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Original Article

Revealing Anti-viral Potential of Siddha Formulation *Manjal noi Kudineer* against Hepatitis C Viral - RNA Dependent RNA Polymerase Using *in-silico* Docking Technique

Shanmugasundaram Visweswaran[1], Sattanathan Iyswarya[1], Narayanan Jegathambal Muthukumar[2]

ABSTRACT

Background: The Hepatitis C virus (HCV) is a dangerous infectious illness that has long been a concern for public health on a worldwide scale. According to calculation, over 170 million individuals are afflicted, with the highest infection rates in Africa and Asia. HCV is a major concern worldwide and eliminating it in its early phase to avoid liver cirrhosis and HCC has long been the aim for studies. To date, there is no verified vaccine available in the market and current approved therapy (standard of care). Siddha formulas have managed pathogenic infections for ages. Siddha practice strengthens the host's immunity and resilience to pathogens. **Materials and Methods:** The main aim of the present investigation is to screen the anti-viral potential of the siddha formulation *Manjal noi Kudineer* against Hepatitis C viral - RNA dependent RNA polymerase (RdRp) using *in-silico* docking technique. **Results:** Result of the study clearly emphasise that the lead cucurbitacin E ranks top with greatest binding free energy -8.96 kcal/mol, followed by Piperidine (-7.71), Curcumin (-7.45), Piperic acid (-6.77), Beta- Humulene (-6.40), Cinnamic acid (-5.89), Oleic acid (-5.59) and Piperine (-5.32). It was also evident that the therapeutics such as oleic acid and Cucurbitacin E revealing potential binding affinity in targeting the activation loop (Leu474, His475, Ser476 and Tyr477) of the viral polymerase enzyme. Followed by which other leads including Limonene, Beta-Pinene, Cinnamic acid, Anethole, Phyllanthin, Piperic acid, Curcumin and Piperine ranked second by offering prominent interactions with the residual bioactive amino acids (His475, Ser476 and Tyr477). **Conclusion:** From the data's of the present *in-silico* screening, it was concluded that the phytochemicals in the siddha formulation *Manjal noi Kudineer* display strong anti-viral property by blocking the target enzyme target enzyme (Hepatitis C viral polymerase) and thereby considered as a novel drug of choice for the clinical management of hepatitis C viral infection.

Keywords: Hepatitis C virus, Siddha, *Manjal noi Kudineer*, Hepatitis C viral RdRp, Docking, *In-silico*.

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INTRODUCTION

HCV causes 15%-20% of acute hepatitis cases. 50-80% of HCV patients acquire chronic infection after acute infection. Chronic hepatitis C (CHC) patients are at high risk for life-threatening consequences, including cirrhosis in 20% of cases and HCC in 4%-5% of cirrhotic patients every year.[1-3]

Patients who are infected with HCV have a significantly increased risk of dying from their condition. Many medications have been explored against HCV, and many have completed clinical trials, but viral resistance and adverse effects have raised questions about generating better therapeutics.[4] Due to a lack of conventional therapy, HCV medication discovery focuses on medicinal plants.

Several combinations of medications are in clinical trials, such as taribavirin which is a prodrug of ribavirin and Alb interferon which is the combination of IFN-α and human albumin.[5-6] The undesirable side effects induced by existing therapy prompted the need to discover antiviral agents that can suppress or remove the virus without toxicity and unwanted effects. This guided the study to try novel antiviral medicines particularly from herbal origin against HCV viral proteins.

Siddha system of medicine signifies great history of treating infective pathogens since centuries.[7-8] Herbal medicine comprises of bioactive therapeutics with viable pharmacological properties. Siddha formulations known for managing infectious disorders without major side/adverse effects because of its unique and reliable combination of herbal ingredients.

Manjal noi Kudineer is a traditional unique siddha preparation comprising six unique blend of herbal

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ingredients such as *Phyllanthus Amarus* (Phyllanthin, Cinnamic acid),[9] *Eclipta prostrata* (Oleic acid),[10] *Trichosanthes cucumerina* (Cucurbitacin E, Curcumin),[11] *Piper nigrum* (Piperic acid, Piperidine and Piperine),[12] *Foeniculum vulgare* (Anethole, Beta- pinene)[13] and *Aegle marmelos* (Limonene, α-Humulene).[14] As suggested in the siddha literature this versatile formulation claims significant anti-viral potential, but as on date there is no proper documentary evidence advocating the desired mechanism of action in managing hepatitis. Hence the main aim of the present *in-silico* investigation is to evaluate the anti-viral potential of the formulation *Manjal noi Kudineer* against Hepatitis C viral - RNA dependent RNA polymerase using autodock virtual screening tool.

Drug research and development might take 10 to 15 years. In recent decades, the pharmaceutical industry has used computer-aided drug design (CADD) to speed drug development and minimize time, costs, and failures.[15] This research calculates drug therapeutic target features and safety liabilities. CADD approaches can be structure-, ligand-, or hybrid-based.[16] Docking and molecular dynamics simulations employ the target molecule's 3D structure to screen possible ligands. These approaches measure target ligand recognition, binding site prediction, and affinity.[17-18] Molecular docking predicts the orientation of a chemical towards the target and characterizes ligand–target interactions.

MATERIALS AND METHODS

Docking Simulation Software

A conventional docking tool was used to predict the potential of the leads under investigation over specified enzyme target (Auto Dock version 4). Observing the binding affinity and interaction behaviour of the lead with protein target Hepatitis C viral -polymerase (PDB-3MWV) and 2.50 resolution.[19]

Target- Protein Preparation

Figure 1 shows the three-dimensional structure of the target protein (Hepatitis C viral -polymerase (PDB-3MWV) (RCSB). Protein construct was optimized by eliminating preloaded lead candidate by cleaving adjoining water molecules. Gasteiger charges with extra polar hydrogen atoms, combining non-polar and rotatable links were calculated using AutoDock 4.[20]

Construction of Lead Compounds

Nearly twelve phytotherapeutics were retrieved from the herbal ingredients present in the siddha formulation *Manjal noi Kudineer* through systematic literature survey. Two and three dimensional structures of the therapeutics including Limonene, Beta-Pinene, Cinnamic acid, Anethole, Beta- Humulene, Phyllanthin, Piperic acid, Piperidine, Cucurbitacin E, Curcumin, Oleic acid and Piperine were constructed by using professional version of ChemDraw sketch software. Figure 2 and 3 shows the 2D and 3D structures of the leads projecting spatial orientation of their functional groups.

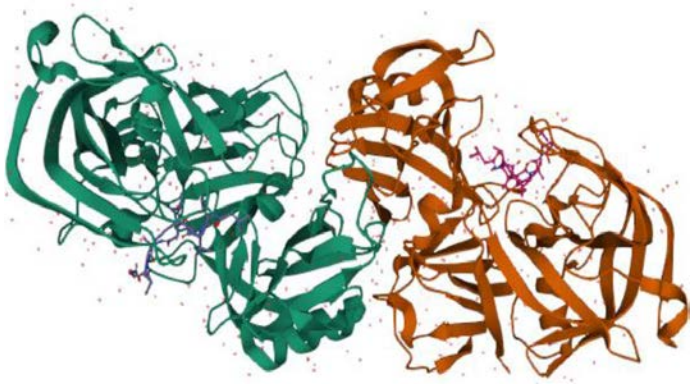

Figure 1: Three-dimensional illustration of the Hepatitis C viral -polymerase (PDB-3MWV)

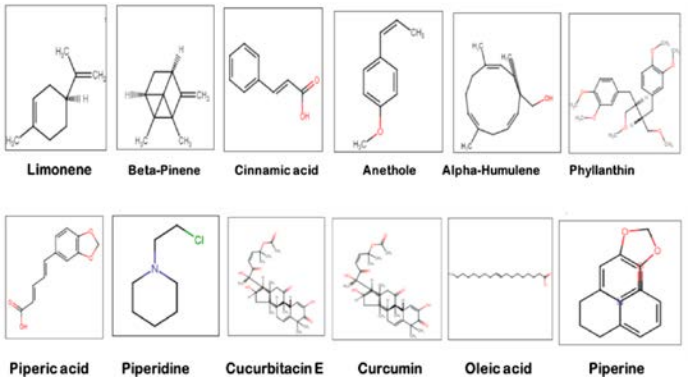

Figure 2: Two-dimensional projection of the phytotherapeutic lead compounds retrieved form the PubChem molecular database.

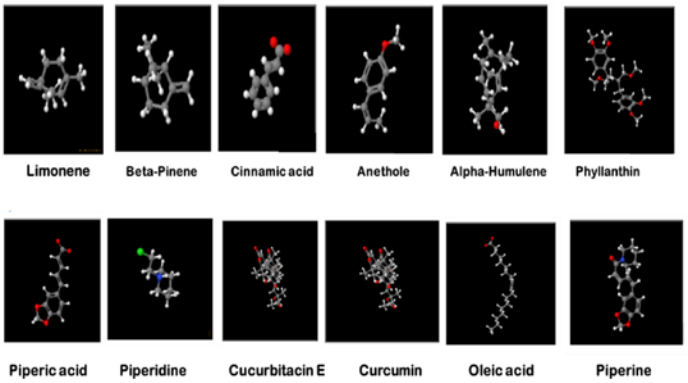

Figure 3: Three-dimensional illustration of the phytotherapeutic lead compounds retrieved form the PubChem molecular database.

In-silico Virtual Screening

AutoDock-4 program was used to anticipate *in-silico* docking of the molecules under investigation. AutoDock virtual screening tool utilised to anticipate the interaction between the lead's functional moieties of the leads over the target viral polymerase (amino acid residue). Gasteiger simulation module with optimized molecular energy and free dynamics algorithm were appropriated before start of docking calculation. Solvation parameters and polar hydrogens were added to the receptor for docking simulation. Since ligands are phytotherapeutics and not peptides, Gasteiger charge was applied and non-polar hydrogens were merged accordingly. AutoDock programming necessitated pre-calculated grid maps for each atom type in the bound ligand, as it stores potential energy. Docking pocket maps were 70×70×70 Å and 0.375 Å. Each docking calculation was based on 100 runs with 250000 energy assessments each. Population was 150. Translational, quaternion, and torsion steps of 5 were applied during the search.[21-22]

RESULTS

Docking simulation demonstrates the binding potential of the chosen viable lead compounds against the target enzyme's active site. Binding energy determines whether the desire leads tend to occupy the target

amino acid residues that mediates the enzyme function and its relative biological action.

Estimating binding free energy causes molecular interaction between investigational compounds and the target site's functional chain. Physicochemical characteristics of substances impose target-site binding conformation. Tabulated physicochemical features of phytotherapeutics, including molecular weight, formula, and H-bond profile were summarised in the Table 1. Estimated binding energy is also one of the key functional characteristics feature in estimating the lead molecule's that are capable of enzyme inhibitors. In the present investigation, Cucurbitacin E ranks top with greatest binding free energy -8.96 kcal/mol, followed by Piperidine (-7.71), Curcumin (-7.45), Piperic acid (-6.77), Beta- Humulene (-6.40), Cinnamic acid (-5.89), Oleic acid (-5.59) and Piperine (-5.32) as shown in Table 2.

Binding of leads with the specific amino acids guarding the biological properties of the viral polymerase attributes to the viability of the compounds in halting the enzyme activity. Therefore, upon screening the efficacy of the herbal leads from the other dimension of interaction analysis, it was evident that the therapeutics such as oleic acid and Cucurbitacin E ranked first by revealing potential binding affinity in targeting the activation loop (Leu474, His475, Ser476 and Tyr477) of the viral polymerase enzyme (Table 3 and illustrated in Figure 4). Followed by which other leads including Limonene, Beta-Pinene, Cinnamic acid, Anethole, Phyllanthin, Piperic acid, Curcumin and Piperine ranked second by offering prominent interactions with the residual bioactive amino acids (His475, Ser476 and Tyr477), as shown in Table 3 and Figures 4.

Table 2: Summary of the binding free energy and electrostatic properties of the phytotherapeutic lead molecules against Hepatitis C viral -polymerase (PDB-3MWV).

Compounds	Binding Free energy Kcal/mol	Inhibition constant Ki µM (*mM)(**nM)	Electrostatic energy Kcal/mol	Intermolecular energy Kcal/mol	Total Interaction Surface
Limonene	-4.86	272.50	-0.01	-5.16	429.263
Beta-Pinene	-4.90	255.71	-0.01	-4.90	406.759
Cinnamic acid	-5.89	48.01	-1.55	-6.49	440.498
Anethole	-4.43	567.09	-0.02	-5.03	425.996
Beta- Humulene	-6.40	20.46	-1.42	-7.29	564.618
Phyllanthin	-1.24	122.59*	-0.55	-2.10	423.351
Piperic acid	-6.77	10.84	-0.84	-7.63	546.493
Piperidine	-7.71	2.21	-0.12	-6.57	747.133
Cucurbitacin E	-8.96	268.96**	-0.18	-8.56	766.532
Curcumin	-7.45	3.48	-0.10	-7.41	782.346
Oleic acid	-5.59	80.15	-1.27	-4.69	396.772
Piperine	-5.32	125.44	-1.40	-5.17	376.244

DISCUSSION

Hepatitis C virus produces an acute infection which can gradually proceed to chronic infection and can cause irreversible liver damage, hepatocellular carcinoma (HCC), cirrhosis and death.[23-24] Each year roughly 3-4 million people are afflicted and > 350000 persons die due to liver disease.

The genomes of various viruses that are impose considerable threat to global health are replicated and transcribed by viral polymerases. These viruses include the Hepatitis C virus (HCV), the human immunodeficiency virus (HIV), and the Ebola virus. They're essential targets for viral infection therapy. Polymerases are essential for viral replication. They are crucial targets for viral infection therapy because they replicate and transcribe the viral DNA.[25]

Table 1: Table summarising the physiochemical properties of the phytotherapeutic lead molecules subjected to docking study.

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Limonene	136.23 g/mol	$C_{10}H_{16}$	0	0	1
Beta-Pinene	136.23 g/mol	$C_{10}H_{16}$	0	0	0
Cinnamic acid	148.16 g/mol	$C_9H_8O_2$	1	2	2
Anethole	148.20 g/mol	$C_{10}H_{12}O$	0	1	2
Beta-Humulene	204.35 g/mol	$C_{15}H_{24}$	0	0	0
Phyllanthin	418.5 g/mol	$C_{24}H_{34}O_6$	0	6	13
Piperic acid	218.2 g/mol	$C_{12}H_{10}O_4$	1	4	3
Piperidine	85.15 g/mol	$C_5H_{11}N$	1	1	0
Cucurbitacin E	556.7 g/mol	$C_{32}H_{44}O_8$	3	8	6
Curcumin	368.4 g/mol	$C_{21}H_{20}O_6$	2	6	8
Oleic acid	282.5 g/mol	$C_{18}H_{34}O_2$	1	2	15
Piperine	285.34 g/mol	$C_{17}H_{19}NO_3$	0	3	3

The structural proteins (Core, E, and E2) and the non-structural proteins (NS3 protease and NS5B RNA dependent RNA polymerase) have been deemed the greatest candidates for the development of new molecular inhibitors, according to previous study. Among these proteins, Viral RdRp been massively explored due to its protease and helicase domains that are critical in viral replication.[26-27]

Molecular dynamics techniques include the torsional movement of the investigational molecules and are used to study binding modes and forecast the stability of ligand–target complexes, offering researchers a greater knowledge of ligand–target interactions.[28] Ligand-based approaches, including similarity searches, pharmacophore modelling, and QSAR investigations, employ groups of small molecules with diverse structures capable of interacting with the target to uncover novel and potent compounds.[29] Binding free energy is one of the key functional characteristics feature in estimating the lead molecule's that are capable of enzyme inhibition. In the present investigation, Cucurbitacin E ranks top with greatest binding free energy -8.96 kcal/mol, followed by Piperidine (-7.71), Curcumin (-7.45), Piperic acid (-6.77), Beta- Humulene (-6.40), Cinnamic acid (-5.89), Oleic acid (-5.59) and Piperine (-5.32)

The biological action of the majority of the enzymes was guarded by active amino acid residues called substrate binding sites. The tendency of the lead molecules in occupying the residue over the target predicts the efficacy of the inhibitors. Strong covalent interactions by the compounds in occupying these active amino acid residues shall prevent the complexation of the site in response of the endogenous substrate which will productively alter the functional modalities of the enzyme. Literature survey emphasise that the active site of the Hepatitis C viral RdRp polymerase managed by series of residues (Leu474, His475, Ser476 and Tyr477). Enzyme inhibitors that possess a specific affinity towards the aforementioned active loop will hinder the action of polymerase in synthesizing the virulence and survival of non-structural proteins essential for medicating infections. From the outcome of the present

Table 3: Interaction of phytotherapeutic lead compounds with biologically significant amino acid residues of Hepatitis C viral -polymerase (PDB-3MWV).

Compound	Interactions	Amino acid residues										
Limonene	2	422 ARG	423 MET	475 HIS	477 TYR	528 TRP	533 LYS					
Beta-Pinene	2	419 LEU	422 ARG	423 MET	475 HIS	477 TYR	528 TRP					
Cinnamic acid	2	419 LEU	422 ARG	475 HIS	477 TYR	528 TRP	533 LYS					
Anethole	2	419 LEU	422 ARG	423 MET	475 HIS	477 TYR	528 TRP					
Humulene	1	419 LEU	422 ARG	423 MET	477 TYR	501 ARG	528 TRP					
Phyllanthin	2	419 LEU	422 ARG	423 MET	473 THR	475 HIS	477 TYR	482 ILE	497 LEU	528 TRP	533 LYS	
Piperic acid	2	376 ALA	419 LEU	422 ARG	423 MET	473 THR	475 HIS	477 TYR	527 ASN	528 TRP	533 LYS	
Piperidine	1	381 VAL	383 TYR	417 PRO	467 HIS	470 SER	471 ALA	474 LEU				
Cucurbitacin E	3	419 LEU	422 ARG	423 MET	475 HIS	476 SER	477 TYR	482 ILE	501 ARG	528 TRP	533 LYS	
Curcumin	2	376 ALA	419 LEU	422 ARG	423 MET	473 THR	475 HIS	477 TYR	482 ILE	527 ASN	528 TRP	533 LYS
Oleic acid	3	419 LEU	422 ARG	423 MET	474 LEU	475 HIS	477 TYR	528 TRP	533 LYS			
Piperine	2	419 LEU	422 ARG	475 HIS	477 TYR	527 ASN	528 TRP	533 LYS				

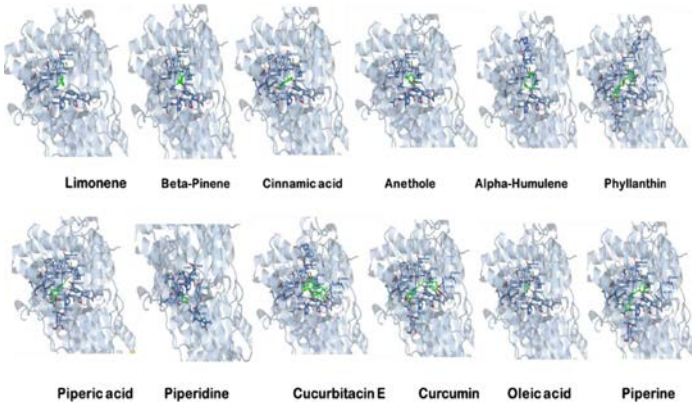

Figure 4: Binding orientation of the selected phytotherapeutic lead compounds against Hepatitis C viral -polymerase (PDB-3MWV).

study, it was strongly evident that the therapeutics such as oleic acid and Cucurbitacin E ranked first by revealing potential binding affinity in targeting the activation loop (Leu474, His475, Ser476 and Tyr477) of the viral polymerase enzyme. Followed by which other leads including Limonene, Beta-Pinene, Cinnamic acid, Anethole, Phyllanthin, Piperic acid, Curcumin and Piperine ranked second by offering prominent interactions with the residual bioactive amino acids (His475, Ser476 and Tyr477).

CONCLUSION

Management of viral infections remains greater challenge for clinicians around the world. The unique mechanistic pathway adopted by the virus in invading the host cellular architecture and related response makes the therapy even more critical. Traditional medicines continues to uphold its eminence and greatness in managing viral infections over several decades. High safety and reliable pharmacological properties of the siddha formulation grabs the attention of the healthcare providers. Results of the present study concluded that the phytochemicals present in the siddha formulation *Manjal noi Kudineer* reveals significant anti-viral property by effectively inhibiting the target enzyme (Hepatitis C viral-polymerase) and thereby be considered as an excellent drug of choice for the clinical management of viral hepatitis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HCV: Hepatitis C virus; **RdRp:** RNA dependent RNA polymerase; **CADD:** Computer-Aided Drug Design; **IFN-α:** Interferon alpha; **HCC:** Hepatocellular carcinoma; **CHC:** Chronic hepatitis C; **QSAR: Quantitative structure–activity relationship.**

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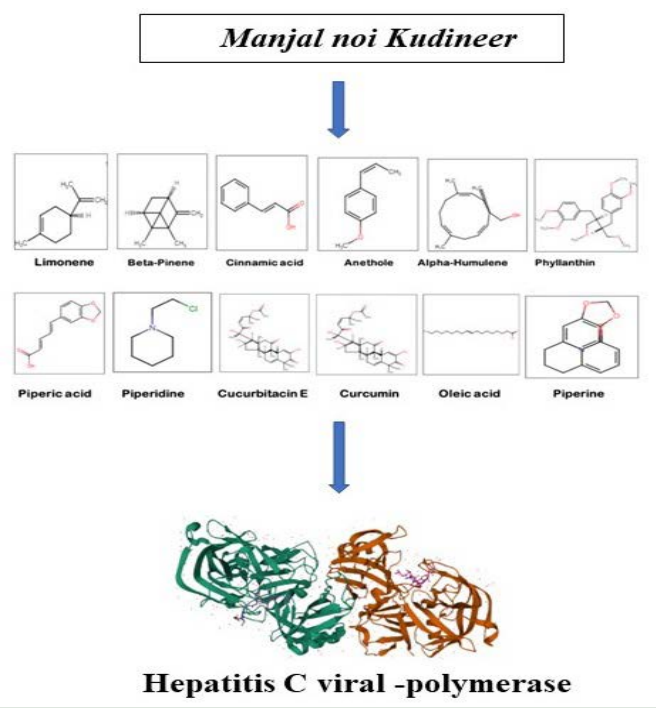
GRAPHICAL ABSTRACT



SUMMARY

It was strongly evident that the therapeutics such as oleic acid and Cucurbitacin E ranked first by revealing potential binding affinity in targeting the activation loop (Leu474, His475, Ser476 and Tyr477) of the viral polymerase enzyme. Followed by which other leads including Limonene, Beta-Pinene, Cinnamic acid, Anethole, Phyllanthin, Piperic acid, Curcumin and Piperine ranked second by offering prominent interactions with the residual bioactive amino acids (His475, Ser476 and Tyr477). High safety and reliable pharmacological properties of the siddha formulation grabs the attention of the healthcare providers. Results of the present study concluded that the phytochemicals present in the siddha formulation *Manjal noi Kudineer* reveals significant anti-viral property by effectively inhibiting the target enzyme (Hepatitis C viral -polymerase) and thereby be considered as an excellent drug of choice for the clinical management of viral hepatitis.

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