Subscription Agency
Exploring and Distributing Knowledge Globally

Journal of Advancement in Pharmacognosy
Volume 4 Issue 2, 2024
ISSN: 2582-8401

Insilico Screening of Phytoconstituents from *Aerva Lanata (L.) Juss* (Amaranthaceae) against SARS- COV2- Main Protease[3cl]

Aswani B S[1], Rekka Raja [1*], Priyanka Shanmugam[2]
[1]Department of Botany, Kongunadu Arts and Science College (Autonomous), Coimbatore, GN Mills Post, Tamil Nadu, India.
[2]Department of Medicinal Botany, Sivraj Siddha Medical College, Salem, Tamil Nadu

***Corresponding Author**
Email id: rekkar_bo@kongunaducollege.ac.in

ABSTRACT
Presently, the search to identify treatments and vaccines for novel coronavirus disease (COVID-19) are ongoing. The increased interest in exploring alternatives of medicinal plant-based therapeutics. Aerva lanata (L.) Juss is an important genus of the family Amaranthaceae known for its ethanomedicinal claims and for a variety of medicinal properties. In search of the anti-COVID-19 compound, the selected five phytocompounds from A. lanata (L.) Juss, which are effective against headache, cough, asthma, anti-inflammatory similar to SARS- COV 2 like symptoms. During the virtual screening process, each compound from Aerva lanata (L.) Juss that bound at different binding pockets of 3 CL pro has been selected. From the results, when the target protein main proteinase interacted with phytocompounds of Aerva lanata (L.) Juss. The two polyprotein enzymes (papain-like protease and 3C-Like protease) essential to SARS-CoV-2 replication: the papain-like protease interacted with the following lead compounds Heptadecanoic acid, methyl ester, 1-Butanol,4-butoxy, Furanone, Propanal, oxime and Pyridine. Among these, Heptadecanoic acid, methyl ester showed better binding affinity of -4.4 Kcal/mol with the amino acid residues Val150, Glu291 and Arg294. In which, the high binding affinity (-3.5 Kcal/mol) was observed between Pyridine from Aerva lanata (L.) Juss and the amino acid residues His41, Leu164 and Pro188 of target protein. Due to the remarkable presence of these compounds in the A. lanata (L.) Juss, extracts, we believe that this in silico study at least points at A. lanata (L.) Juss, as a whole as an interesting herb opening novel therapeutically horizons for COVID-19 treatment.

***Keywords:** Aerva lanata (L.) Juss, Amaranthaceae, Protease, Insilico analysis, Therapeutics*

INTRODUCTION
The (COVID-19) pandemic is rapidly progressing with promptly varying presentations. Updates from the Indian Council of Medical Research (ICMR) regarding the spread, treatment, and disease outcome are continuously being provided. Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by the SARS-associated coronavirus (SARS-Cov). SARS-CoV-2 is an enveloped spherical or pleomorphic particle containing single-stranded (positive-sense) RNA paired with a capsid nucleoprotein. One way to control the infection is to seek protease inhibitors to prevent the S-protein of SARS-CoV-2 cleavage to the S1 domain. Inhibiting the ACE2 receptor is likely to induce a conformational change of ACE2, therefore blocking the interaction between spike protein and ACE2 receptor (1). Molecular docking can predict the ligand–protein interactions by recognizing the apt active sites in the protein, getting the best geometry of the ligand–receptor complex, and computing the interaction energy for various ligands to design additional effective ligands (2).

Journal of Advancement in Pharmacognosy
Volume 4 Issue 2, 2024
ISSN: 2582-8401

The herbal medicines containing bioactive compounds that possess anti-inflammatory, antipyretic, anti-viral, and immune-modulating properties can be further explored as therapeutic agents for COVID-19 [3 & 4]. Potential medicinal plants that may be beneficial in the prevention and treatment of COVID-19. Medicinal plants are important sources of structurally novel compounds that functions as a lead for the development of novel drugs. *Aerva lanata* (L.) Juss, is an important genus of the family Amaranthaceae known for its ethanomedicinal claims and for a variety of medicinal properties. In addition, it possesses wide range of chemical constituents such as tannins, terpenoids, flavonoids, alkaloids and steroids. Hence, the plant can be used to treat many diseases such as painkiller in the treatment of headache and for cough, diarrhea, cholera, dysentery, kidney stone treatment and skin infections and can be used in various pharmaceutical formulations and drug development studies (5). [6]Arun Thangavel (2014) investigated the GC-MS analysis of whole plant extract *Aerva lanata* Juss, and identified sixteen bioactive compounds such as Heptadecanoic acid methyl ester, 1-Butanol-4-butoxy, Furanone, propanal oxime and pyridine. Owing to the numerous activities reported for these classes of compounds, we pursue a virtual screening against receptor of SARS COV-19 to determine the inhibitory activity of the bioactive constituents of *Aerva lanata*, which has been used for folk medicine for various diseases. This study was conceived with a strategy of exploring the natural compounds which may impede the SARS-Cov-19 infection by blocking the viral entry in to the host cell or inhibiting the viral poly protein processing in cell.

MATERIALS AND METHODS

Insilico characterization of proteins of *Aerva lanata* (L.) Juss.

Sequence Retrieval:

The FASTA sequence of the proteins [TABLE: 1] were retrieved from Genbank database hosted by the NCBI (http://www.ncbi.nlm.nih.gov) [7].

Primary Structure Prediction

For Physio-chemical characterization, theoretical Isoelectric Point (pI), molecular weight, total number of positive and negative residues, extinction coefficient, instability index, aliphatic index and grand average of hydropathy (GRAVY) were computed using the Expasy Protparm server [8] (http://us.expasy.org/tools/ protparam.html).

Secondary Structure Prediction

SOPMA (Self Optimized Prediction Method with Alignment) was used for the secondary structure prediction.

Functional Characterization

SOSUI and TMHMM v.2.0 tools were used to characterize whether the protein is soluble or trans membrane in nature. Inter Pro is an integrated resource for protein families, domains and functional sites. Inter Pro incorporates the major protein signature databases into a single resource. These include: PROSITE, which uses regular expressions and profiles, PRINTS, which uses Position Specific Scoring Matrix-based (PSSM-based) fingerprints, ProDom, which uses automatic sequence clustering, and Pfam, SMART, TIGRFAMs, PIRSF, SUPERFAMILY, Gene3D and PANTHER, all of which use hidden Markov models (HMMs). Superfamily and molecular function were predicted by Inter pro protein sequencing and classification [11]. (http://www.ebi.ac.uk/interpro/).

Journal of Advancement in Pharmacognosy
Volume 4 Issue 2, 2024
ISSN: 2582-8401

Docking studies of *Aerva lanata* (L.) Juss. against 3-chymotrypsin-like protease (3CL pro):

Target protein selection & Preparation

Main proteinase (3CLpro) is a target protein for COVID19 which was selected from the literature. The 3D structure of the target protein was retrieved from Protein Data Bank (https://www.rcsb.org/) and the PDB ID is 1P9U. Target protein was prepared using Discovery Studio 2021.

Ligand selection & Preparation

The ligands or phytocompounds of medicinal plant were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and all the ligands were prepared using Open Babel in the PyRx software.

Docking Studies

Docking studies were performed using PyRx software for the target protein Main proteinase and phytocompounds (ligands) of medicinal plant and the results were analyzed using Discovery Studio 2021. In the results, the lowest binding affinity indicates good result.

RESULTS AND DISCUSSION

Aerva lanata (L.) Juss. is an important genus of the family Amaranthaceae known for its ethanomedicinal claims and for a variety of medicinal properties. *Aerva lanata* (L.) Juss**.** contains enormous amount of bioactive constituents. In addition, it possesses wide range of pharmacological activities. Hence the plant can be used to treat many diseases, and can be used in various pharmaceutical formulations and drug development studies.

Insilico characterization of proteins of *Aerva lanata* (L.) Juss.:

The primary structure prediction was done with the help of protparam tool. The parameters were computed using Expasy's protparam tool which revealed that the molecular weights for three different proteins as 28750.60 (Truncated maturase K), 17647.46 (Maturase K), 28157.35 (Ribulose-biphosphate carboxylase large sub unit). The pI of three proteins was greater than 7 which showed that it is basic in character. The proteins are found to be compact and stable at their pI. Among the three proteins one is showed instability index 40, indicating that the proteins are stable. Aliphatic index of the proteins ranged between 83.45 - 99.35. The computed extinction coefficients help in the quantitative study of protein–protein and protein–ligand interactions in solution. The range of GRAVY (Grand Average of Hydropathicity) of *Aerva lanata* (L.) Juss**,** proteins was found to be -0.030-0.340. The lowest value of GRAVY indicates the possibility of better interaction with water (Table: 1 & 2).

Table: 1 Primary Structures of Proteins of Aerva Lanata (L.) Juss.

S.No.	Accession Number	Protein Name	Gene	Length
1	G8GBA5	Truncated maturase K	Mat K	240
2	Q3V591	Maturase K	Mat K	153
3	A0A7G8ARK2	Ribulose-biphosphate carboxylase large subunit	rbcl	249

Journal of Advancement in Pharmacognosy
Volume 4 Issue 2, 2024
ISSN: 2582-8401

Table: 2 Parameters Computed Using Expasy's Protparam Tool

S. No	Protein	Accession Number	Length	Mol. Wt	PI	R^-	R^+	EC	II	AI	Gravy
1.	Truncated maturase K	G8GBA5	240	28750.60	9.88	15	33	59610	43.98	92.54	-0.030
2.	Maturase K	Q3V591	153	17647.46	9.75	15	26	20190	44.02	99.35	-0.211
3.	Ribulose-bisphosphate carboxylase large subunit	A0A7G8ARK2	249	28157.35	9.19	28	36	26275	40.46	83.45	-0.340

The secondary structure prediction of *Aerva lanata* (L.) Juss**.** proteins was analyzed by SOPMA which revealed that alpha helix, extended strand, beta turn and random coil, were more predominant. In all the three proteins alpha dominates which are followed by random coil, extended strand and beta turn. The secondary structure was predicted by using default parameters (Window width: 17, similarity threshold: 8 and number of states: 4). TMHMM v.2.0 and SOSUI predicted that 2 proteins were soluble protein (Table: 3).

Table: 3 Secondary Structures of Proteins Of Aerva Lanata (L.) Juss.

S.No	Secondary Structure	G8GBA5	Q3V591	A0A7G8ARK2
1	Alpha helix (Hh)	41.67%	54.25%	46.18%
2	^{3}10 helix (Gg)	0.00%	0.00%	0.00%
3	Pi helix (Ii)	0.00%	0.00%	0.00%
4	Beta bridge (Bb)	0.00%	0.00%	0.00%
5	Extended strand (Ee)	18.75%	13.07%	16.06%
6	Beta turn (Tt)	4.58%	3.27%	5.22%
7	Beta region (Ss)	0.00%	0.00%	0.00%
8	Random coil (Cc)	35.00%	29.41%	32.53%
9	Ambiguous state(?)	35.00%	0.00%	0.00%
10	Other state	0.00%	0.00%	0.00%

Secondary structure prediction of proteins by SOPMA revealed that α-helix, random coil, β-turn and extended strand were more prevalent. In RBCL, maturase K, α-helix predominates whereas RBCL, maturase k random coil region was frequent. Domains are evolutionary units, often identified as recurring sequence or 3D structure of proteins was shown in figure 1, 2 & 3.

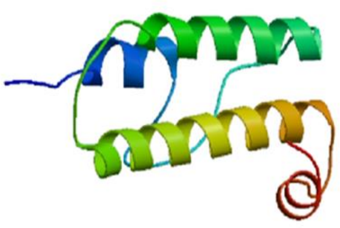

Figure 1: 3D structure of Maturase K

Figure 2: 3D structure of Ribulose-bisphosphate carboxylase large subunit

Figure 3: 3D structure of Truncated maturase K

Docking studies of *Aerva lanata* (L.) Juss. against 3-chymotrypsin-like protease (3CL pro)

COVID-19 pandemic has threatened global public health with devastating impact on the world economy in a fast and rapidly expanding manner (9). Currently, there is no suitable

Journal of Advancement in Pharmacognosy
Volume 4 Issue 2, 2024
ISSN: 2582-8401

vaccine available which can be used to cure infections caused by the novel coronavirus. It is highly needed to design a drug or a vaccine to treat this virus as well as to reduce the viral deportment so that its spread could be limited. Repurposing of drugs is a remarkable approach to opt antiviral compounds as COVID-19 drug candidates. Researches into drugs able to inhibit the several therapeutic targets in SARS-CoV-2 are present of great scientific interest. A significant advantage in the exploration of SARS-CoV-2 drugs is the use of herbal medicine preparations, as they are a potential source of likely new compounds that may be developed into new antiviral drugs, since they can be selected based on their ethnomedicinal use (10), for example, against infectious diseases including viruses such as SARS-CoV-2 the causative agent of the current pandemic. These plants produce a variety of phytochemical constituents with the potential to inhibit viral attachment and replication a requirement for the viral pathogenesis (11).

A. lanata (L.) Juss. traditionally used as painkiller in the treatment of headache and for cough, cutaneous infections, in white urine, diarrhea, cholera, dysentery, in kidney stone treatment, anthelmintic, strangury (slow to be and painful discharge of urine), headache, demulcent, anti-inflammatory, diuretic, hepatoprotective, hypoglycemic, antidiabetic, antiparasitic, antimicrobial, antiasthmatic, antifertility, hypolipidemic, antidiuretic, and nephroprotective property also used in the treatment of infections, cough, antidote, emollient, and skin infections. Based on this ethnomedicinal information, we selected *A. lanata* (L.) Juss. for docking studies against 3-chymotrypsin-like protease (3CL pro). Molecular docking can predict the ligand-protein interaction by recognizing the apt active sites in the protein, getting the best geometry of the ligand-receptor complex and computing the interaction energy for various ligands to design additional effective ligands. We initiated virtual screening of compounds, molecular docking and molecular dynamics to single out new drug leads that target the 3CLPro (12). The main protease (Mp) or 3-chymotrypsin -like protease (3CL pro) has critical role in cleavage of poly protein at eleven distinct sites to generate various NSPS that are essential for viral replication. The maturation of NSPS, which is crucial in the virus life cycle is directly mediated via 3CL pro. The detailed inspection on catalytic mechanism of 3CL makes it an attractive target for anti-covid-19 drug development (13). In search of the anti-COVID-19 compound, we selected five phytocompounds from *A. lanata* (L.) Juss. which are effective against headache, cough, asthma, anti- inflammatory (similar to SARS- COV 2 like symptoms). Therefore, the present study involves the analysis of five bioactive compounds from *A. lanata* (L.) Juss. against the structure of SARS-COV-2 3CL pro through structure based *Insilico* molecular docking and identify potent anti COVID-19 natural compounds. During the virtual screening process, each compound from *A. lanata* (L.) Juss. that bound at different binding pockets of 3 CL pro has been selected. From the results, when the target protein main proteinase interacted with phytocompounds of *A. lanata* (L.) Juss. The two polyprotein enzymes (papain-like protease and 3C-Like protease) essential to SARS-CoV-2 replication: the papain-like protease interacted with the following lead compounds Heptadecanoic acid, methyl ester, 1-Butanol,4-butoxy, Furanone, Propanal,oxime and Pyridine. Among these, Heptadecanoic acid, methyl ester showed better binding affinity of -4.4 Kcal/mol with the amino acid residues Val150, Glu291 and Arg294. In which, the high binding affinity (-3.5 Kcal/mol) was observed between Pyridine from *Aerva lanata Juss* and the amino acid residues His41, Leu164 and Pro188 of target protein. The interaction of phytocompounds with the target protein Main proteinase (3CLpro) and their corresponding energy value are listed in table: 4 and structure of target compounds were shown in the figure 4-8.

Journal of Advancement in Pharmacognosy
Volume 4 Issue 2, 2024
ISSN: 2582-8401

Table: 4 Interaction of Aerva Lanata (L.) Juss. Phytocompounds with Main Proteinase (3CLPRO)

S. No.	Compound Name	Plant Name	PubChem CID	Binding Affinity (Kcal/mol)	No. of bonds	Interacting residues
1	Heptadecanoic acid,methyl ester	*Aerva lanata* (L.) Juss.	15609	-4.4	3	Val150, Glu291, Arg294
2	1-Butanol,4-butoxy	*Aerva lanata* (L.) Juss.	20111	-3.7	2	Phe111, Glu291
3	Furanone	*Aerva lanata* (L.) Juss.	140765	-3.6	1	His41
4	Propanal,oxime	*Aerva lanata* (L.) Juss.	641641	-3.6	2	Val127
5	Pyridine	*Aerva lanata* (L.) Juss.	1049	-3.5	3	His41, Leu164, Pro188

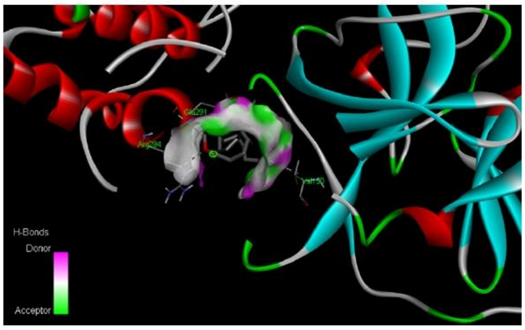

Figure 4: Interaction of Heptadecanoic acid, methyl ester with Main proteinase (3CLpro)

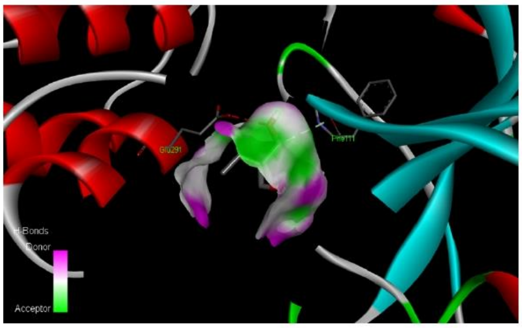

Figure 5: Interaction of 1-Butanol, 4-butoxy with Main proteinase (3CLpro)

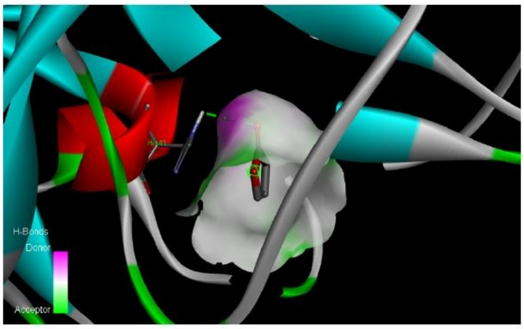

Figure 6: Interaction of Furanone with Main proteinase (3CLpro)

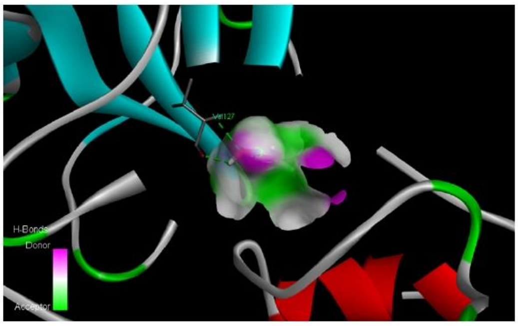

Figure 7: Interaction of Propanal, oxime with Main proteinase (3CLpro)

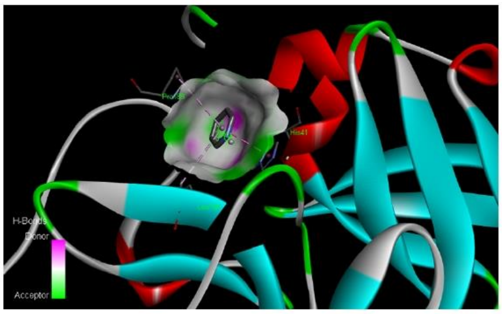

Figure 8: Interaction of Pyridine with Main proteinase (3CLpro)

CONCLUSION

The coronavirus pandemic is a serious public health crisis due to high mortality, high basic reproduction numbers, and neither approved neither drugs nor vaccines. Potential inhibitors of this enzyme could have a major contribution in the reduction, prevention, or eradication of the viral load of patients. Due to the remarkable presence of these compounds in the *A. lanata* (L.) Juss herb opening novel therapeutically horizons for COVID-19 treatment. Based on our findings, we believe that *A. lanata* (L.) Juss should be taken into consideration in looking for COVID-19 treatments. Further study into the absorption, distribution, metabolism, excretion, toxicity of these lead compounds COVID-19 therapeutic interventions to identify the drug target identification.

REFERENCES

1) Palaniyandi Umadevi, Subramanian Manivannan, Abdulkabeer Muhammed Fayad and Sreekumar Shelvy. In silico analysis of phytochemicals as potential inhibitors of proteases involved in SARS-CoV-2 infection. 2022. 40(11):5053-5059. doi: 10.1080/07391102.2020.1866669.
2) Shaghaghi, "Molecular Docking study of Novel COVID-19 Protease with Low Risk
3) Terpenoides compounds of plants", https://doi.org/10.26434/chemriv.11935722.v1. 2020.
4) WHO, 2003. SARS Clinical trials on treatment using a combination of traditional Chinese
5) medicine and Western medicine. Geneva: 53-61.
6) Li Y, Liu X, Guo L, Li J, Zhong D, Zhang Y, et al. Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: Protocol for a systematic review and meta-analysis. Syst Rev 2020;9:75.
7) Manoj Gyal, Anil Pareek, B.p. Nagori and D. Sasmal. 2011. Aerva lanata: A review on phytochemistry and Pharmacological aspects. Pharmacognosy Reviews. 5(10):1-4.
8) Arun Thangavel, Senthilkumar Balakrishnan, Aarthy Arumugam, Senbagam Duraisamy and Sureshkumar Muthusamy. 2014. Phytochemical screening, gas chromatography-mass spectrometry (GC-MS) analysis of phytochemical constituents and anti-bacterial activity of Aerva lanata (L.) leaves. African Journal of Pharmacy and Pharmacology, 8(5): 126 – 135.
9) Vijayabharathi, S, "Insilico analysis of protein *Curcuma caesia* Roxb", International Journal of Pharmacy and Pharmaceutical Sciences, 6(2): 216-220, 2014.
10) Ganeshpurkar A., Saluja A.K, "The Pharmacological potential of Rutin", Saudi Pharmaceutical Journal, 25(2): 149 – 164, 2016.
11) Chirsty Joy and Marria C. Cyriac. 2023. Phytochemicals as potential drug candidates for SARS Cov-2: An RDRp based In-silico drug designing. ABSR 24, 58-69.
12) Debadash Panigrahi. 2021. Molecular docking analysis of the phytochemicals from Tinospora cordifolia as potential inhibitor against Multi Targeted SARS-CoV-2 & cytokine storm. Journal of Computational Biophysics and Chemistry, 20(6): 559-580.
13) Muhammad Irfan, Muhammad Adil, Areej Fatima, Arooj Fatima and Ammara Khalid. 2022. Insilico determination of phytochemicals against spike protein of Covid 19. Journal of Bioresource Management, 9(1):1-15.
14) Anamika Basu, Anasua Sarkar and Ujjwal Maulik. 2020. Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE 2. Scientific Reports, 10: 17699.
15) Arkaniva Sarkar, Rushali Agarwal, Boudhayan Bandyopadhyay. 2022. Molecular docking studies of phytochemicals from Terminalia chebula for identification of potential multi-target inhibitors of SARS-CoV-2 proteins. Journal of Ayurveda and Integrative Medicine, 13: 100557.