Journal of Pharmaceutical Research International

33(46B): 477-484, 2021; Article no.JPRI.73343
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

In Silico Drug Discovery of 4-Hyroxypanduratin A, 6-Gingerol and Luteolin Targeting Nipah Virus

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i46B32964
Editor(s):
(1) Dr. Sachin Kumar Jain, IPS Academy College of Pharmacy, India.
Reviewers:
(1) Salman Ahmed, University of Karachi, Pakistan.
(2) Chinky Goyal, Shri Krishna Ayush University, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/73343

Original Research Article

Received 25 June 2021
Accepted 27 August 2021
Published 23 October 2021

ABSTRACT

Nipah Virus is a zoo tonic virus and has re-emerged again with more deadliness. NiV has infected many animals and humans worldwide and a huge loss to life has been faced. NiV contains a Fusion protein on its outer membrane which helps in the virus entry into the host cell. This fusion protein is a virulent factor and is a major anti-viral target. Many medicinal plants have been used against viral diseases, current research aims towards the potential of three daily dietary food elements that can be used as an anti-viral agent. In-silico studies are performed with 4-hyroxypanduratin A, 6-gingerol and Luteolin against the NiV-F and binding energies were calculated. It was reported that these phyto-compounds have good negative binding energies and they have the promising potential against Nipah Virus. Further in-vitro research can be performed with these phyto-compounds to design a specific drug against Nipah Virus.

Keywords: Human life; 4-hyroxypanduratin A; 6-gingerol; AutoDock; Luteolin; Nipah Virus; health care.

1. INTRODUCTION

The Nipah virus belongs to the Henipavirus class of the Paramyxoviridae family and outbreaks of the Nipah virus are zoonotic in nature. Nipah virus encephalitis is of critical public health concern and two distinct strains of Nipah virus (NiV) have been identified based on diffusion

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trends and mortality rates, notably NiV Malaysia (NiVM) and NiV Bangladesh (NiVB), among which NiVB is even more pathogenic than the other. The first outbreak was reported in Malaysia and after that, it was reported in Bangladesh. In 2018, 18 people were infected by the Nipah virus and 17 people died due to this disease in Kerala [1].

It has been reported that Fruit bats or flying foxes are the spreader and are responsible for the transmission of the virus to humans as well as animals. NiV has been found in wild bats and also on fruits like date palm which is infected by the urine or saliva of these animals [2]. It is also reported that drinking the water which is contaminated by these animals is also a major reason for the infection in India and Bangladesh. Symptoms like sore throat, vomiting, fever, headache and myalgia followed by unconsciousness if reported in humans. In few cases, typical pneumonia with severe seizures leads to coma.

4-hyroxypanduratin A: Several Asian nations, including China, India, Indonesia, Thailand, and Malaysia, use the *Boesenbergia rotunda* as a food component. It's often grown on small family ranches and utilized as a spice in dishes like soups and curry because of its fragrant flavour, which stimulates hunger. Rheumatism, peptic ulcer, dyspepsia, stomach ache, carminative, flatulence, gastrointestinal problems, gout, febrifuge, and muscular discomfort are among conditions that this herbal plant is utilized to cure. *B. rotunda* is commonly utilized in Indonesia to make "jamu," a common ingredient medicine for females after delivery, and also a cosmetic help for young women and a leukorrhea preventative. Fresh rhizomes are utilized to cure inflammatory disorders including dental caries, dysentery, diarrhoea, wounds, swelling, gum and tooth problems, colds and dry cough, and dermatitis and to act as a diuretic [3]. 4-hyroxypanduratin A is the main constituent of *B. rotunda* and it has been established in several studies that 4-hyroxypanduratin A is effective against several diseases. This study is conducted to find the efficacy of this compound against the NiV and develop an effective anti-viral.

6-gingerol: Several studies have shown that eating specific fruits and vegetables daily can lower the risk of a variety of illnesses. The rhizome of Zingiber officinale (ginger) is used as a spice and herbal medicine all over the world. It includes gingerols, a group of spicy phenolic compounds. Ginger's most pharmacologically active component is 6-gingerol. It is recognized to have several biological properties, especially anti-cancer, antioxidant, and anti-inflammatory properties. 6-Gingerol has been discovered to have anti-cancer properties through its effects on several biological processes associated with angiogenesis suppression, cytotoxic action, cell cycle regulation, and apoptosis [4]. As a result of its effectiveness and regulation of many targets, including its safety for human usage, 6-gingerol has attracted a lot of attention as a possible therapeutic agent against a variety of illnesses. This study is conducted to find the efficacy of this compound against the NiV and develop an effective anti-viral.

Luteolin: There are numerous varieties of plants that contain luteolin (3′,4′,5,7-tetrahydroxyflavone). It has been utilized in Chinese traditional medicine to treat cancer, illnesses, inflammation, and hypertension with herbs enriched with luteolin. In addition to its anti-cancer, anti-allergy, and anti-inflammation properties, luteolin is biochemically both an anti-oxidant and a pro-oxidant. Functionally, luteolin's biological actions might be linked to other diseases. Its anti-inflammatory action, for example, might be connected to its anti-cancer properties. The anti-cancer activity of luteolin is linked to the activation of apoptosis as well as the suppression of cell growth, metastasis, and angiogenesis [5][6]. This study is conducted to find the efficacy of this compound against the NiV and develop an effective anti-viral.

Structure of Nipah Virus: Before designing any drug or vaccine against any disease it is important to understand the structure and function of its proteins. NiV genome consists of six coding regions and several non-coding regions. The six coding regions include Nucleoprotein (N), Polymerase (L) protein, Phosphoprotein (P), Matrix (M) protein, Fusion (F) protein and Glycoprotein (G) (Fig. 1) wherein, nucleoprotein is used to make nucleocapsid and acts as a model for replication and transcription of the virus [7]. Membrane fusion of host cell and virus is initiated by the Fusion protein whereas Glycoprotein is held responsible for fusion and attachment.

Still, there are no approved specific vaccines or drugs against NiV available, this scarcity of treatment increases the necessity of the need for purposeful research in finding the inhibitor of the Nipah virus. To combat viral infectious diseases,

medicinal plants have always shown effectiveness and with less toxicity, large accessibility. The current research was conducted on three Indian Medicinal plants; 4-hyroxypanduratin A, 6-gingerol and Luteolin to find the potential therapeutic inhibitor of NiV through structure-based docking studies [8][9].

2. LITERATURE REVIEW

A research was conducted to target the Nipah virus by taking various naturally occurring phyto-compounds. The research was based on the in-silico studies which concluded that the Neoandrographolide from Andrographis paniculata, Hexahydrocurcumin from Zingiber officinale and Nirphyllin from Phyllanthus amarus is having the potential ability to act as the best inhibitor for the target protein of NiV [10]. Another In-Silico research was conducted on the small lead compounds that were targeting the proteins that were involved in the binding of the Nipah virus to the host cell. It was concluded that novel bioisosteres of favipiravir have promising potential to target NiV‑G/ephrin interactions to disrupt viral entry and provide the foundation for structure‑based antiviral drug design [11].

2.1 Research Questions

What are the effects of 4-hyroxypanduratin A, 6-gingerol and Luteolin on Nipah Virus Fusion Protein?

3. METHODOLOGY

Design: 3-dimensional structures for Nipah Fusion protein was downloaded from RCSB PDB and 3-dimensional structures for 4-hyroxypanduratin A, 6-gingerol and Luteolin was downloaded from PubChem. RCSB gives the file format .pdb but files downloaded from PubChem need to be converted to .pdb format [5]. This can be done with the help of the Open Babel tool. After getting both files in .pdb format they are used for docking. MGL tools provide the tool that is used for docking, AutoDock. After getting the .dlg file, the complex is formed using Autodock and it is visualized in BOVIA drug discovery studio (Fig. 2).

Sample: Files containing the 3D structure of ligand and receptor were downloaded from PubChem and protein data bank respectively. Fig. 3 is representing the ball and stick model of (A) 6-gingerol, (B) 4-hyroxypanduratin A and (C) Luteolin, Green balls represent carbon, red represents the oxygen and white ball represents the hydrogen molecule. The single stick between the balls is for a single bond while the double-stick represents the double bond. In Fig. 4, the Quaternary structure of Nipah Fusion protein is shown where red spirals are representing the α-helices and the cyan coloured ribbons are the β-plated sheets.

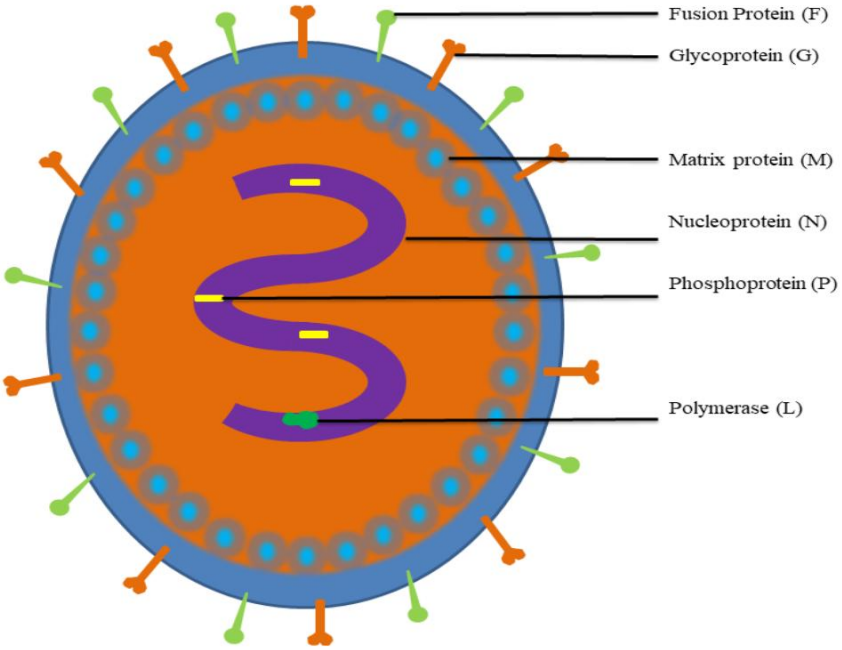


Fig. 1. Structure of Nipah Virus

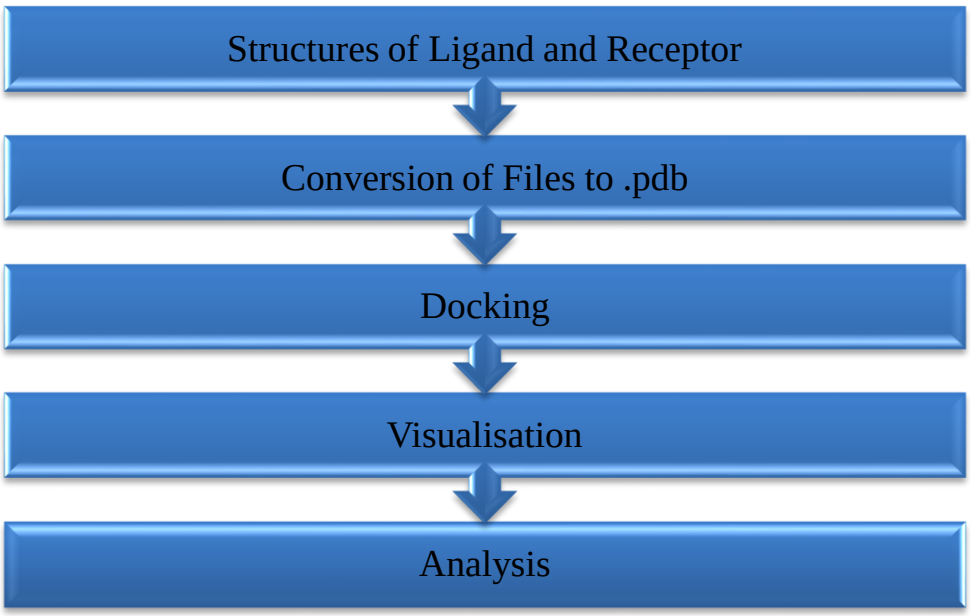


Fig. 2. Flow chart representing the protocol followed

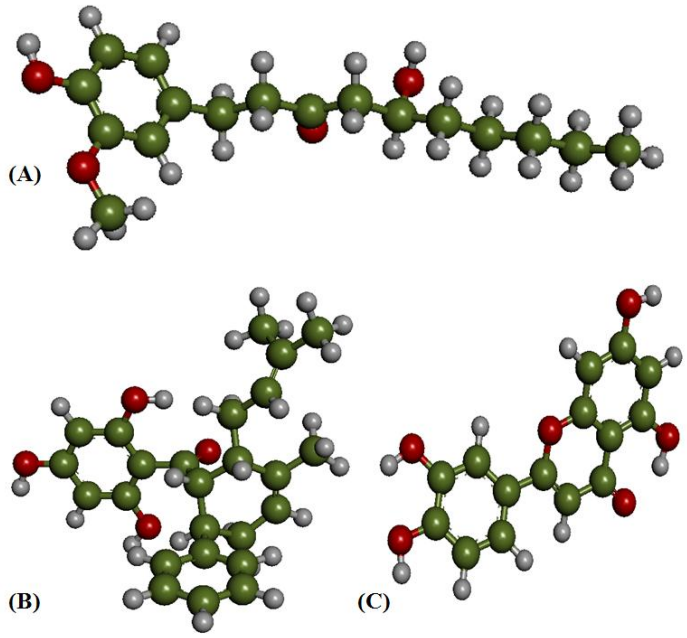


Fig. 3. Ball and stick structure of (A) 6-gingerol, (B) 4-hyroxypanduratin A and (C) Luteolin

Instrument: Public Chemistry (PubChem) is accessed to download the 3D structure of 4-hyroxypanduratin A, 6-gingerol and Luteolin in SDF format. PubChem is a freely accessible database of chemical information servers which is launched by the National Institute of Health (NIH) in 2004. Anyone can access this information by the means of a computer and the internet, you can upload the chemical information and it can be accessed by anyone worldwide [12]. It consists of chemical information like Molecular structure, patents, toxicity information and chemical properties. This chemical information is very useful to many researchers in finding out many important drugs.

3D structure of Nipah Fusion Protein was downloaded from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) in PDB format. It is an open database led by Helen M. Berman. Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB), here all the information about the different viral, bacterial and any other protein information can be found and can be downloaded. This information is used by many researchers to complete their research and further help the world. Open Babel is an easily accessible tool that converts the different chemical molecules file formats into another format. It is used to convert the SDF format of 4-hyroxypanduratin A, 6-gingerol and Luteolin 3D structure file to PDB format.

These structures are further used for the molecular docking experiment using AutoDock4. It is an open and easily accessible tool that is used to calculate how one small molecule will bind or how will it interact with the receptor of a known structure in 3D. Apart from docking it also calculates the binding affinity that helps in finding a better binding molecule to a receptor [13]. After retrieving the docked complex, it was visualised in Drug Discovery Studio. Distance between bonds, type of bonds formed was calculated and binding energy was calculated. BOVIA Drug Discovery Studio is used to visualise the bonds and distance between the formed bonds. It is a molecular modelling suite that has various features that helps in molecular modelling and simulation.

Data collection: After forming the DLG file type with the help of AutoDock, different conformations were analysed and based in the different binding energies model with the least binding energy was selected and it was visualised using AutoDock and BOVIA Drug Discovery Studio (Fig. 5). In Fig. 5: (a) 3D docked complex of Luteolin (b) 3D docked complex of 4-hyroxypanduratin A and (c) 3D docked complex of 6-Gingerol with the Nipah Fusion protein represents that all three phyto-compounds were interacting with the Viral protein and bonds were formed.

Data analysis: The length of a stronger bond will be less than a weaker one. For a better understanding of the docked complex, their 2D structures were constructed which represented the types of bonds formed and the distance between them. In Fig. 6: (a) 2D docked complex of Luteolin with Nipah virus fusion protein is represented and the distance between the bonds is ranging from 4.9-2.07 Angstrom (b) 2D docked complex of 4-hyroxypanduratin A with Nipah virus fusion protein is represented and the distance between the bonds is ranging from 2.07-2.96 Angstrom and (c) 2D docked complex of 6-Gingerol with Nipah virus fusion protein is represented and the distance between the bonds is ranging from 2.59-3.02 Angstrom.

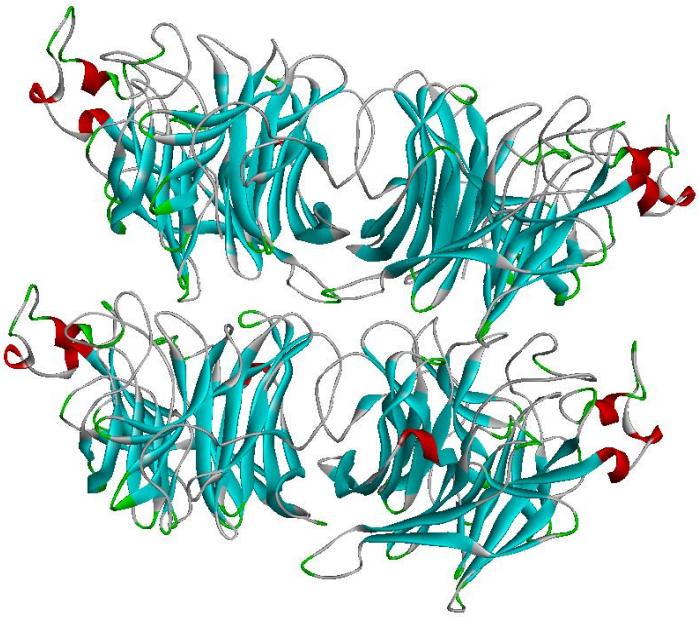


Fig. 4. Quaternary structure of Nipah Fusion Protein

4. RESULTS AND DISCUSSION

The binding energy of a compound toward its target is used as the measurable quantity in designing a drug, the negativity of binding energy determines the stability of the Ligand-receptor complex. The more negative the binding energy means the more stability of the complex. Binding energy is the sum of Intermolecular Energy, Total Internal Energy and Torsional Free Energy while Unbound System's Energy is being subtracted from the total. Binding energies of Luteolin, 4-hyroxypanduratin A and 6-Gingerol was recorded as -4.83 kcal/mol, -4.58 kcal/mol and -3.98 kcal/mol respectively (Table 1).

Table 1. Binding energies of Luteolin, 4-hyroxypanduratin A and 6-Gingerol

Sl. No.	Compound	Binding Energy (kcal/mol)
1.	Luteolin	-4.83
2.	4-hyroxypanduratin A	-4.58
3.	6-Gingerol	-3.98

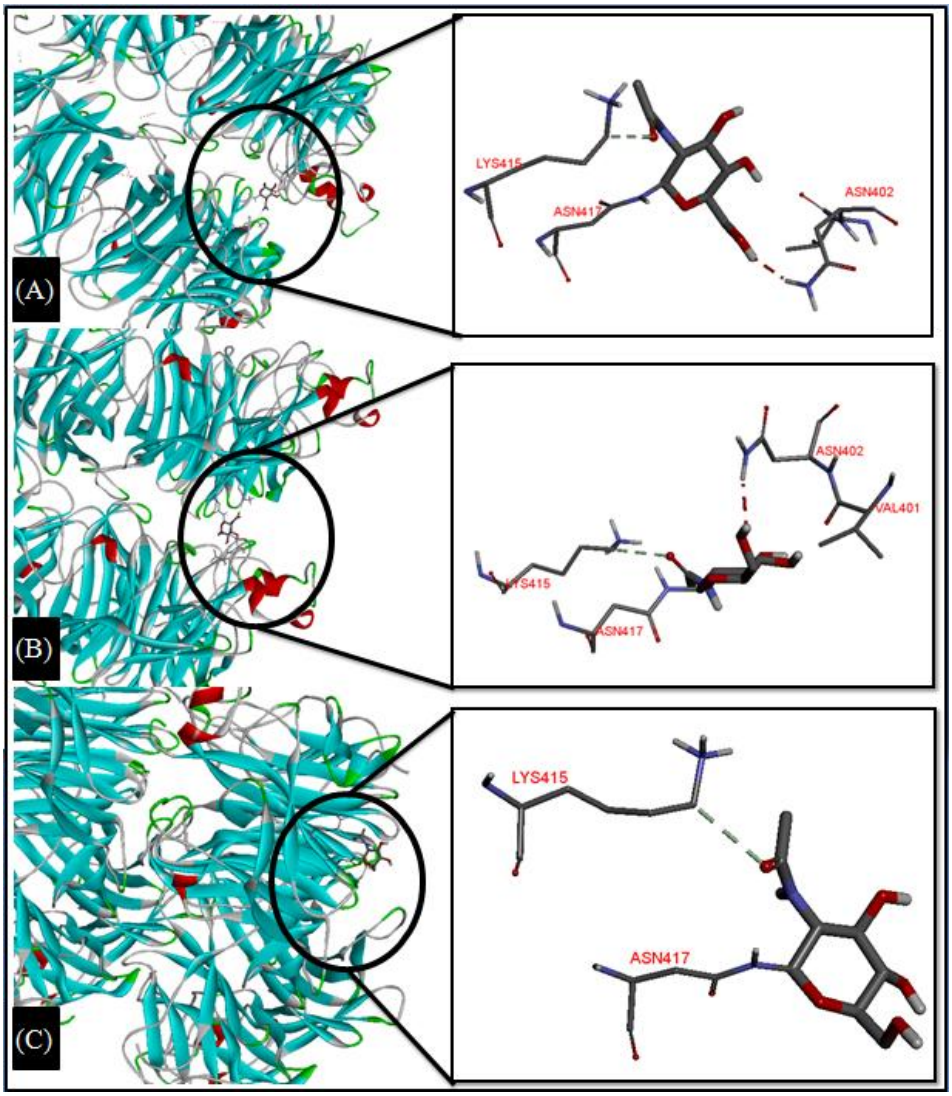
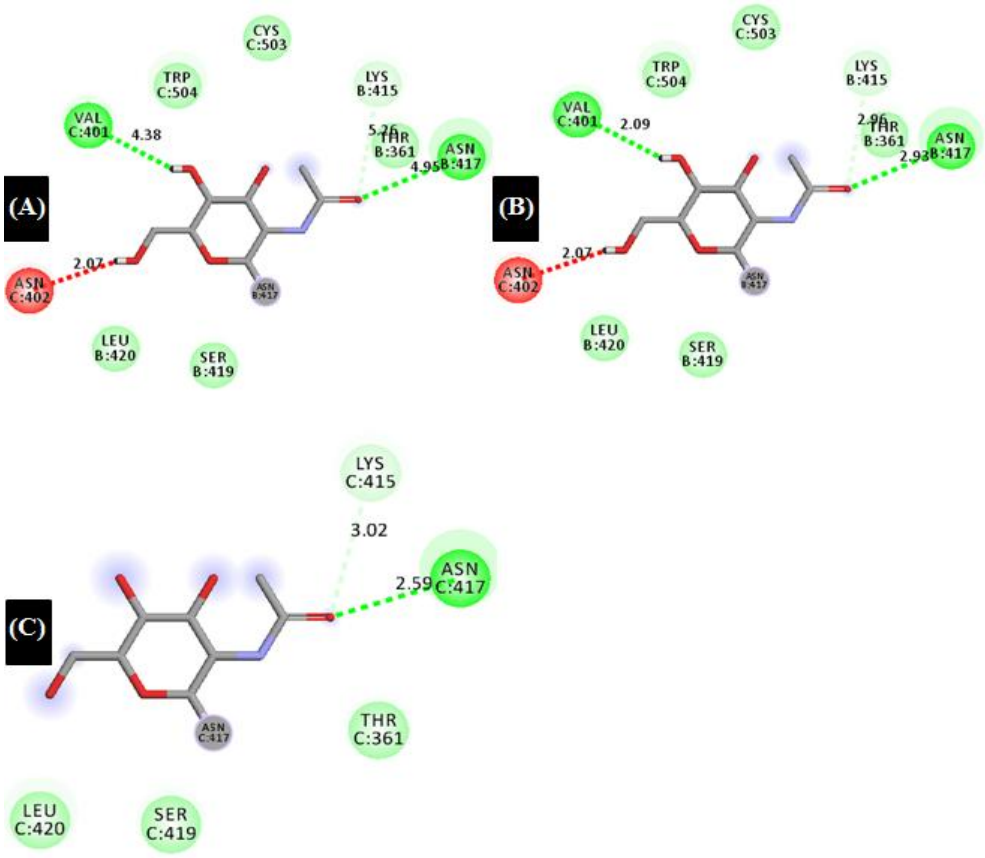


Fig. 5. 3D Docked complex of Fusion Protein with (A) Luteolin (B) 4-hyroxypanduratin A and (C) 6-Gingerol



Fi. 6. 2D docked complex of Fusion Protein with (A) Luteolin (B) 4-hyroxypanduratin A and (C) 6-Gingerol representing the distance between the formed bonds

5. CONCLUSION

Nipah virus is remerged with a more deadly rate and has infected a wholesome amount of people in recent times. Due to the scarcity of vaccines or drugs against this disease, the necessity of treatment has been increased. The attachment NiV‑F on the surface of the host cell is an important virulent factor and a promising antiviral target. All the selected medicinal compounds showed a noteworthy inhibition effect. Luteolin, which is found in many daily dietary foods has been found to be with the best binding energy. These findings indicate that the aforementioned phyto-compounds have a promising potential to target the Nipah Virus Fusion Protein to disrupt the attachment of the virus. Further *in-vitro* researches are needed on this topic to validate the use of Luteolin, 4-hyroxypanduratin A and 6-Gingerol completely against NiV-F.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Halpin K, Young PL, Field HE, Mackenzie JS. Isolation of Hendra virus from pteropid bats: A natural reservoir of Hendra virus. J. Gen. Virol. 2000;81(8): 1927–1932.
DOI: 10.1099/0022-1317-81-8-1927.
2. Dabra A, Arya P, Guarve K. Nipah Virus (NiV): Diagnosis, pathophysiology and treatment," Asian J. Pharm. Pharmacol; 2018.
DOI: 10.31024/ajpp.2018.4.6.3.
3. Eng-Chong T, et al. Boesenbergia rotunda: From ethnomedicine to drug discovery,"

Evidence-based Complementary and Alternative Medicine. 2012.
DOI: 10.1155/2012/473637.

4. Wang S, Zhang C, Yang G, Yang Y. Biological properties of 6-Gingerol: A brief review," Natural Product Communications; 2014.
DOI: 10.1177/1934578x1400900736.
5. Lin Y, Shi R, Wang X, Shen HM. Luteolin, a Flavonoid with Potential for Cancer Prevention and Therapy," Curr. Cancer Drug Targets, 2008,
DOI: 10.2174/156800908786241050.
6. Sathya S, Devi KP. The use of polyphenols for the treatment of alzheimer's disease," in Role of the Mediterranean Diet in the Brain and Neurodegenerative Diseases; 2017.
7. Guo D. Old Weapon for New Enemy: Drug Repurposing for Treatment of Newly Emerging Viral Diseases," Virologica Sinica; 2020.
DOI: 10.1007/s12250-020-00204-7.
8. Amaya M, Broder CC. Vaccines to Emerging Viruses: Nipah and Hendra," Annual Review of Virology; 2020,
DOI: 10.1146/annurev-virology-021920-113833.
9. Broder CC, et al. A treatment for and vaccine against the deadly Hendra and Nipah viruses, Antiviral Research; 2013.
DOI: 10.1016/j.antiviral.2013.06.012.
10. Eaton BT, Broder CC, Middleton D, Wang LF. Hendra and Nipah viruses: Different and dangerous," Nature Reviews Microbiology; 2006.
DOI: 10.1038/nrmicro1323.
11. Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol," J. Ethnopharmacol; 2010.
DOI: 10.1016/j.jep.2009.10.004.
12. Raja T, Ravikumar P, Srinivasan MR, Vijayarani K, Kumanan K. Identification of Potential Novel Inhibitors for Nipah Virus – An in silico Approach. 9;9:3377–3390.
DOI: 10.20546/ijcmas.2020.909.420.
13. Shah A, Parmar B, Ghodawala M, Seth A. In silico drug discovery of novel small lead compounds targeting nipah virus attachment glycoprotein," J. Integr. Heal. Sci. 2018;6(2):60.
DOI: 10.4103/jihs.jihs_21_18.

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Peer-review history:
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