornam has been studied for its RT enzyme inhibition activity through Molecular Docking methods and all the compounds shown marked interactions with the RT as when compared with standard Nevirapine. The compound Eugenol shown maximum no: of interactions with aminoacid Tyrosine, Tryptophan and Phenylalanine.The present molecular docking study results reveal that Eugenol has specific interactions with aminoacid residues 181TYR, 188TYR, 227 PHE, 318TYRincluding the highly conservedresidueTRP229 similar to that of the standard Nevirapine. Eugenol and its derivatives are natural flavanoids that have been identified in various aromatic plants. A previous Study by Behbahani et al., (2013) showed that Eugenol and its derivates significantly increased peripheral blood mononuclear cells (PBMC) and showed anti-HIV-1 activity with inhibition

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of viral replication. [10]The other two phytocompounds Kaempferol and Atlantone showed similar interactions of binding with aminoacid residues when compared with standard Nevirapine except for 229 TRP . In a study by Behbahani M et al.,(2014) Antiviral activity of kaempferol and kaempferol-7-*O*-glucoside as isolated compounds from *S. securidaca* was evaluated by the HIV-1 p24 Antigen kit which confirmed that addition of 50 µg/ml of the kaempferol added before and during the initial stages of infection showed strongest HIV proliferation inhibition. [11] The study results showed that 100 µg/ml kaempferol and kaempferol-7-*O*-glucoside inhibited HIV-1 multiplication with an inhibition rate of 82 ± 3.1% and 95 ± 1.2%, respectively.In review of various studies all the 6 compounds selected for docking had validated pharmacological background that supports its Anti HIV property. In a synergetic mode the compounds may check opportunistic infections which is one of the leading complications of AIDS. [12]

Table. 5 Pharmacological significance of lead molecules from DC

S.No	Name of the Compound	Pharmacological Activity
1.	**Eugenol**	Anti-Viral, Anti-herpetic, candidicide, Anti staphylococcic, fungicide, Anti-bacterial, Anti-inflammatory, Anti-oxidant, hepato protective, Anti-septic.
2.	**A-Pinene**	Anti-Viral, Anti-bacterial, Anti-flu, Antipneumonic, Anti staphylococcic, Anti-septic, Anti-inflammatory.
3.	**Atlantone**	Anti Oxidant, Anti tumor, Anti fungal
4.	**Myrcene**	Anti-bacterial, Anti-oxidant, fungicide.
5.	**Luteolin**	Anti Hiv, Anti-Viral, Anti-herpetic, Anti-bacterial, Anti-histaminic,Anti-inflammatory, Anti-oxidant, Anti-polio, hepato protective.
6.	**Apigenin**	Anti Hiv, Anti-Viral, Anti-herpetic, Anti-bacterial, DNA protective, Anti-allergic, Anti-histaminic, Anti-inflammatory, Anti-oxidant.
7.	**Kaempferol**	HIV-RT-Inhibitor , Anti-Viral, Anti herpetic, Anti-bacterial, Anti-allergic, Anti histaminic, Anti-oxidant, Anti septic.

Conclusion

Deva Choornam, a polyherbal formulation, is given successfully for HIV conditions with its outcome of improving the general health, digestion, and overall wellbeing of the subject. Further clinical trials are progressing to authenticate the safety and efficacy of the formulation in HIV sufferers. The preliminary molecular docking studies justifies the claim of DC as an Anti HIV formulation in siddha medicine and this may further strengthen the global acceptability of this unique formulation

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