# MOLECULAR DOCKING INVESTIGATION OF ANTI-VIRAL ACTION OF ILLICIUM VERUM (STAR ANISE) AGAINST MARBURG VIRUS THROUGH BIOVIA DISCOVERY STUDIO VISUALIZER 21.1.0.0

**Gomathi Swaminathan[1], Laliteshwar Pratap Singh[2], Anchal Arora[3], Mahendra Dwivedi[4]*, Anshu Tripathi[5], Vipul Negi[6], Sonali Vinod Uppalwar[7]**

**Article History: Received:** 12.12.2022 **Revised:** 29.01.2023 **Accepted:** 15.03.2023

**Abstract**

**Objective:** In different investigations, phytoconstituents of star anise have demonstrated outstanding antiviral activity against diverse viral species. Consequently, the study's goal was to use in-silico methodologies to assess the effectiveness of star anise phytoconstituents against the Marburg virus protein.
**Method :** Auto Dock was employed to test chosen star anise phytochemical molecules on Marburg virus protein, and Discovery Studio visualizer was used to make 3D and 2D interface images.
**Result :** Blind docking all eight phytochemicals revealed that two of the eight phytochemicals created conventional carbon-hydrogen bonds, and that eugenol and Farnesol both formed carbon-hydrogen bonds. The lowest binding energy was determined to be -6.00 kcal/mol for beta -eudesmol.
**Conclusion :** Based on the substantial binding energies of phytoconstituents during blind docking, our findings revealed that star anise phytoconstituents can have a beneficial effect against Marburg virus. Beta eudesmol might be a viable alternative to Marburg virus.

[1]Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamilnadu, India, Pin code- 643001
[2]Department of Pharmacy, Narayan Institute of Pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram, (Rohtas), Bihar, India, Pin Code - 821305
[3]Department of Pharmacology, All India Institute of Medical Sciences, Bathinda, Punjab, India, Pin Code - 151001
[4*]Department of Pharmacology, RKDF School of Pharmaceutical Science, Bhopal, Madhya Pradesh, India, Pin Code- 462026
[5]Department of Pharmacy, Raj Kumar Goel Institute of Technology (pharmacy), Ghaziabad, Uttar Pradesh, India, Pin Code- 201004
[6]Department of Pharmacy, College of Pharmacy Shivalik Campus ,Dehradun, Uttarakhand, India, Pin Code 248197
[7]Department of Pharmacy, Ideal Institute of pharmacy, Wada, Palghar, Maharashtra, India, Pin Code- 421303

***Corresponding author: Mahendra Dwivedi, Department of Pharmacy, RKDF School of Pharmaceutical Science, Bhopal, Madhya Pradesh, India, 462026,** mahendradwivediji@gmail.com

**DOI: 10.31838/ecb/2023.12.s3.091**

## 1. **Introduction**

Both the Marburg and Ebola viruses are members of the Filoviridae virus family (filoviruses). Although the structures of these two virus species differ, they both cause haemorrhagic fever in humans and non-human primates. The first cases that surfaced involved virus transmission from these fruit bats to humans. Human-to-human transmission of viruses through direct contact, the exchange of bodily fluids through blood or bodily secretions, or on naturally occurring surfaces like bedding or clothing were secondary cases. Humans are susceptible to the deadly Marburg virus disease, which is brought on by the Marburg virus(1,2).

High fever, excruciating headache, severe muscle aches, watery diarrhoea, abdominal cramping, nausea, vomiting, and malaise are all symptoms of the Marburg virus, which can cause illness suddenly and last up to three days. Between 2 and 7 days after the onset of symptoms, a non-itchy rash has developed. The body begins to bleed in several places, including the nose, gums, and vagina, as well as fresh blood in the sputum and feces. Injuries to the central nervous system can lead to agitation, agitation, and aggression (3,4) . Due to the severe blood loss and shock, fatal cases typically end in death 8 to 9 days after onset (5). Although secondary transmission of MARV can be prevented by adhering to all general preventive measures used for all other haemorrhagic fevers, including EBOV, such as avoiding direct physical contact with infected people and wearing protective masks, gloves, and gowns, primary transmission of MARV is still under extensive research and is difficult to prevent. To reduce the likelihood of unintentional transmission of infection, infected individuals should be properly quarantined and needles and other equipment used for such individuals should be disposed of properly (6–10). Recent outbreaks indicate that the viciousness of the strain, the contagious dose, the general health of the infected individual, and the accessibility to medical care all have an impact on how severe the disease is (11).Therefore, ensuring proper treatment is essential to battling the MVD. Humans and nonhuman primates are both susceptible to the lethal haemorrhagic fever caused by the filoviruses Ebola and Marburg, for which no human vaccines or treatments are available. Due to the clinical limitations of viral medicine ,it is critical to develop efficient and non-toxic antiviral medication depend on new antiviral targets. (12,13). Major pharmacological compounds that inhibit the VP24 protein enzyme were suggested as possible anti-viral treatment drugs. It is the VP24 protein enzyme that is bound to the virion's ribonucleoprotein complex and influences the formation of infectious virus particles. A previous study suggested that the Vp24 protein enzyme could be a promising target for the development of anti-viral drugs since a similar structure occurs in individuals. By focusing on a Marburg virus protein, we discuss our thoughts on the potential application of Star Anise bioactive compounds as a Marburg Virus treatment strategy(14).

Star anise is an aromatic plant in the Magnoliaceous family with the scientific name Illicium verum Hook. It is a revered medicinal plant in China and India, with a variety of therapeutic benefits. Numerous phytochemicals from SA have been reported to have biologically significant properties. Additionally, it has antioxidant, antiviral, and antimicrobial properties. As effective in treating dyspepsia, flatulence, spasmodic colonic pain, dysentery, rheumatoid arthritis and other conditions in ayurveda, a traditional Indian medical system (15–17). We believe that the phytochemicals in star anise can shield against Marburg Virus infection. The goal of the current study was to analyse star anise phytochemicals in relation to the VP24 Protein enzyme using in silico methods and to conduct molecular docking studies. Results of the current study will enable researchers to determine a most efficient virucidal agents during Marburg virus treatment. as mentioned in table 1.

## 1. Materials & methods

**Preparation of Ligand**

The phytochemicals' SDF files were obtained from PubChem, and discovery visualizer was used to convert the SDF files into PDB files. For docking studies, SDF files are unable to be utilized effectively.

**Molecule preparation**

The X-ray crystal structure of the Marburg virus VP24 was obtained using the PDB web site (PDB

ID: 4OR8). After completely removing all $H_2O$ atoms from the protein, Kollman charges were added, hydrogen polarities were assigned and polar hydrogen atoms were added. The protein as well as 4OR8 protein structure file PDB to 4OR8 PDBQT reformation also received Gasteiger charges.

**In-silico interaction analysis**

Using Autodock 4.2 software, MGL tools and connection energies among both active compounds and Marburg virus proteins had been predicted. The LGA was used to examine interactions . AutoDock calculates the ligand and receptor interaction binding energy as follows:

$$\Delta G_{binding} = \Delta G_{gauss} + \Delta G_{repulsion} + \Delta G_{hbond} + \Delta G_{hydrophobic} + \Delta G_{tors}$$

Ggauss denotes the scatter of two Gaussian functions. Grepulsion: If the distance is greater than a certain threshold, the square of the distance is repelled. Ghbonad: a ramp function used to simulate metal ion interactions. Gtors: expresses the ratio to the total count of bonds that can be rotated, Ghydrophobic: ramp function (18).

H20 was also detached during the alteration of the native PDB file of the Marburg virus's chosen 3 dimensional structures. In all eight docking tests, the pharmaceutical compounds were given hydrogen atoms, Kollman unified charges, and a Gasteiger charge. In every docking experiment, the grid box has been constructed to encompass the majority of the protein, resulting in blind docking(19).

There was a total of 10 LGA cycles permitted. The generated conformations of chosen Marburg virus proteins and drug complexes were exhaustively analysed for the development of different kinds of reactions employing Discovery Studio 2019 molecular visualization tool as mentioned in figure 1 after the docking procedures were done successfully.

## 2. Result

It is determined that eight phytoconstituents engage with Marburg virus in certain manner after analysing molecular interaction data from docking tests with diverse medicines. End intermolecular energy, RMSD lower bound, RMSD upper bound, and production of carbon-hydrogen bonds during drug-receptor contact may all be utilized to analyse the docking data shown in Table 2 and fig. 2 While blind docking all eight phytoconstituents , it was discovered two of the eight phytochemicals formed conventional carbon-hydrogen bonds, and that both eugenol and Farnesol formed carbonhydrogen bonds. However, as shown in Table 1, The binding energy and inhibition characteristic of eight phytoconstituents have been calculated. The lowest binding energy was found to be -6.00 kcal/mol for beta -eudesmol. Nevertheless, the binding energy reported in the table is mostly owing to the chemical interactions illustrated in Figure 2.

## 3. Discussion

In-silico experiments with star anise phytoconstituent against the Marburg virus indicated that all eight star anise phytonutrients interact with the protein of the Marburg virus. Many studies have found that the phytochemicals in star anise have antiviral properties. Similarly, our findings suggest that star anise phytochemicals may have a beneficial effect on Marburg virus. During blind docking, all the phytoconstituent demonstrated significant binding energies. As a result, star anise phytoconstituent and betaeudesmol may be useful in the treatment of the Marburg virus(18–21).

**Acknowledgements**

We would like to express our special thanks of gratitude to our Institutions for facilitating this research work.

**Funding**

The authors declare that they have not received any financial aid from any source in this study.

**Declarations**

The authors declare that they have no competing interests.

## 4. References

1. Chakraborty S, Chandran D, Mohapatra RK, Alagawany M, Yatoo MI, Islam MA, et al. Marburg Virus Disease – A Mini-Review. J Exp Biol Agric Sci [Internet]. 2022 Aug 30;10(4):689–96. Available from: https://jebas.org/ojs/index.php/jebas/article/view/808
2. Sohan M, Shahriar M, Bhuiyan MA, Islam MR. Recent outbreak of Marburg virus disease: Could it be a threat for global public health? Heal Sci Reports [Internet]. 2023 Jan 29;6(1). Available from: https://onlinelibrary.wiley.com/doi/10.1002/hsr2.971
3. Agnihotri P, Bhattacharya S. Marburg Virus Disease: An Emerging Public Health Challenge. Malaysian J Med Res [Internet]. 2023;07(01):11–8. Available from: https://ejournal.lucp.net/index.php/mjmr/article/view/1982
4. Abir MH, Rahman T, Das A, Etu SN, Nafiz IH, Rakib A, et al. Pathogenicity and virulence of Marburg virus. Virulence. Virulence [Internet]. 2022 Dec 31;13(1):609–33. Available from: https://www.tandfonline.com/doi/full/10.1080/21505594.2022.2054760
5. Asad A, Aamir A, Qureshi NE, Bhimani S, Jatoi NN, Batra S, et al. Past and current advances in Marburg virus disease: a review. Le Infez Med [Internet]. 2020 Sep 1;28(3):332–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32920568
6. Brauburger K, Hume AJ, Mühlberger E, Olejnik J. Forty-Five Years of Marburg Virus Research. Viruses [Internet]. 2012 Oct 1;4(10):1878–927. Available from: http://www.mdpi.com/1999-4915/4/10/1878
7. Nyakarahuka L, Shoemaker TR, Balinandi S, Chemos G, Kwesiga B, Mulei S, et al. Marburg virus disease outbreak in Kween District Uganda, 2017: Epidemiological and laboratory findings. van Griensven J, editor. PLoS Negl Trop Dis [Internet]. 2019 Mar 18;13(3):e0007257. Available from: https://dx.plos.org/10.1371/journal.pntd.0007257
8. Hussain Z. Ghana declares its firstoutbreak of Marburg virus disease after two deaths. BMJ [Internet]. 2022 Jul 19;o1797. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj. o1797
9. Kortepeter MG, Dierberg K, Shenoy ES, Cieslak TJ. Marburg virus disease: A summary for clinicians. Int J Infect Dis [Internet]. 2020 Oct;99:233–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1201971220305865
10. CDC. Marburg hemorrhagic fever (Marburg HF) [Internet]. 2019. Available from: https://www.cdc.gov/vhf/marburg/resources/outbreak-table.html
11. Gene O, Julia B, Vanessa M, Victoria W-J, Thomas G, Lisa H. Drug Targets in Infections with Ebola and Marburg Viruses. Infect Disord - Drug Targets [Internet]. 2009 Apr 1;9(2):191–200. Available from: http://www.eurekaselect.com/openurl/content.p hp?genre=article&issn=1871-5265&volume=9&issue=2&spage=191
12. Cross RW, Mire CE, Feldmann H, Geisbert TW. Post-exposure treatments for Ebola and Marburg virus infections. Nat Rev Drug Discov [Internet]. 2018 Jun 29;17(6):413–34. Available from: http://www.nature.com/articles/nrd.2017.251
13. Mehedi M, Groseth A, Feldmann H, Ebihara H. Clinical aspects of Marburg hemorrhagic fever. Future Virol [Internet]. 2011 Sep;6(9):1091–106. Available from: https://www.futuremedicine.com/doi/10.2217/fvl.11.79
14. Zhang APP, Bornholdt ZA, Abelson DM, Saphire EO. Crystal Structure of Marburg Virus VP24. Sundquist WI, editor. J Virol [Internet]. 2014 May 15;88(10):5859–63. Available from: https://journals.asm.org/doi/10.1128/JVI.03565-13
15. Patra JK, Das G, Bose S, Banerjee S, Vishnuprasad CN, Pilar Rodriguez_Torres M, et al. Star anise ( <scp> *Illicium verum* </scp> ): Chemical compounds, antiviral properties, and clinical relevance. Phyther Res [Internet]. 2020 Jun 29;34(6):1248–67. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ptr.6614
16. Boota T, Rehman R, Mushtaq A, Kazerooni EG. Star Anise: A review on benefits, biological activities and potential uses. Ijcbs [Internet]. 2018;14(January):110–4. Available from: www.iscientific.org/Journal.html
17. Astani A, Reichling J, Schnitzler P. Screening for Antiviral Activities of Isolated

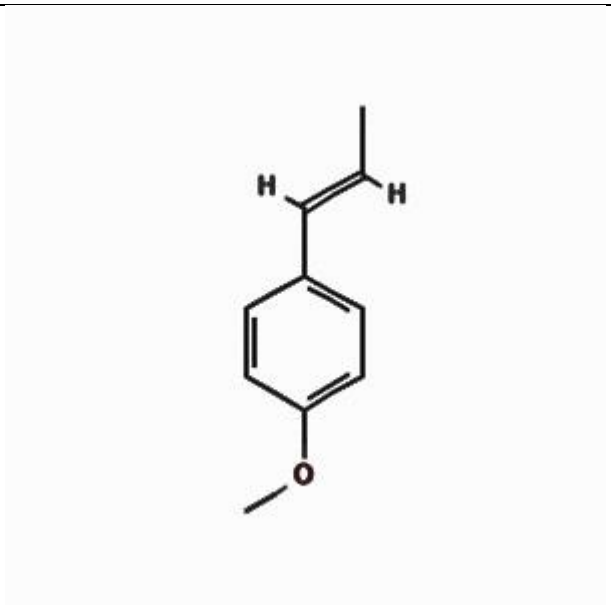
Compounds from Essential Oils. EvidenceBased Complement Altern Med [Internet]. 2011;2011:1–8. Available from: http://www.hindawi.com/journals/ecam/2011/253643/

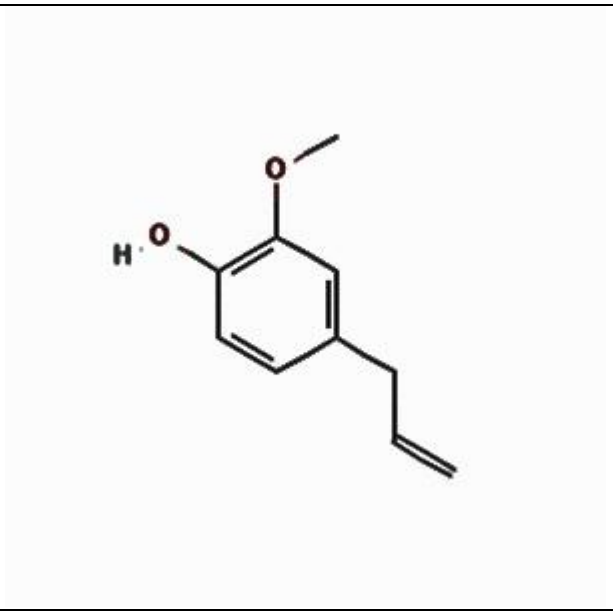
18. Morris GM, Goodsell DS, Halliday RS, Huey R, Hart WE, Belew RK, et al. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J Comput Chem [Internet]. 1998 Nov 15;19(14):1639–62. Available from: https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1096-987X(19981115)19:14%3C1639::AID-JCC10%3E3.0.CO;2-B

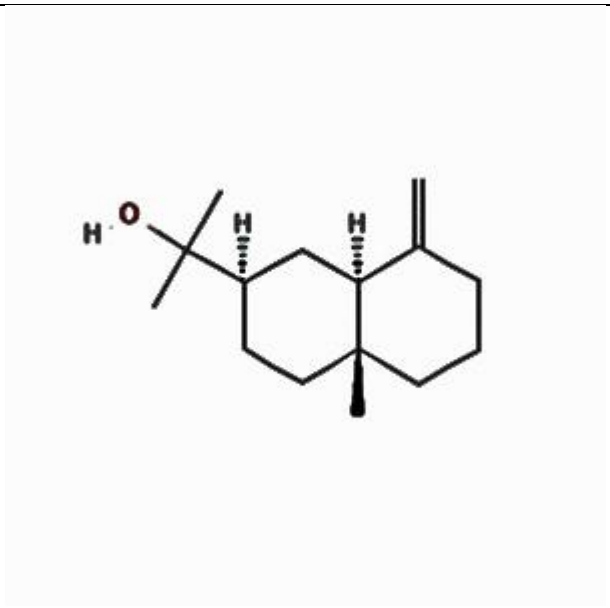
19. Allouche A. AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility. J Comput Chem. 2012;32:174–82.

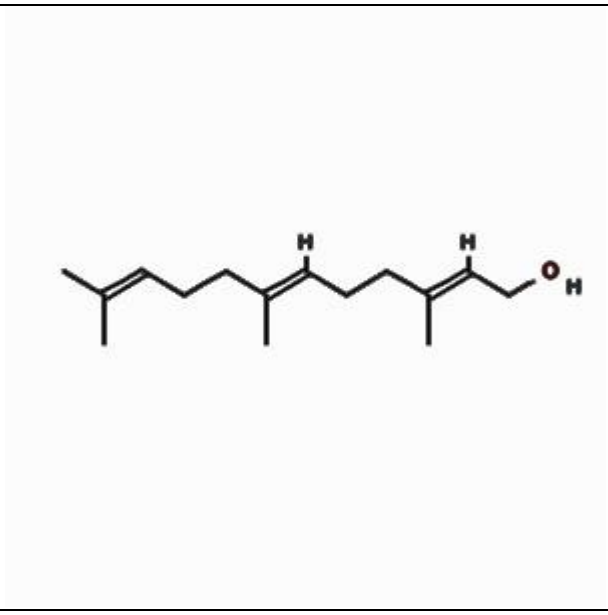
20. https://autodock.scripps.edu/ 21. https://www.3ds.com/productsservices/biovia/products/molecular-modelingsimulation/biovia-discoverystudio/visualization/

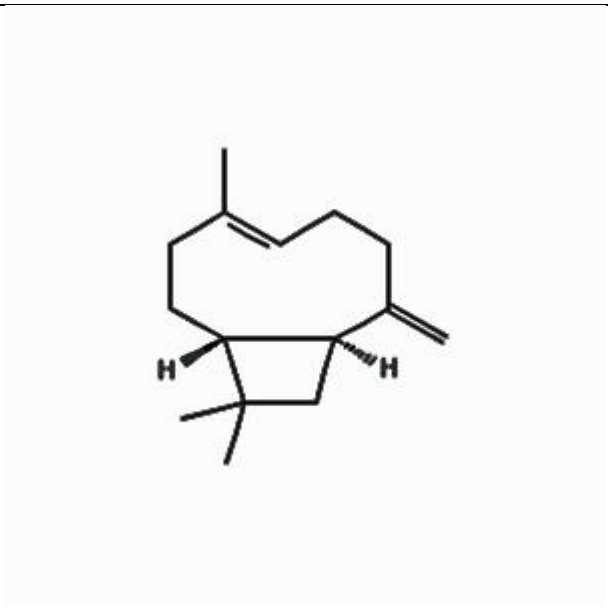
Table 1: List and structures of compounds from Star Anise

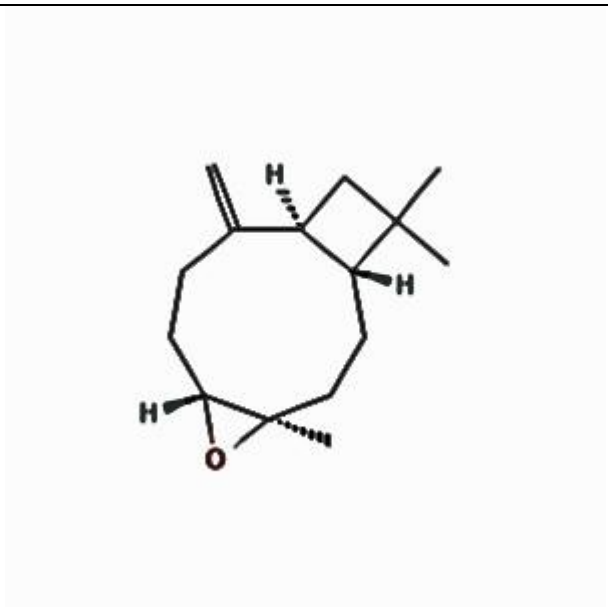
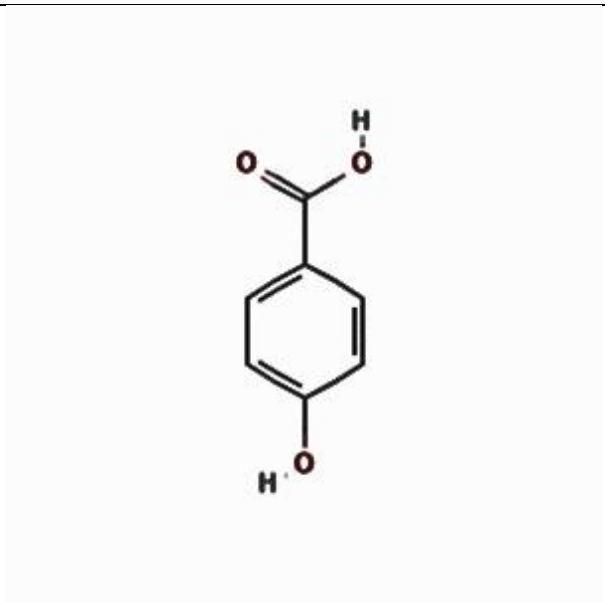
| **Compounds** | **Structure** | **Molecular Formula** |
|---|---|---|
| Trans-anethole |  | C10H12O |

| | | |
|---|---|---|
| Eugenol |  | C10H12O2 |

| | | |
|---|---|---|
| β-eudesmol |  | C15H26O |

| | | |
|---|---|---|
| Farnesol |  | C15H26O |

| | | |
|---|---|---|
| β-caryophyllene |  | C15H24 |

| | | |
|---|---|---|
| β-caryophyllene-oxide |  | C15H24O |
| ρ-Hydroxybenzoic acid |  | C7H6O3 |

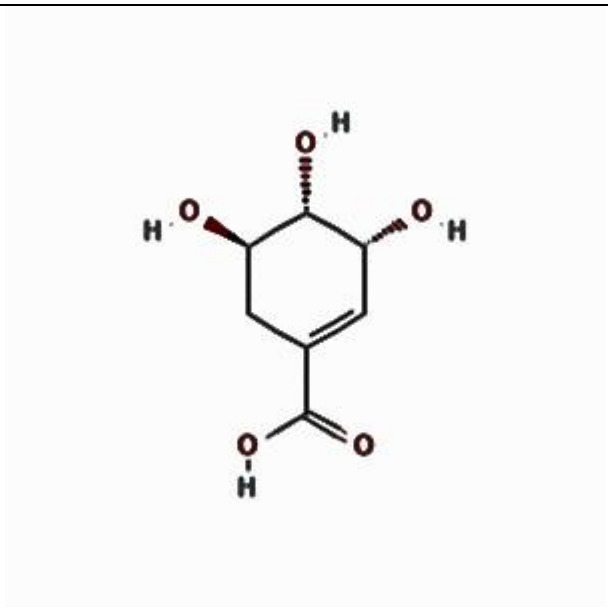
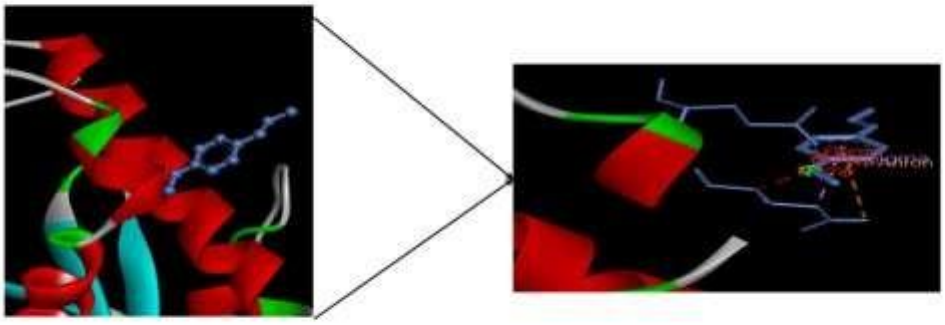
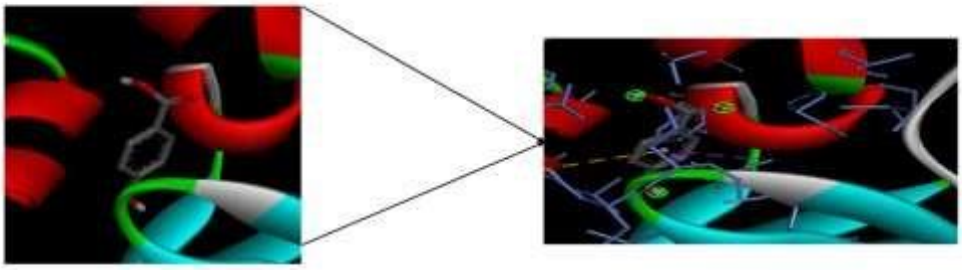
| | | |
|---|---|---|
| Shikimic acid |  | C7H10O5 |

Table 2: Depicting the Binding Energy, RMSD Lower Bound, RMSD Upper Bound, And Carbon-Hydrogen Bond of All Eight Phytochemicals

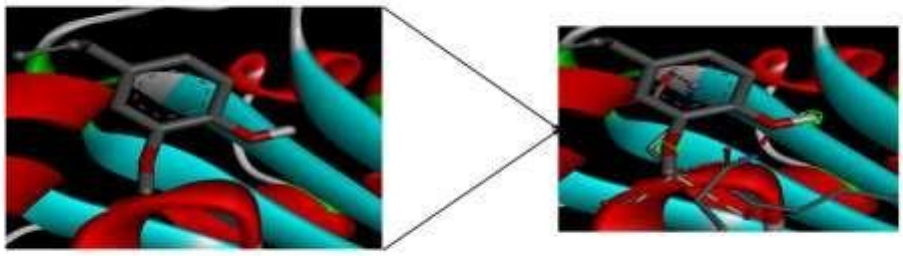
| **Phytochemicals** | **Lowest Binding Energy (Kcal/mol)** | **RMSD Lower Bound** | **RMSD Upper Bound** | **Carbon-Hydrogen Bond** |
|---|---|---|---|---|
| Trans-anethole | -5.6 | 0 | 0 | No Carbon-Hydrogen Bond |
| Eugenol | -5.1 | 0 | 0 | GLN A:105 |
| β-eudesmol | -6.0 | 0 | 0 | No Carbon-Hydrogen Bond |
| Farnesol | -5.0 | 0 | 0 | GLN A:105 |
| β-caryophyllene | -5.5 | 0 | 0 | No Carbon-Hydrogen Bond |
| β-caryophylleneoxide | -5.4 | 0 | 0 | No Carbon-Hydrogen Bond |
| Shikimic Acid | -4.7 | 0 | 0 | No Carbon-Hydrogen Bond |
| ρ-Hydroxybenzoic acid | -4.9 | 0 | 0 | No Carbon-Hydrogen Bond |



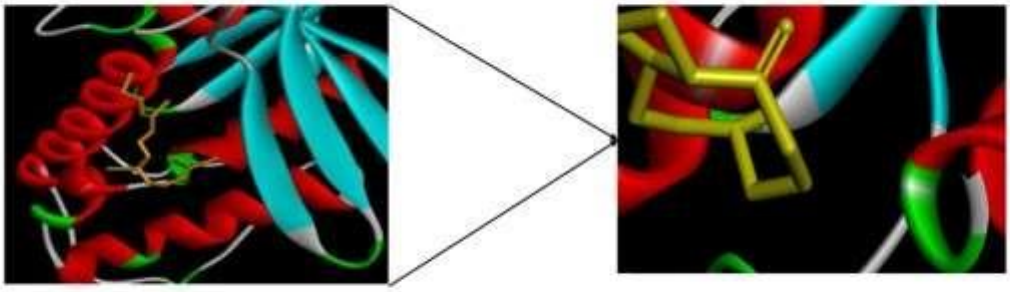
A. Trans-anethole



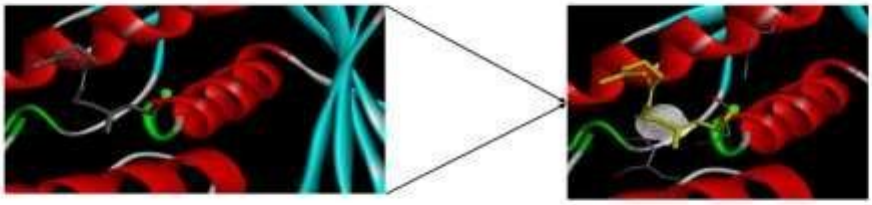
B. Para-hydroxybenzoic acid



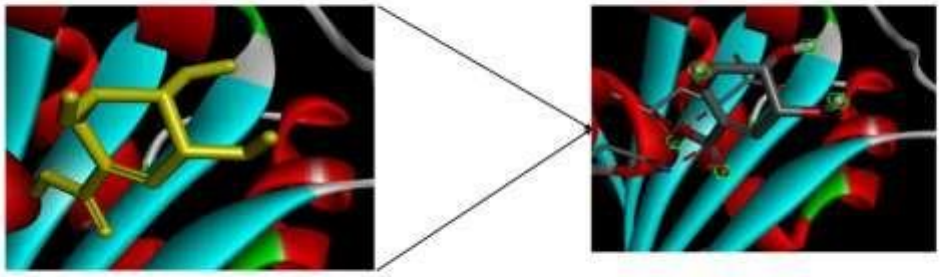
C. Eugenol



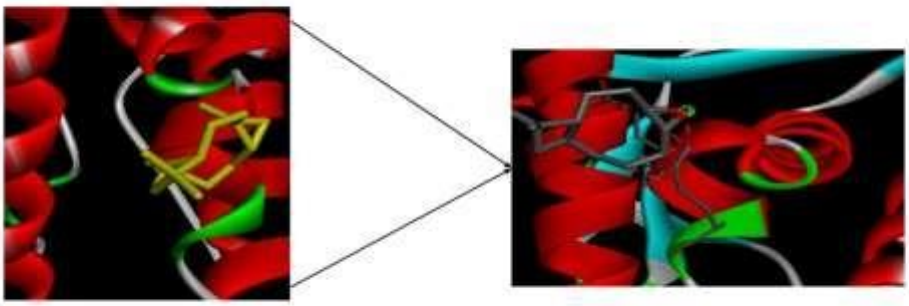
**D. β-caryophyllene**



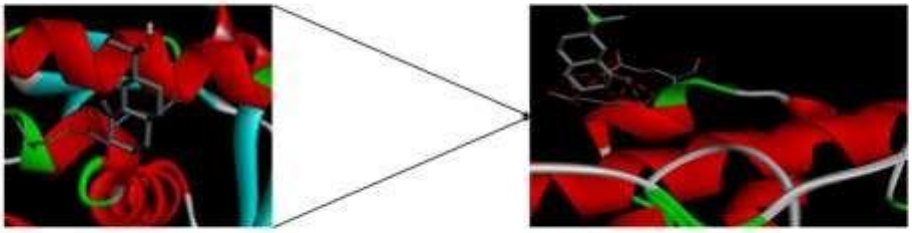
**E. Farnesol**



F. Shikimic Acid



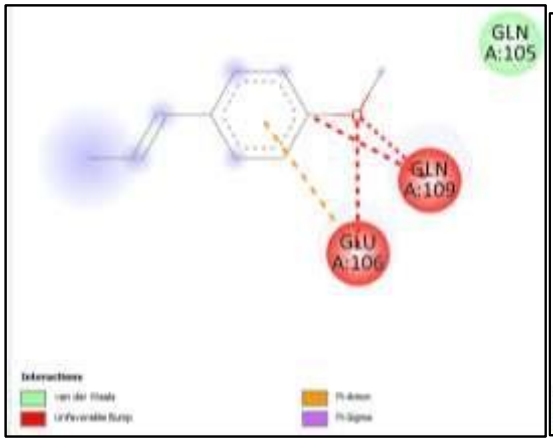
G. β-caryophyllene-oxide



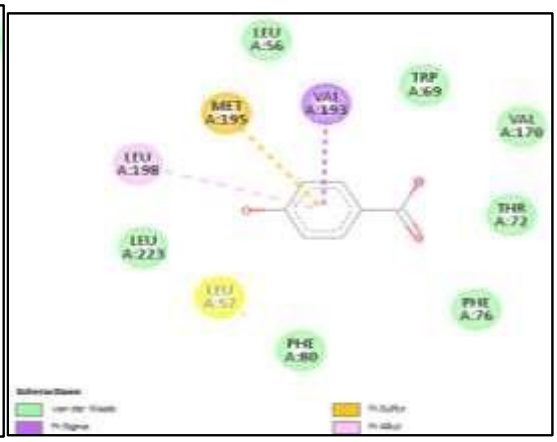
H. β-eudesmol

Figure 1: A to H images were created by using BIOVIA discovery studio visualizer 21.1.0.0 and showing the interaction between the Marburg virus protein and star anise phytochemicals. Complete structure with interaction on left side and zoomed interaction on right side. (Https://Www.3ds.Com/Products-Services/ Biovia/Products/Molecular-Modeling-Simulation/Biovia-Discovery-Studio/ Visualization., n.d.)

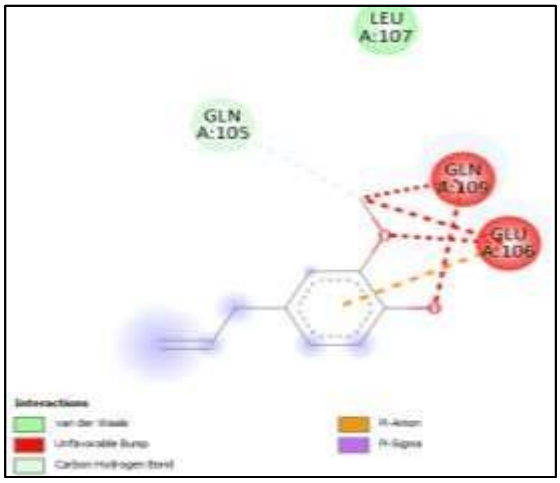
**A. Trans-anethole**



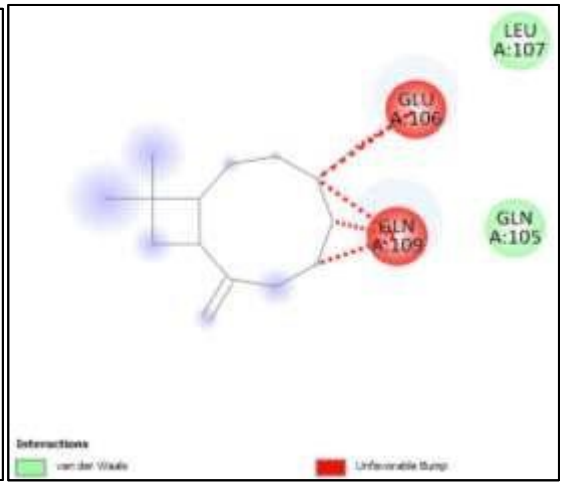

**B. ρ-Hydroxybenzoic acid**




**C. Eugenol**

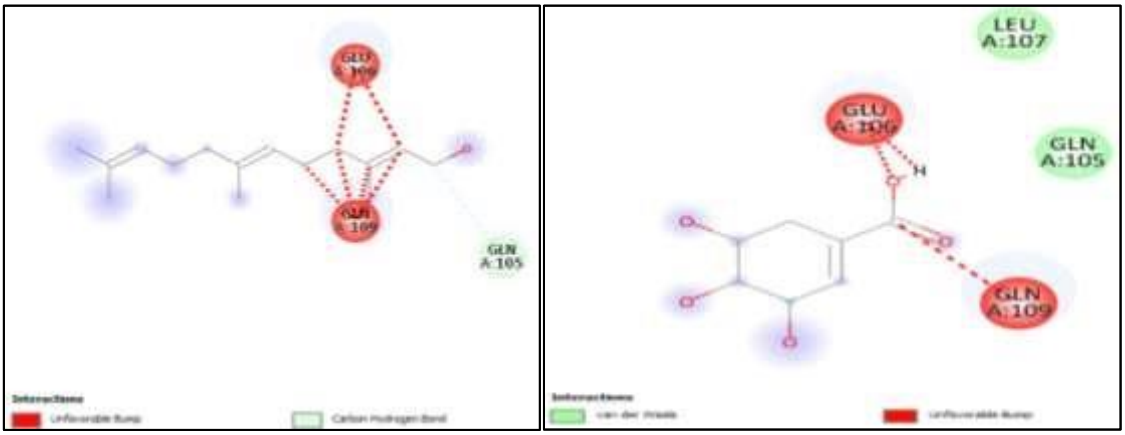



**D. β-caryophyllene**




**E. Farnesol**

**F. Shikimic Acid**




**G. β-caryophyllene-oxide**

**H. β-eudesmol**

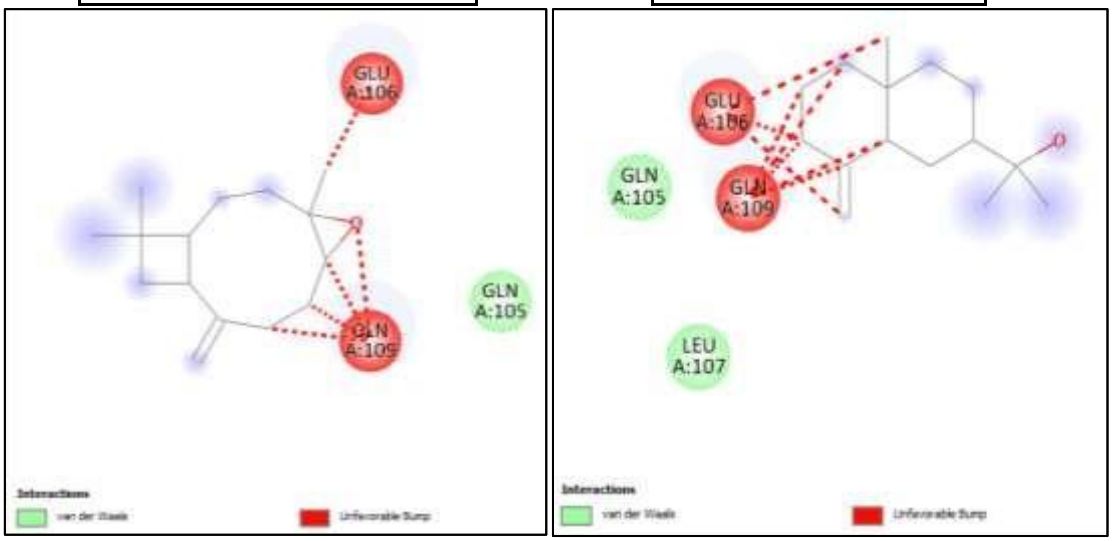



Figure 2: Images (A) to (H) were created by using BIOVIA discovery studio visualizer 21.1.0.0, showing 2 D interactions and amino acids taking part in interactions with different star anise phytochemicals.