Effect of Natural Compounds to Inhibit Human Respiratory Syncytial Virus

Debanjan Mitra[1], Pradeep K. Das Mohapatra[1]*

[1] Department of Microbiology, Raiganj University, India
*Corresponding Author: [1]pkdmvu@gmail.com

Abstract. Current COVID-19 effects are forcing us to think about other deadly viral diseases. Respiratory syncytial virus (RSV) is one of them. Every year thousands of children lost their lives due to respiratory diseases which are occurred by this RSV. Nowadays, bioactive compounds show an enormous effect on many deadly diseases and show excellent therapeutic effects. In this study, we have identified five bioactive compounds from the plant which will be used in the treatment of RSV. Molecular docking on the protein was done by Autodock. Hydrogen was added and routable bonds were fixed in the preparation time of protein for docking. All those compounds show their non-toxic nature which is evaluated by Lipinski's Rule of Five. Molecular docking on RSV matrix protein and surface glycoprotein with those bioactive compounds shows very promising results. Between all those compounds Baicalein appears as a lead compound. It shows -8.1 Kcal/mol in the case of matrix protein and -7.9 kcal/mol in the case of the surface glycoprotein of RSV. Due to its availability and non-toxic nature, it can be used in the treatment of RSV. AS it is derived from plants, it also has very fewer side effects than chemical drugs.

Index Terms: Respiratory syncytial virus, Molecular docking, Lipinski Rule of Five, Matrix protein, Bioactive compounds

I. INTRODUCTION

In infants under the age of two years, the human respiratory syncytial virus (RSV) is the most common cause of severe respiratory tract infections [1]. Premature newborns and children having chronic pulmonary or congenital cardiac disorders are particularly vulnerable, although sick adults and the aged have also been identified as high-risk populations. RSV infection causes rhinitis and typical cold-like symptoms, but it can also lead to acute pneumonia or bronchiolitis, necessitating hospitalization [2-4]. Throughout Europe and North America, seasonal epidemic outbreaks of RSV illness occur in the winter and early spring, with a peak incidence in December [5]. There is a link between higher RSV infection rates and rainy seasons in tropical nations [6]. RSV activity is influenced by relative humidity, however, the exact impact on the illness trajectory or viral transmission dynamics is uncertain [7]. Antibody cross-reactivity patterns indicated two antigenic subgroups (A and B), which were then divided into genotypes based on genetic divergence within the highly variable G gene [8-10]. A preventative method based on a humanized neutralizing antibody against RSV is sufficient to protect newborn newborns at elevated danger, such as premature babies, those with cardiovascular disorders, and those with immunodeficiencies. However, major public health systems throughout the world cannot sustain this method [11-12]. Two membrane proteins, a trimeric fusion (F) glycoprotein, and an attachment (G) glycoprotein are involved in RSV's entrance into host cells.

Nowadays, insilico studies are playing a very crucial role in research and development [13-15]. Molecular docking and dynamics are important methodologies in drug design and synthesis [16-19]. Douglas and colleagues discovered that MDT-637 (VP-14637) and JNJ-2408068 (R-170591) prevent RSV fusion by a similar mechanism [20]. Computational investigations on pyrethroids revealed a glide score of -4.54, and it interacted with two key residues of an RSV target protein, LYS46 and HIS151 [21]. Recent research examined the effect of 2,20-dithiopyridine (aldrithiol, AT-2), which is known to inactivate HIV-1 by altering the NC zinc finger, on RSV infectivity, based on the shared function and geometry of the zinc finger motif across Retroviruses and RSV. The results demonstrated that this chemical may inactivate RSV at a dose of 10 mM, likely by M2-1 protein alteration [22]. VP-14637 and JNJ-2408068, as well as GS-5806, BMS-433771, P13, C15, and BTA-C585, all inhibit RSV fusion by a mechanism involving a similar interaction with the F protein, according to several studies [23]. The allosteric inhibitor of the F-protein GS-5806 prevents viral entrance. It is the first of the orally accessible medication candidates to have completed a phase 2 clinical study. In vitro, GS-5806 was demonstrated to be active against a variety of RSV clinical isolates [24]. MDT-637 has been reformulated as VP-14637 for enhanced aerosol delivery. With an EC50 value of 1.4 nM, VP-14637 has antiviral efficacy against RSV-A strain A2. It attaches to the F protein directly and prevents the virus from fusing with the host cell [25]. AZ-27 is a non-nucleoside L-protein inhibitor that suppresses RSV-A replication (both lab strains and clinical isolates) with EC50 values in the 10– 40 nM

Debanjan Mitra, Pradeep K. Das Mohapatra – "Effect of Natural Compounds to Inhibit Human Respiratory Syncytial Virus", Pg no: 97 – 101. 2022
doi.org/10.36647/978-93-92106-02-6.18

range and is a follow-up to YM-53403, which was found in a CPE-based screening effort. The activity against RSV-B is significantly lower (EC50 1 lM) [26]. RSV604 is a micro drug RSV A and B replication inhibitor having an EC50 of 0.8 lM against both viruses. The chemical was created by optimizing a hit discovered via a CPE-based screening attempt [27].

Nowadays, bioactive compounds are showing a remarkable effect on many diseases [16, 17, 19]. Due to their natural availability and low toxicity profile, they can be used safely. In this study, several bioactive compounds have been identified as drug compounds. Those compounds are Arjunone, Baicalein, Kaempferol, Emodin, Anthraquinones, and Acyclovir. These bioactive compounds are already used in many diseases. Arjunone is used in diabetes [28]. In periodontal ligament cells exposed to lipopolysaccharides, baicalein suppresses the inflammatory response and enhances osteogenic activity [29]. Kaempferol shows its therapeutic effect on osteoarthritis, mastitis, rheumatoid arthritis, etc. [30]. Emodin is used as an anti-cardiovascular drug [31]. Purgation, anti-inflammation, immunoregulation, antihyperlipidemic, and anticancer properties are all treated using anthraquinones [32]. Acyclovir is already used as an antiviral disease [33].

II. MATERIAL AND METHODS

2.1 Retrieved of bioactive compounds and target proteins

All structures of drug compounds i.e., Arjunone, Baicalein, Kaempferol, Emodin, Anthraquinones, and Acyclovir (Figure 1) were downloaded from the PubChem database [34]. The structure of target proteins i.e., Fusion glycoprotein (F protein) and matrix protein (M protein) were retrieved from the RCSB PDB database [35].

2.2 Descriptor properties of ligand compounds

Descriptor properties are very important parameters for drug molecules. Algorithms construct mathematical representations of molecule attributes, which are known as molecular descriptors. The physical and chemical information of molecules is quantitatively described using the numerical values of molecular descriptors [36-37]. Drug-likeness of Arjunone, Baicalein, Kaempferol, Emodin, Anthraquinones, and Acyclovir was evaluated by the “Lipinski’s Rule of Five” [38]. This rule implicated only oral drugs.

2.3 Preparation of ligand and proteins for molecular docking

All ligand molecules were optimized by semi-empirical [39] method (PM3) by using VEGA ZZ [40] software. Ligand optimization is a critical step in achieving proper protein-ligand interaction. AUTODOCK 4.2 [41] generated PDBQT files for the protein and ligand. This program was also used to perform molecular docking. Grid space and its dimensions were taken from the previous study [16-18]. All rotatable ligand bonds were frozen. Protein has polar hydrogens added to it. Finally, protein-ligand complexes were formed by PyMol software [42].

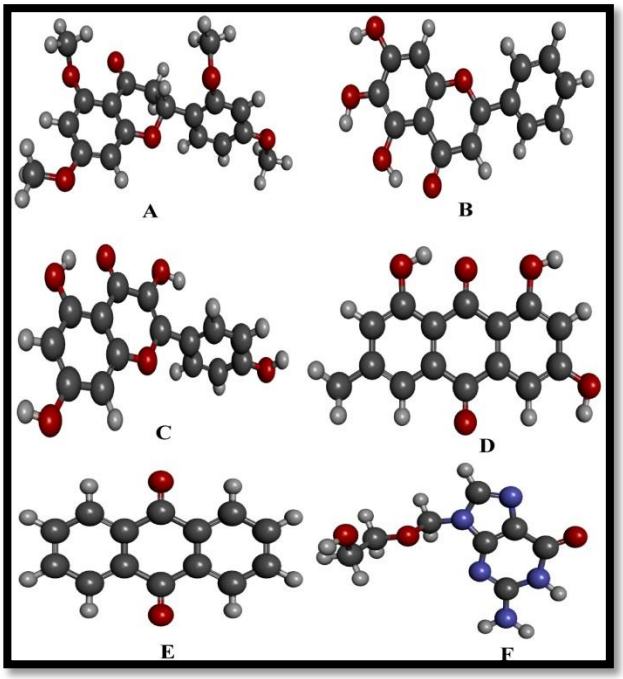

Figure 1- 3d structures of A. Arjunone B. Baicalein C. Kaempferol D. Emodin E. Anthraquinones F. Acyclovir

III. RESULT AND DISCUSSION

3.1 Calculation of drug-likeness properties

Lipinski's rule of five states about four properties of drug compounds. The molecular weight (MW) of medicine or lead molecule must be less than 500 Dalton, the hydrogen bond acceptor (HBA) must be less than or equal to 10, and the hydrogen bond donor must be less than or equal to 5. The LogP or octanol-water partition coefficient must always be less than +5. A single violation of any of those conditions can be tolerated.

Results of drug-likeness indicate that all drug compounds are fulfilled all the parameters. So, they can be used as oral drugs. All drug compounds have a molecular weight of less than 500 Dalton or g/mol. Drugs with a molecular weight of less than 500 g/mol can pass through the skin and blood vessels [43]. Arjunone shows the highest molecular weight i.e., 344.4 g/mol. All lead molecules have a positive LogP value, indicating that they are all lipophilic. Only Acyclovir shows negative LogP that means it is lipophobic. Lipophilic medications have an advantage over hydrophilic pharmaceuticals in terms of absorption [44]. HBD is high in Kaempferol whereas Arjunone shows the highest HBA. It has also the highest number of rotatable bonds. The amount of rotatable bonds is a measure of molecular flexibility that plays a role in determining medication oral bioavailability. The penetration rate decreases as the number of rotatable bonds increases [45]. Drugs having a bigger polar

surface cannot be absorbed by the human body. A larger surface area isn't important for injectable drugs because they go straight into the vein. Acyclovir shows the highest polar surface area whereas Anthraquinones shows the lowest polar surface area.

Table1- Drug-likeness properties with Lipinski's rule of five parameters and some other descriptor parameters

Name	PubChem ID	M.W (g/mol)	LogP	HBD	HBA	Rotatable bond	Polar Surface Area (Å^2)
Arjunone	14034821	344.4	2.8	0	6	5	63.2
Baicalein	5281605	270.24	1.7	3	5	1	87
Kaempferol	5280863	286.24	1.9	4	6	1	107
Emodin	3220	270.24	2.7	3	5	0	94.8
Anthraquinones	6780	208.21	3.4	0	2	0	34.1
Acyclovir	135398513	225.2	-1.9	3	5	4	115

3.2 Molecular docking

All sdf formatted structures were converted to PDBQT file before the molecular docking analysis. Docking is a molecular modelling tool for predicting how drug compounds (ligands) interact with proteins (enzymes). Among all those drug compounds, Baicalein appeared as the best drug compound followed by Kaempferol and Emodin (Table 2). Baicalein showed the highest molecular docking score i.e., -8.1 Kcal/mol energy in interaction with matrix protein (2VQP) of RSV. Emodin appeared as the best inhibitor of Fusion glycoprotein (5KWW) of RSV with good binding energy (-7.9 Kcal/mol). Baicalein shows 2 conventional hydrogen bonds, one pi-alkyl bond, and 4 Van der Waal interactions with Matrix protein of RSV (Figure 2A and 2B). Kaempferol shows 2 conventional hydrogen bonds, one pi-donor hydrogen bond, and 5 Vans der Waals in interaction with Matrix protein of RSV (Figure 2C and 2D). In the case of ligand and F glycoprotein interaction, Emodin shows 1 unfavourable donor-donor interaction, 2 pi-donor hydrogen bonds, 2 pi-alkyl, 2 alkyl bonds, 2 pi-sigma bonds, 6 Van der Waals interactions (Figure 3A and 3B). Baicalein shows 1 carbon-hydrogen bond, 1 pi-donor hydrogen bond, 1 pi-cation bond, 3 pi-alkyl bonds, and 7 Van der Waal interactions in binding with F glycoprotein of RSV (Figure 3C and 3D).

Table 2- Drugs name and their binding energies in interaction with matrix protein (2VQP) and F glycoprotein (5KWW) of RSV

Drug name	Matrix protein (2VQP) Kcal/mol	F glycoprotein (5KWW) Kcal/mol
Arjunone	-7.1	-6.7
Baicalein	-8.1	-7.7
Kaempferol	-7.9	-7.5
Emodin	-7.3	-7.9
Anthraquinones	-6.5	-6.2
Acyclovir	-6.1	-5.6

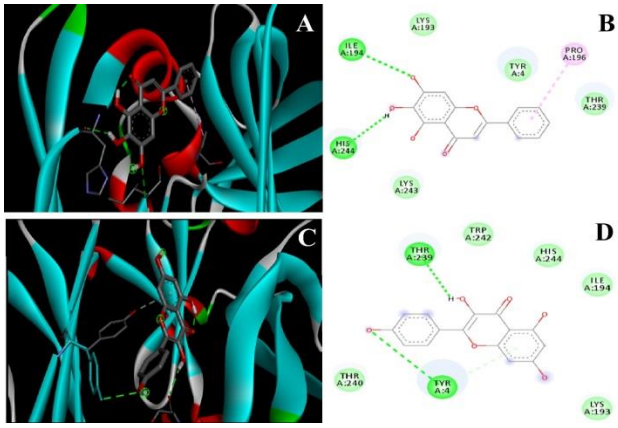

Figure 2- A. 3d interactions of Baicalein and matrix protein of RSV B. 2d interactions of Baicalein and matrix protein of RSV C. 3d interactions of Kaempferol and matrix protein of RSV D. 2d interactions of Kaempferol and matrix protein of RSV

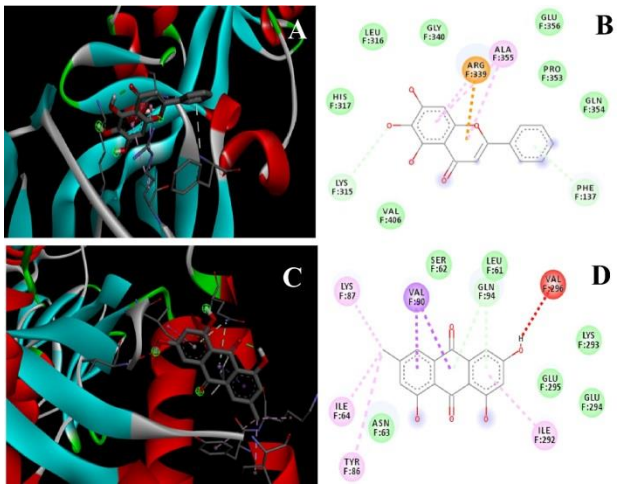

Figure 3- A. 3d interactions of Emodin and F glycoprotein of RSV B. 2d interactions of Emodin and F glycoprotein of RSV C. 3d interactions of Baicalein and F glycoprotein of RSV D. 2d interactions of Baicalein and F glycoprotein of RSV

IV. CONCLUSION

RSV can be inactivated by drugs that inactivate retroviruses by targeting their matrix protein and F glycoprotein, as demonstrated in this study. All those bioactive compounds show multi-target inhibiting effects on RSV. So, they can perform better than other drugs. Due to their oral bioavailability and non-toxic nature, they are very safe in use. Among all bioactive compounds, Baicalein appeared as the best lead compound with very high binding energies. Kaempferol and Emodin also show very promising results. The current exploratory molecular docking investigation might be a significant step forward in experimentally understanding their antiviral nature and mechanism. However, it might be a useful research tool for better understanding the immunobiology of RSV illness.

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