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Molecular Docking Studies Of Alkaloids As Antiviral Agents

[1]Dr. J. Monisha, Department of Pharmaceutical Chemistry, Periyar College of Pharmaceutical Sciences, Tiruchirappalli-620012, Tamilnadu, India

[2]Dr. S. Shakila Banu, Department of Pharmaceutical Chemistry, Periyar College of Pharmaceutical Sciences, Tiruchirappalli-620012, Tamilnadu, India

[3]Dr. G. Krishnamoorthy, Department of Pharmaceutical Chemistry, Periyar College of Pharmaceutical Sciences, Tiruchirappalli-620012, Tamilnadu, India

[4]Dr. R. Senthamarai, Department of Pharmaceutical Chemistry, Periyar College of Pharmaceutical Sciences, Tiruchirappalli-620012, Tamilnadu, India

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Corresponding Author: [1]Dr. J. Monisha, Department of Pharmaceutical Chemistry, Periyar College of Pharmaceutical Sciences, Tiruchirappalli - 620012, Tamilnadu, India

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ABSTRACT

The traditional practice of medicinal plants for healing and averting illness has become predominant in almost every house hold. It is necessary to study medicinal plants to advocate the use of herbal medicines and to regulate their possibility as a source for new drugs. Now a days abundance of drugs are derived from plants, of those medicinal plants are rich in secondary metabolites and these metabolites are pharmacological active, economical and safe. The secondary metabolites include alkaloids, terpenoids, flavonoids, terpenes which possess anti-viral activity. Current study reveals that alkaloids possess therapeutic anti-viral activity. A virtual library of 51 alkaloids from various antiviral plants were docked against targets like HIV-1, Human Hepatitis B and SARS- CoV -2 viruses to identify alkaloids with wide spectrum of anti-viral activity using Autodock vina. Drug capability and Toxicity profile of the alkaloids were evaluated using bioinformatics tools such as Molinspiration and Osiris Toxicity calculator .From the study three alkaloids namely Liriodenine, Crytoheptine and Alsotinine had potential interaction and significant hydrophobic contact with active residues of viral targets and can be concluded that these alkaloids could be used as potential drug against several viral diseases.

Keywords: SARS CoV-2, HIV-1, Hepatitis-B, Autodock, Toxicity profile, Drug capability

INTRODUCTION

Human beings are susceptible to many viral infections, most of them are not causing diseases, and

some will do. The new pandemic situation in global development and comfort to travel have highlighted their protection as a crucial problem in people's health[1] and safety even though significant advancements are being made in the making of vaccines and drugs. The provenance of viral mutants generally threatens immunization and effective anti-viral treatments. Therefore, the discovery of novel anti-viral drugs is of paramount importance. The secondary metabolites from the plants with pharmacological activities are regarded as an exemplary repository for this diagnosis. An extensive study of phytochemicals and their mechanisms of action against the viruses might help in controlling harmful viruses. Many phytochemical entities, including terpenes, flavonoids, polyphenol, and phenolic compounds, have been studied for their anti-viral activity. Particularly in alkaloids [2] cutting edge study is making way to uncover innovative therapeutic strategies.

Most of the alkaloids are being used as anti-viral agents, act against few prominent viral pathogens such as coronavirus (CoV) [3] human immune deficiency virus (HIV), systemic acute respiratory syndrome (SARS) and respiratory virus (RSV). Literature survey implies that plant-derived alkaloids exhibit anti-nociceptive activity, anti-psychotic, anti-cholinergic, opioid analgesic, anti-malarial, anti-microbial, anti-oxidant, anti-viral [4], antifungal, analgesic, anti-diuretic, cerebellum stimulator, demulcent, hepatoprotective, antispasmodic, anti-inflammatory, anti-neoplastic, sympathomimetic activity and anti-hypertensive activities.

COMPUTATIONAL APPROACH

Recent innovations in computational biology practice have expanded the prospects of research in the vicinity [5] of drug designing. For prediction of molecular docking foremost binding mode of a ligand with a three-dimensional structure of protein is taken as a key technique in drug designing and screening of recently discovered anti-viral compounds against adverse diseases. Molecular docking is a method which predicts the binding orientation of small molecules with their protein targets. These computational methods give information about the binding affinity of the molecules against their target protein. Hence, molecular docking is believed as unique method in drug designing and screening of new antiviral compounds against severe diseases.

EMERGING VIRAL DISEASES IN INDIA

India the second most populous country in the world is at risk due to viral diseases that emerging as fast as possible. Over 30 new infectious agents have been reported worldwide in last two decades. In India due to existing environmental, socioeconomic and demographic factors the emergence of viral infections are increased. It posed a serious threat to global health security, the health system capacities to cope where health workers were at risk and the stability and growth of economics. There are many viral diseases that cause infection, the most common viral infections [6-9] that invaded in India are corona, influenza [10], chikunguniya,, dengue [11], nipah virus. More cases of H1N1 influenza was reported in mexico in march 2009, then followed by spread to united states and to India by September. It is clear that, new pathogens particularly viruses are likely to continue to emerge and spread across countries for a variety of reasons and challenge public health as never before.

MATERIALS AND METHODS

In the present work Crystal Structure of HIV-1 Protease in Complex with KNI-10772, Human Hepatitis B Viral Capsid (HBCAG), Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2 and SARS-Cov-2 RNA-dependent RNA polymerase in complex with cofactors were selected as the target

proteins, considering their role in viral disease. Thorough literature review was performed in order to find the efficient and valuable alkaloids [12-13] against viral diseases especially against Hepatitis B, HIV-1[14] and SARS-CoV-2 Viruses. Chemical structures of alkaloids were downloaded from Pubchem database [15]. Each and every ligands molecules was saved in PDB format using Discovery Studio Visualizer.

Molecular Properties of nearly 51 Alkaloidal phytoconstituents were calculated using Molinspiration server [16] to make sure that the compounds hold appropriate molecular properties to be a potential drug candidate. Molecular properties and druglikeness of the compounds are evaluated by molinspiration server on the basis of "Lipinski's Rule of Five". The rule illustrates molecular properties significant for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion

Furthermore, we also carried out insilico screening of Toxicity profiles of selected fifty one alkaloidal phytoconstituents using Osiris Property calculator. Based on the results obtained from Molinspiration software and Osiris Property calculator, Out of 51 Alkaloidal phytoconstituents 19 compounds were selected further to perform docking studies since they reported to have no side effects and proved to have appropriate molecular properties.

Three-dimensional crystal structure of Human Hepatitis B Viral Capsid (HBCAG (PDB ID: 1QGT)) Crystal Structure of HIV-1 Protease in Complex with KNI-10772 (PDB ID: 3NLS), Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2 (PDB ID: 6M0J) and SARS-CoV-2 RNA-dependent RNA polymerase in complex with cofactor (PDB ID: 6M71) were retrieved from Protein Data Bank (https://www.rcsb.org). [17]

The specified 3D structure of the ligands in SDF format were downloaded from PUBCHEM Database and saved in PDB format using Accelrys Discovery Studio Visualizer [18]. The Ligands were energy minimized using Open Babel Platform to obtain energetically stable conformation with the least steric strain and saved in PDBQT format for further use in Auto Dock Vina.

The water molecules, cofactors, and other ligands were removed from target protein structures through Molegro molecular viewer. Then they were used for molecular docking studies [19-20] using AutoDock Vina. The Kollaman charges, polar hydrogen were added and charged protein molecule was saved in pdbqt format. Ligands were energy minimized and saved in pdbqt format. Molecular docking studies docking studies were carried out using AutoDock Vina [21] software which uses PyRx open source software to perform virtual screening. In which docking score are based on the binding affinity between the ligand and protein. The higher negative binding energy for a target shows potency of the ligand. The conformational pose of best scores possessing the least energy is the best possible for molecule. The binding affinity between the ligand and protein [22] was pursued by considering the hydrogen bond (intermolecular) interaction and hydrophobic interactions which were observed between the amino acid residues with the functional group of the small molecules. Visualisation of Protein – Ligand interactions were carried out using Discovery Studio Visualizer [23].

RESULTS

Molecular physicochemical properties (molecular descriptors) and the Drug-Likeness are the two properties that are significant for considering a compound to become a successful drug candidate. The important molecular descriptors for the selected 51 alkaloidal phytoconstituents were calculated. The

molecular descriptors were used to determine, whether the molecules satisfied the Drug-Likeness criteria based on the Lipinski's rule. Molinspiration software was used to calculate the physicochemical properties for all the 51 alkaloidal phytoconstituents.

The molecular descriptors for alkaloidal phytoconstituents showed that the compounds have a molecular weight in the range of 163.22 to 606.72g/mol. The results also indicate the presence of no. of. Rotatable bonds in the range of 0 to 8. The calculated partition coefficient (LOGP) of the compounds falls in the range of -4.91 to 7.95. Also, the polar surface value (PSA) indicated in the above result generated for the compounds ranges from 6.48 to 247.11. Number of hydrogen bond donors and acceptors were in accordance with the rule i.e. less than five and ten respectively. This indicates, most of the compounds except Cepharanthine, Betanin, Cryptospirolepine, Strychnopentamine and Isostrychnopentamine has a greater probability of being a good Drug like candidate, with good oral bioavailability after oral administration and hence, most of the compounds except those three had been taken as a lead for antiviral drug targeting HIV-1, Human Hepatitis B and SARS-Cov-2viruses. Those compounds that satisfied Lipinski's Rule of five were further subjected for Toxicity studies. All 51 alkaloidal phytoconstituents were screened for their toxicity like Mutagenicity, tumourgenicty, skin irritancy using Osiris molecular property explorer and most of the compound found to be non-toxic in nature except few.

Three-dimensional crystal structure of Human Hepatitis B Viral Capsid (HBCAG (PDB ID: 1QGT)), Crystal Structure of HIV-1 Protease in Complex with KNI-10772 (PDB ID: 3NLS), Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2 (PDB ID: 6M0J) and SARS-CoV-2 RNA-dependent RNA polymerase in complex with cofactor (PDB ID: 6M71) were retrieved from Protein Data Bank (https://www.rcsb.org .

Alkaloidal phytoconstituents that passed both molecular properties and toxicity evaluation were subjected for docking studies. The docking or binding free energy were determined

which reflected that the binding affinity of 19 ligands to 5 different viral targets. The docking studies signify the fact that out of ninteen phytochemicals Liriodenine shows the highest binding affinity of −7.0,-8.1,-7.7,-7.9 and -7.9 kcal/mole with Crystal Structure of HIV-1 Protease in Complex with KNI-10772 (PDB ID:3NLS), Human Hepatitis B Viral Capsid (HBCAG (PDB ID:1QGT), Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2 (PDB ID:6M0J) and SARS-Cov-2 RNA-dependent RNA polymerase in complex with cofactor (PDB ID:6M71) respectively.

Next Cryptoheptine showed the highest binding affinity of − 6.8,-7.7,-7.7and-7.8 kcal/mole with Crystal Structure of HIV-1 Protease in Complex with KNI-10772 (PDB ID: 3NLS), Human Hepatitis B Viral Capsid (HBCAG (PDB ID: 1QGT) and SARS-CoV-2 RNA-dependent RNA polymerase in complex with cofactor (PDB ID: 6M71) respectively.

Alstonine also showed the highest binding affinity of − 6.7,-7.7,-7.9and-7.8 kcal/mole with Crystal Structure of HIV-1 Protease in Complex with KNI-10772 (PDB ID: 3NLS), Human Hepatitis B Viral Capsid (HBCAG) (PDB ID: 1QGT), and SARS-CoV-2 RNA-dependent RNA polymerase in complex with cofactor (PDB ID: 6M71) respectively. This proved that compounds Liriodenine, Cryptoheptine and Alstonine contain potential antiviral inhibitory activity and proved that the effective binding sites are present in Liriodenine,

Cryptoheptine and Alstonine. It also proved the ability of Liriodenine, Cryptoheptine and Alstonine in inhibiting viral targets.

DISCUSSION

In our study, fifty one alkaloidal phytocompounds were selected from different antiviral medicinal plants and screened for their drug likeness and toxicity parameters. Out of that, 19 phytocompounds fulfils all the criteria of Lipinski's rule of five and Toxicity profile.

Molecular docking studies explored the interaction of 19 alkaloidal phytoconstituents of selected antiviral medicinal plants with different viral targets like HIV-1, Human Hepatitis B and SARS-Cov-2[Table 1]. The molecular docking study showed that out of 19 alkaloidal phytoconstituents, three phytocompounds such as Liriodenine[Figure 1], Cryptoheptine[Figure 2] and Alstonine[Figure 3] showed efficient binding affinity with protein targets of HIV-1, Human Hepatitis B and SARS-Cov-2 viruses. Thus, Liriodenine, Cryptoheptine and Alstonine exhibited potent viral inhibitory activity.

Table 1. Comparative Analysis of Binding Energies of Alkaloids with Viral Targets

Ligand	Crystal Structure of HIV-1 Protease in Complex with KNI-10772 (PDB ID 3NLS)	Human Hepatitis B Viral Capsid (HBCAG) (PDB ID 1QGT)	Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2 (PDB ID 6M0J)	SARS-Cov-2 RNA-dependent RNA polymerase in complex with cofactors (PDB ID 6M71)
Castanospermine	-4.8	-4.9	-5.3	-5.7
Lycorine	-7.4	-7.4	-7.1	-7.3
1-Acetyllycorine	-7.0	-7.1	-6.8	-7.1
Matrine	-6.8	-7.4	-6.5	-6.8
Hippeastrine	-7.2	-7.4	-7.4	-7.5
Neoechinulin B	-7.9	-7.8	-7.4	-7.5
Aloperine	-6.8	-6.8	-6.6	-5.9
Sophoramine	-7.0	-7.1	-7.6	-6.5
Sparteine	-6.9	-7.3	-6.2	-6.1
Isocryptolepine	-6.9	-7.7	-7.8	-7.4
Liriodenine	-8.1	-7.7	-7.9	-7.9
Hydroxycryptolepine	-7.7	-7.3	-8.2	-7.3
Cryptoheptine	-7.7	-7.7	-7.5	-7.8
Alstonine	-7.7	-7.9	-6.7	-7.8
Vasicoline	-7.9	-7.2	-7.5	-7.4
Vasicolinone	-8.2	-7.5	-6.8	-6.9
Buchapine	-7.2	-7.2	-6.4	-7.0
Nitidine	-7.7	-7.4	-7.5	-7.6
Hirsutine	-7.0	-6.8	-7.6	-6.8

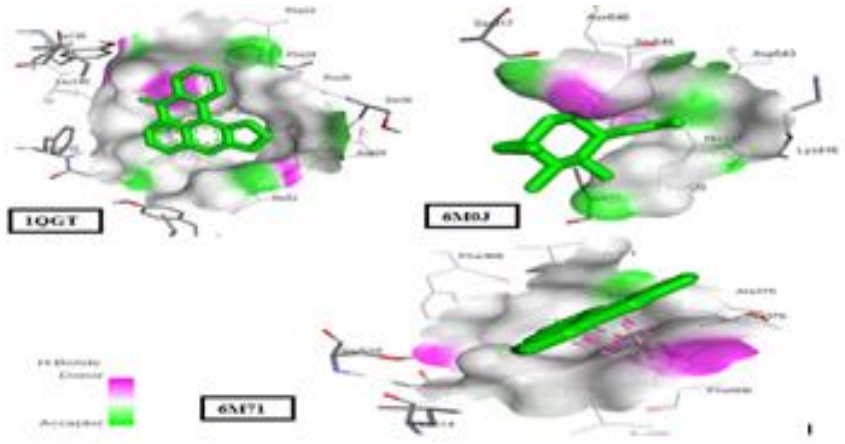


Figure 1. Docked poses of Liriodenine with viral targets

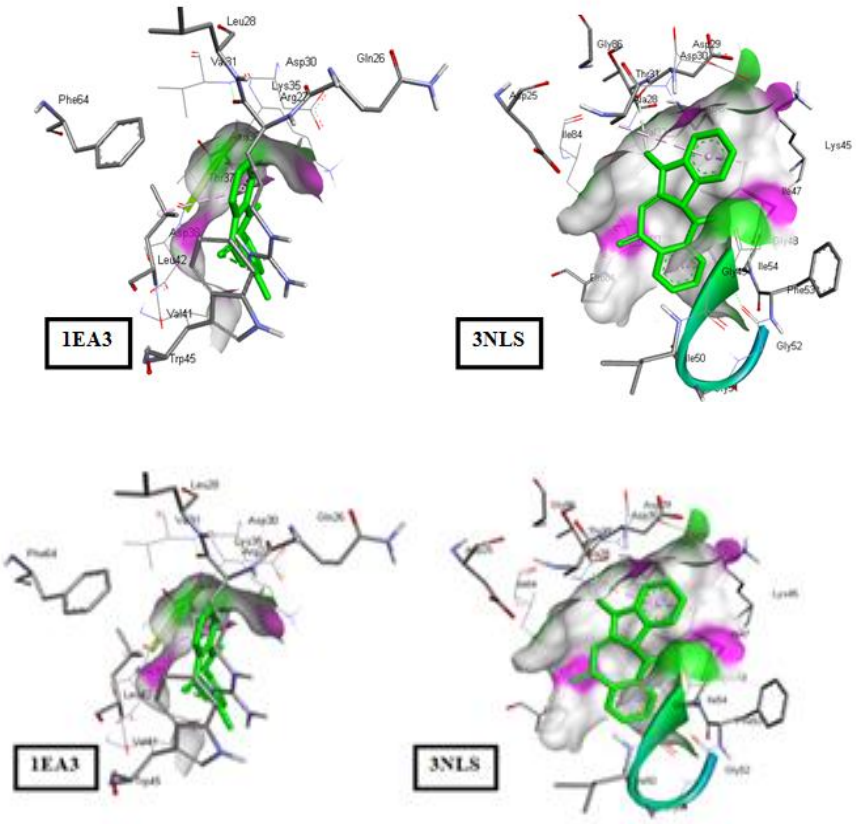
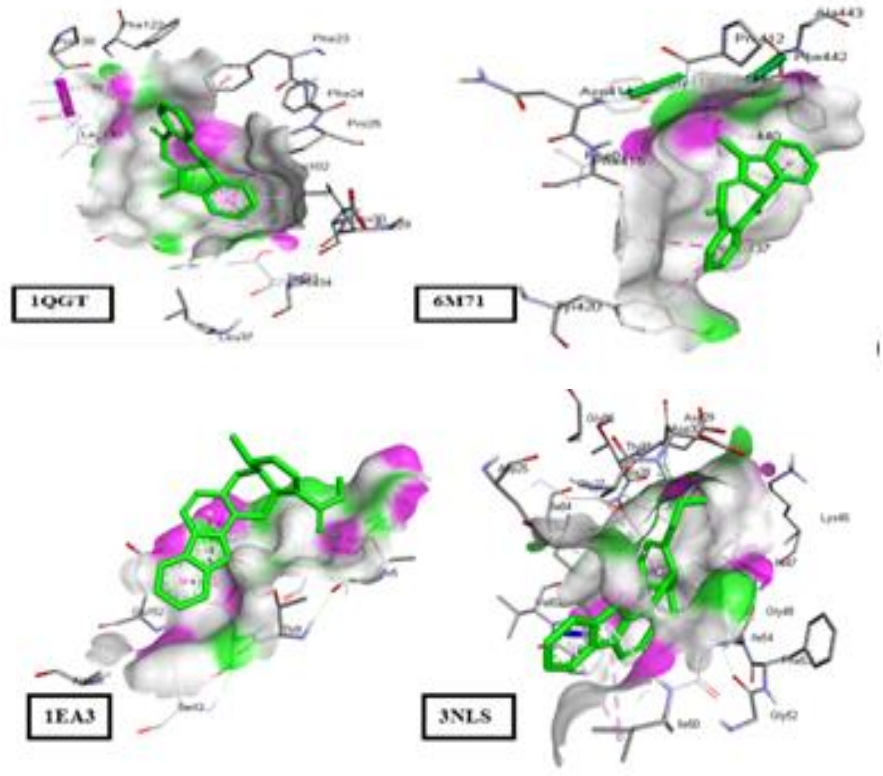


Figure 2. Docked possess of Cryptoheptine with Viral Targets



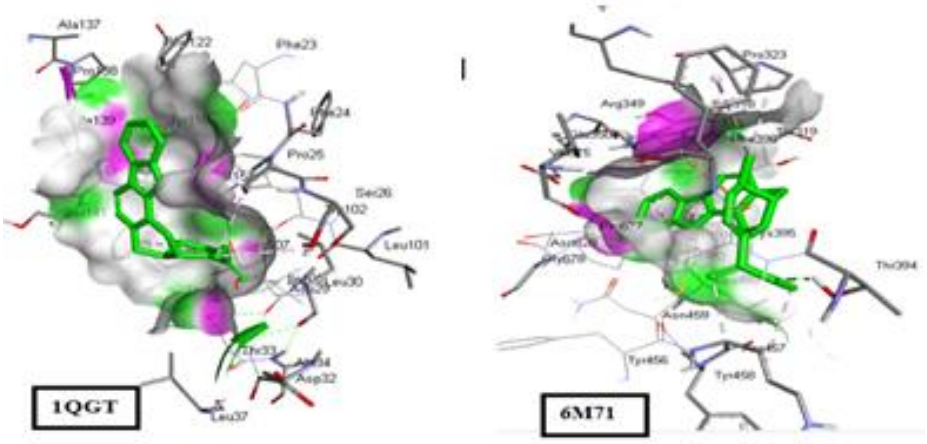


Figure 3. Docked possess of Alstonine with Viral Targets

CONCLUSION

Researches had summarised various sources and biological activities of reported alkaloids for the past four decades. A variety of natural, semi-synthetic, their analogues and synthetic alkaloids have been identified as potential anti-viral agents that are active to encounter a wide range of respiratory viruses. Alkaloids possess anti-viral activities at various stages of replication of the virus, such as the inhibition of production of envelope proteins but the steps they inhibit in the viral replication cycle are not clear. But there are certain alkaloids which inhibit certain enzymes such as reverse transcriptase, which is required for the viral replication and translation.

Numerous groups of derelict alkaloids could be further enriched by their effectiveness, target selectivity or attaining optimum drug response and exposure properties. Because of all these impressive outcomes and as the potential candidates with anti-viral activity, alkaloids can be used further as a drug. We examined the potential of 51 alkaloids against various viral targets. They were screened for their drug likeness and Toxicity profile. 19 alkaloidal phytoconstituents that fulfils the criteria of being drug candidate were docked to find their affinity as inhibitors for viral targets.

Through the study it was found that three alkaloids namely Liriodenine, Cryptoheptine and Alstonine have potential interaction and significant hydrophobic contact with active residues of viral targets. Thus, it can be concluded that these alkaloids could be used as potential drug against several viral diseases and this report will undoubtedly serve us with a contemporary frontier of anti-viral drug research as well as provides a profound description of the importance of such agents in infections.

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