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MOLECULAR DOCKING STUDIES OF spike and ACE2 INHIBITORS IN THE TREATMENT OF COVID-19

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ABSTRACT

Angiotensin converting enzyme 2 (ACE2) is a transmembrane protein which is considered as a receptor for spike protein binding of novel corona virus (SARS-CoV2). Since no specific medication is available to treat COVID-19, designing of new drug is important and essential. In this regard, this study was to seek potential natural compounds that can resist COVID-19 using *in silico* molecular docking on ACE2 proteins. Molecular docking was achieved by using the Argus lab software. Natural products are safe and easily available to treat corona virus affected patients, in the present alarming situation. The natural phytocompounds acting on spike protein of SARS-CoV2 with its human receptor ACE2 molecule were then selected from siddha medicine one of the traditional systems of India Sundaikai vattral Choornam (*Solanum torvum*) have valuable properties of cold, cough, tuberculosis, hepatotoxicity, cancer, etc. Results: eight potential natural anti-COVID-19 phytocompounds were selected and were evaluated for absorption, distribution, metabolism and excretion (ADME) and Lipinski rules. The content of the eleven phytocompounds from *Solanum torvum* were determined via a literature search. Conclusion: *Solanum torvum* show promise for resisting COVID-19 and are thus recommended as supplements to prevent the infection of COVID-19 during its outbreak period.

Keywords:

In silico, *Solanum torvum*, COVID-19, Argus Lab, phytocompounds, SARS-CoV2 and ACE2.

INTRODUCTION

COVID-19 is a deadly disease, where the infection is caused by severe acute respiratory syndrome corona virus 2(SARS-CoV-2 formerly known as 2019-ncov) by the International Commission on the Classification of Viruses on February 11, 2020. On the same day, the World Health Organization named the disease caused by this virus as COVID-19. Corona viruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV). The Symptoms of corona virus include Fever, dry Cough, and Chills or repeated shaking with chills, fatigue, muscle pain, headache, sore throat, loss of smell or taste, congestion or runny nose, nausea or vomiting, diarrhea and difficulty in breathing [Zhou *et al*., 2020]. However, older and co morbid people who suffer from cardiovascular diseases, diabetes, and chronic respiratory diseases are more likely to develop severe symptoms (dyspnea, respiratory failure, septic shock, and multiple organ dysfunction/failure). Recently, some other symptoms like bluish spots on the feet, clotting, and stroke also noticed in COVID-19 positive patients (Avula A *et al*., 2020). It takes a minimum of 5-6 days to indicate symptoms when the person is affected from virus. The foremost promising test for the identification of virus is RT - PCR technique.

The COVID 19 belongs to the subfamily Orthocoronavirinae, within the family Coronaviridae, order Nidovirales and realm Riboviria. COVID 19 is an envelope, positive sense single stranded RNA genome encoding quite 20 proteins. The genome size of Covid ranges from around 26 to 32 kilobases, one among the greatest among RNA viruses. The corona virus particles are spherical in shape having spike proteins around them. These proteins are responsible for virus replication in human host cells. Spike proteins after attaching with human cells; undergo structural changes, which results in a fusion of viral particle membrane with human host cell membrane. Thus, the viral RNA enters into the host cell and produces more viruses after copying its genome. SARS-CoV-2 spike proteins bind to the receptor proteins, on the host cell surface, known as angiotensin converting enzyme 2 (ACE2). The molecular level structure of SARS-CoV-2 spike protein has a Receptor Binding Domain (RBD) for binding to host human cells. Receptor Binding Domain (RBD) of spike glycoprotein interacts with ACE2 receptor in Protease Domain (PD) of the host human cell, causing viral infection.

Scientists have been focusing on searching antiviral phytocompounds with low toxicity and high curative effect from natural plants in recent years. Herbal remedies are widely used in both developed and developing world countries to treat various illnesses indispensable (Chintamunnee V *et al*., 2012). The WHO reported, about 80% of the world's population depends primarily on traditional medicine to treat their illnesses. Traditional medicine is often considered to be a kind of complementary or alternative medicine

(Gurib-Fakim A., 2006) .Herbal medicines include herbs, herbal preparations, and finished herbal products (tea varieties), as well as additives derived from different kinds of herb/ plant parts (ginger, garlic, lemon, and so on), which are used when preparing food in many Asian countries, including India and China. The active components of these herbs have many advantages, like lower toxicity and allergenicity than some commercial medications, regulating immunological responses, and causing viral destruction (Lin LL *et al*., 2016). Various common herbs have been used to prevent viral infections, and their efficacy has been demonstrated in research trials (Lin LT *et al*., 2014) (Dhama K *et al*., 2018). Herbal plants like *Bupleurum* spp., *Heteromorpha* spp., and *Scrophularia scorodonia* have been used in the treatment of coronaviruses in China (Cheng *et al*., 2010), and *Azadirachta indica, Carica papaya*, and *Hippophae rhamnoides* have been scientifically proven to be effective in treating or preventing Dengue fever in India. Solanum torvum Sw. (Family: Solanaceae), commonly known as Turkey Berry [Ashok D Agarwal *et al*., 2010] is native to Mexico, Peru and Venezuela. It is widely distributed in Africa, West Indies, India, Bermuda, Indonesia, Malaya, China, Philippines and tropical America [Muhammed Arif et al., 2011]. The researches done on Solanum torvum had shown that the plant possesses significant antimicrobial, anticancer, diuretic, anti-inflammatory, anti-influenza activity [Zubaida Yousaf.]. The use of the plant to treat SARS-CoV by the traditional people is not yet scientifically validated.

Molecular docking is a method of drug design based on the characteristics of the receptor and the way the receptor interacts with the drug molecule. As an emerging research method combining the physical and chemical principles with scientific calculation algorithms, molecular docking provides a feasible strategy for exploring the basis and mechanism of the phytocompounds [Hirayama N, 2017]. This study took SARS-CoV-2 spike proteins and ACE2 as receptors, and molecular docking was performed to select potential antiviral active ingredients for the development of effective and quick-acting chemical components that can resist COVID-19. These studies have brought hope to the search for effective drugs to prevent and control the COVID-19, and may help us to develop a more effective way to fight COVID-19.

MATERIALS AND METHODS

Protein data bank

The protein data bank (PDB) archive is the single worldwide repository of information about the 3D structure of large biological molecules, including proteins and nucleic acids. PDB is a repository for the three-dimensional structure data of large biological molecules, such as protein and nucleic acids. [Dykstra et al., 2007] The structure of human ACE2 was retrieved from PDB (1R42).

Active site prediction of human ACE2 **receptor**

After obtaining the final model, the possible binding sites of 1R42 were searched using Computed Atlas of Surface Topography of Proteins (CASTp). These include pockets located on protein surfaces and voids buried in the interior of proteins. CASTp includes a graphical user interface, flexible interactive visualization, as well as on-the-fly calculation for user uploaded structures. [Binkowski *et al.*, 2003]

Absorption, distribution, metabolism and excretion analysis and Lipinski's rule of five

Pharmacokinetic (PK) analysis of biological or pharmaceutically active compounds was conducted to select drug candidates [Daina *et al*., 2014]. Absorption, distribution, metabolism and excretion (ADME) screening criteria for ligands in this study included oral bioavailability (OB) >30% and drug-likeness (DL) >0.18. Values were obtained from the TCMSP database. Lipinski's rule of five is also called Pfizer's rule, which specifically includes relative molecular weight <500, ClogP <5, number of hydrogen bond donors <5, number of hydrogen bond receptors <10, number of keys _10, which are used to evaluate the DL and durability of a phytochemical or chemical compound. Compounds that conform to Lipinski's rule of five will have better PK properties and higher bioavailability in the metabolic process in vivo, and are therefore more likely to be made into oral drugs. In this study, the phytocompounds were further chosen from the small molecule database, which was an efficient way to find compounds with good PK properties and high bioavailability. Ligands of this particular study were analyzed using http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp based on Lipinski's rule of five.

Preparation of ligand structure

Using Chemsketch the structures of the drugs were generated by their SMILES notation obtained from pubchem and the structural analogues of these drug were generated and the three dimensional optimizations were done and then saved.mol file (a file format for holding information about the atoms, bonds, connectivity and coordinates of a molecule). The selected ligand 3D structure is shown in Fig.1.

Docking

Docking the inhibitors against the active site of the 1R42 Docking is a computational technique that samples conformations of small molecules in protein binding sites; scoring functions are used to assess which of these conformations best complements the protein binding site (Warren *et al.*, 2006). The inhibitor and target protein was geometrically optimized and docked using docking engine Argus Dock.

Discussion

Molecular modeling (docking) study was carried out for compound like from Phenol, 2,5-bis(1,1-dimethylethyl), Catechin, Myricetin, Caffeic acid, Solasodine, Solanidine, Rubijervine and Isorubijervine from *Solanum torvum* fig 1(A,B,C,D and H) for COVID-19.

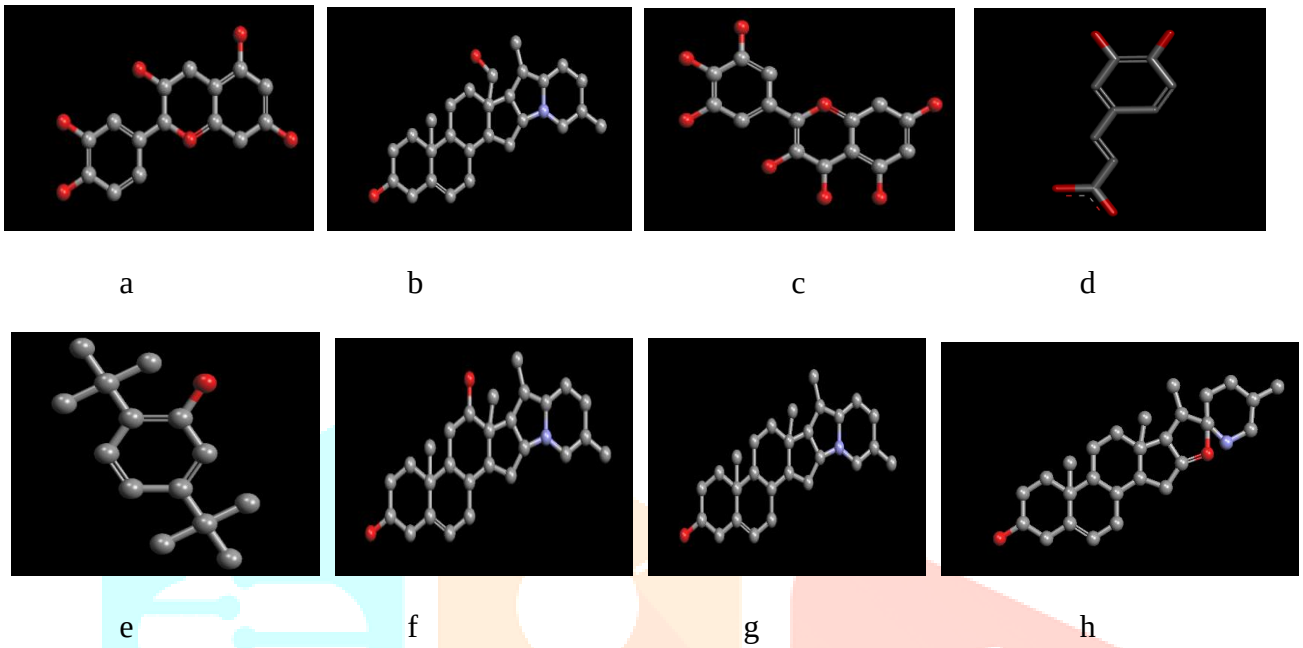

Fig -1 a, 1b, 1c, 1d, 1e, 1f, 1g and 1h: It Shows compound from *Solanum torvum* plant Phenol, 2,5-bis(1,1-dimethylethyl), Catechin, Myricetin, Caffeic acid, Solasodine, Solanidine, Rubijervine and Isorubijervine

The potential active site amino acids were predicted using Castp. Among the 52 active sites predicted, pocket 1 found to be the best active site which contains 108 amino acids. Thus, the protein was targeted against pocket 1.Given the three-dimensional structure of a target receptor molecule usually a protein; chemical compounds having potential affinity towards it are designed rationally, with the aid of computational methods (Dundas, 2006). Figure 2 shows the structure of inhibitors target against the ACE2.

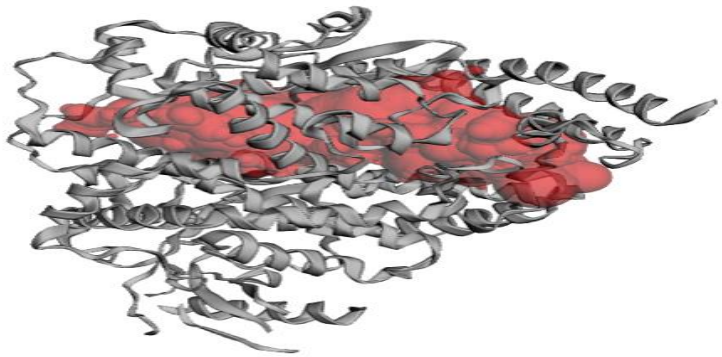

Fig. 2: Shows the Structure Targeted ACE2 Protein Predicted Using Castp

The target protein and inhibitors were geometrically optimized .Given the three-dimensional structure of a target receptor molecule usually a protein; chemical compounds having potential affinity toward sit are designed rationally, with the aid of computational methods. Detailed bioinformatics analysis

offers a convenient methodology for efficient *in silico* preliminary analysis of possible function of new drug. Figure 3 shows the structure ACE2 protein.

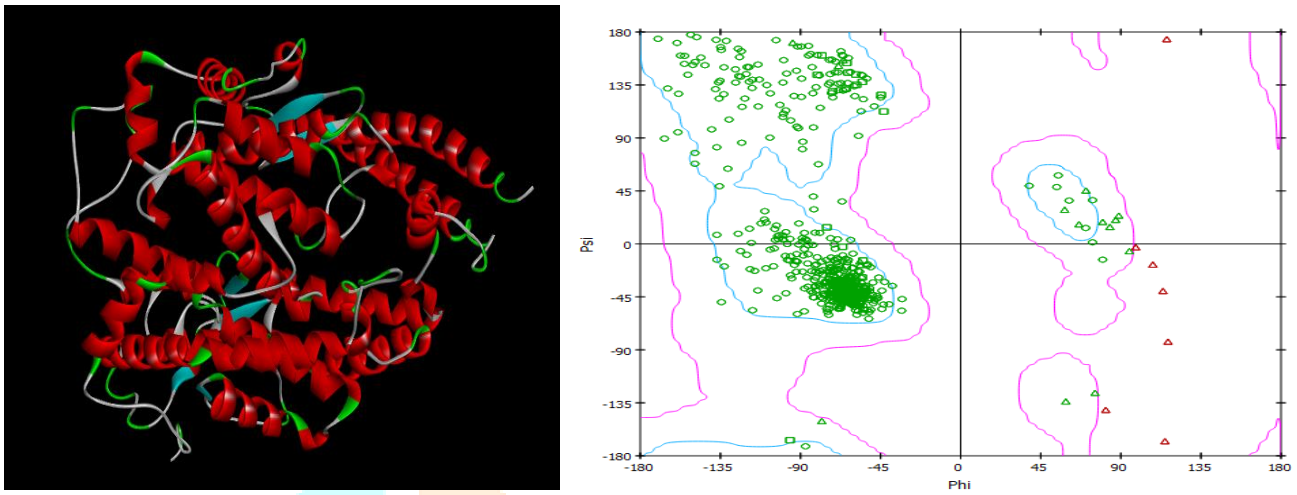

Fig. 3: Shows the structure ACE2 protein and Ramachandran plot visualized using Discovery studio

Molecular docking is an important tool in structural molecular biology and computer- assisted drug designing. It finds the suitable inhibitors for receptors. The molecular docking predicts the binding ability of the ligand molecule with the receptor molecule. This computational technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of drug-receptor interaction. In the present study, docking results revealed the binding interactions between the Human ACE2 protein. Out of 8 inhibitors analyzed i.e. Catechin, Isorubijervine, Myricetin, Caffic acid, Phenol, 2,5-bis (1,1-dimethylethyl), Rubijervine, Solanidine and Solasodine has showed higher binding energy of -14.677 Kcal/mol against the target protein. The binding energy of all the inhibitors was shown in Table 1.

S.No	Compound Name	Molecular formula	Molecular Weight [g/mol]	Hydrogen bond	Energy value Kcal/mol 1R42
1	Phenol, 2,5-bis (1,1-dimethylethyl)	C14 H22 O	206.32	5	-12.848
2	Catechin	C15 H10 O6	290.26	6	-8.784
3	Myricetin	C15 H10 O8	318.23	6	-7.335
4	Caffeic acid	C9 H8 O4	180.15	3	-9.291
5	Solasodine	C27 H43 NO2	413.63	2	-13.522
6	Solanidine	C27H43NO	397.63	9	-14.677
7	Rubijervine	C27 H43 NO2	413.63	2	-14.405
8	Isorubijervine	C27H43NO2	413.63	3	-12.807

Table 1.shows the binding energy of all inhibitors

After complete protein ligand docking the result was obtained in histogram format it shows the overall interaction, hydrogen bond and hydrophobic interaction. Fig. 4 shows the 3D surface was created and colored by hydrogen bond character, with receptor donors colored in green and receptor acceptors in cyan. 2 D diagram defined nine hydrogen bond interaction at ASP350, PHE390, LEU391,PHE 32, LEU100, LEU73, SER 77, TRP 69 and PHE 40 . Solvent accessibility of the ligand atom and the amino acid residues. Heavier shading indicates more exposure to solvent.

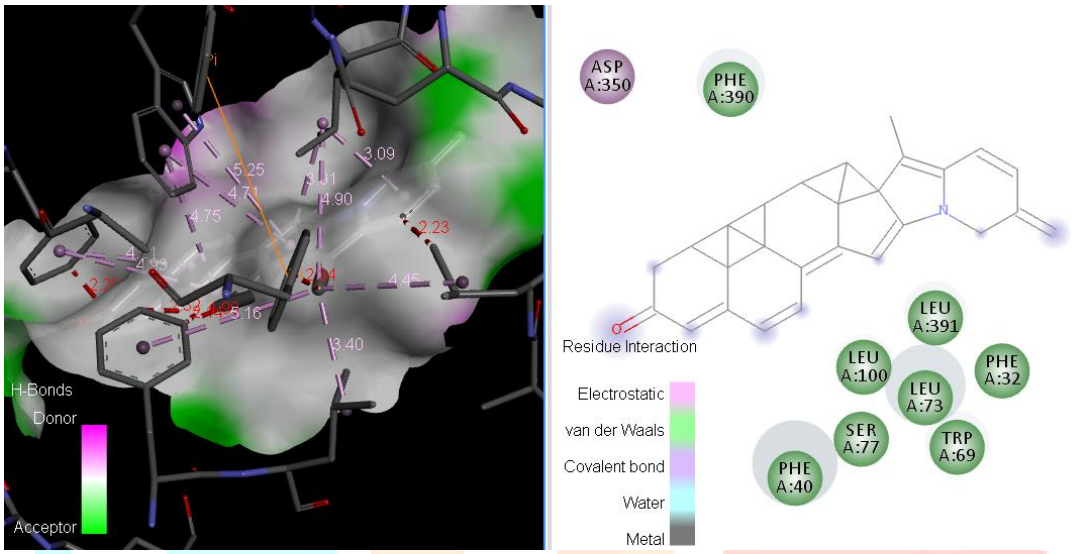

Fig .4, shows the 3D and 2D Hydrogen Bond Interaction

The 3D surface was created and colored by hydrophobic interaction character, with receptor donors colored in blue and receptor acceptors in brown. 2 D diagram defined five hydrophobic interaction region at PHE 32, PHE 40, TRP 69, LEU 73 and LEU 100 is illustrated in Figure 5. Solvent accessibility of the ligand atom and the amino acid residues. Heavier shading indicates more exposure to solvent.

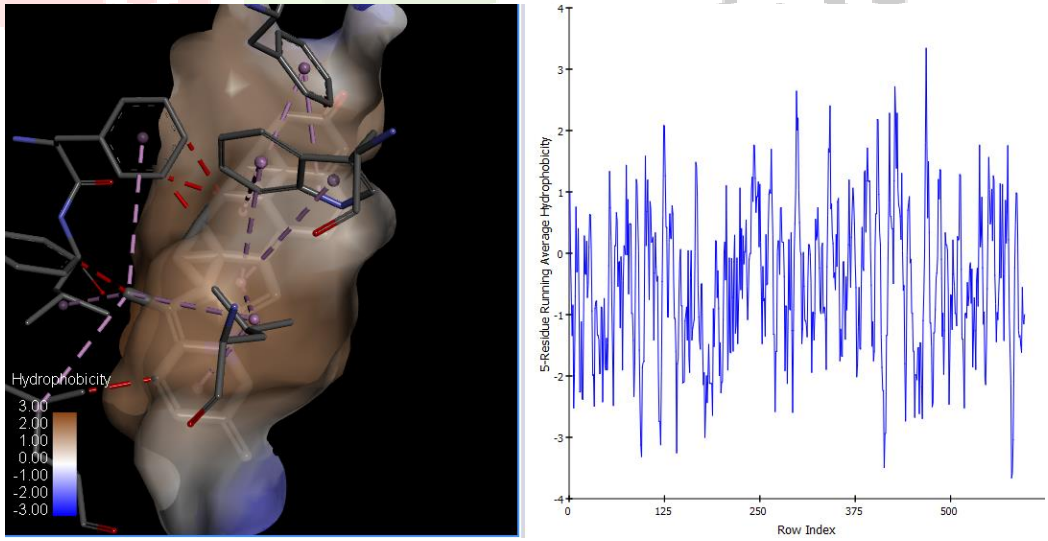

Fig .5, shows the 3D and 2D Hydrophobic Bond Interaction

CONCLUSION

The present study indicates that the herbal plant *Solanum torvum* can be used in the treatment of Covid 19, which shows a strong binding affinity towards ACE2 protein . This brings a strong focus towards these plant that, when administered during the treatment of Covid 19 may block ACE2. Solanidine showed the highest affinity towards ACE2 compared to other compounds.

This creates a strong hypothesis that the effects of complex formation by ACE2 and *Solanum torvum* contribute towards combating against Covid 19. Hence, ACE2 protein may become a prospective target for inhibition of Covid 19 and may unlock a strong initiative in developing novel ligand which is specified towards it. Hence the compound specified in this work can undergo certain specification to improve its drug properties and could act as a best drug for Covid 19. The mechanism of action is Solanidine to inhibit the activity of ACE2 that is involved in Covid 19.

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REFERENCE:

1. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. Brain Behav. Immun. 2020; in press. https://doi.org/10.1016/j.bbi.2020.04.077
2. Binkowski TA, Naghibzadeh S, Liang J. CASTp: Computed atlas of surface topography of proteins. Nucleic Acids Res, 2003; 31: 3352-55.
3. Cheng HM, Li CC, Chen CY, et al. Application of bioactivity database of Chinese herbal medicine on the therapeutic prediction, drug development, and safety evaluation. J. Ethnopharmacol. 2010;132:429- 437. https://doi.org/10.1016/j.jep.2010.08.022
4. Chintamunnee V, Mahomoodally MF. Herbal medicine commonly used against non-communicable diseases in the tropical island of Mauritius. J Herb Med. 2012;2:113-125. https://doi.org/10.1016/j.hermed.2012.06.001
5. Daina A, Michielin O, Zoete V. iLOGP: a simple, robust, and efficient description of n octanol/water partition coefficient for drug design using the GB/SA approach. J Chem Inf Model 2014;54:3284–301.
6. Dhama K, Karthik K, Khandia R, et al. Medicinal and therapeutic potential of herbs and plant metabolites/ extracts countering viral pathogens – Current knowledge and future prospects. Curr

7. Dundas J, Ouyang Z, Tseng J, Binkowski A, Turpaz Y, Liang J. CASTp: computed atlas of surface topography of proteins with structural and topographical mapping of functionally annotated residues. Nucleic Acids Res. 2006; W116–W118.

8. Dykstra KD, Guo L, Birzin ET. Estrogen receptor ligands. Part 16: 2-Aryl indoles as highly subtype selective ligands for ERalpha. Bioorg Med Chem Lett, 2007; 17: 2322-8.

9. A. Medicinal plants: traditions of yesterday and drugs of tomorrow. Mol aspects of Med. 2006; 27(1):1-93. https://doi.org/10.1016/j. mam.2005.07.008

10. Hirayama N. Docking simulations between drugs and HLA molecules associated with idiosyncratic drug toxicity. Drug Metab Pharmacokinet 2017;32:31–9.

11. Lin LL, Shan JJ, Xie T, et al. Application of traditional Chinese medical herbs in prevention and treatment of respiratory syncytial virus. Evid. Based Complement. Alternat. Med. 2016;6082729. https://doi. org/10.1155/2016/6082729

12. Lin LT, Hsu WC, Lin CC. Antiviral natural products and herbal medicines. J Tradit Complement Med. 2014;4(1):24-35. PMID: 24872930; PMCID: PMC4032839. https://doi.org/10.4103/2225-4110.124335

13. Muhammed Arif, Sheeba Fareed. (2011) Pharmacognostical studies and evaluation of total phenolic and flavonoid contents of traditionally utilized fruits of Solanum torvum Sw. India J Nat Prod Resour 2:218-24.

14. Warren G.L, C.W Andrews, A.M Capelli, B. Clarke, J. LaLonde, M.H Lambert, M. Lindvall, N. Nevins, S.F Semus, S. Senger, G. Tedesco, I.D Wall, J.M Woolven, C.E Peishoff and M.S Head,Acritical assessment of docking programs and scoring functions. J Med Chem. 49(20): 5912-31, (2006).

15. Zhou, P., Yang, X., Wang, X. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273 (2020). https://doi.org/10.1038/s41586-020-2012-7