(RESEARCH ARTICLE)

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Evaluation of *Vernonia amygdalina* del. containing phyto constituents a medicinal plant compound as new potential inhibitors of Monkey pox virus using molecular docking analysis

Sudhanshu Kumar Jha [1, *], Mojahidul Islam [1], Ravindra Kumar [2], Lalit Rana [1], Mohammad Adnan Saifi [1], Shahzeb Ali [1], Sneha Singh [1], Sahil [1] and Noor Alam [1]

[1] Department of Pharmaceutical sciences, Vishveshwaraya Group of Institutions, Dadri, G. B. Nagar, U.P. India.
[2] Department of Pharmaceutical sciences, Vishveshwaraya College of Pharmacy, Dadri, G. B. Nagar, U.P., India.

Abstract

Monkeypox is a viral zoonosis (a virus transmitted to humans from animals) with symptoms similar to those seen in the past in smallpox patients, although it is clinically less severe. With the eradication of smallpox in 1980 and subsequent cessation of smallpox vaccination, *Monkeypox* has emerged as the most important *orthopoxviral* for public health in recent years, great progress has been made in developing new antiviral drugs, and natural products, are important sources of potential and new antiviral drugs. The present study aimed to assess some biologically active compounds present in medicinal plants as potential *Monkeypox* inhibitors, using molecular docking methods. The Docking study was performed by Maestro 12.8. Comparing antiviral drug Tecovirimat (TPOXX) with Luteolin, Luteolin-7-o- β-glucoside, Vernodalol, Vernolepin, Vernodalin phytoconstituents present in Vernonia amygdalina del. The results demonstrate the effectiveness of this screening strategy, which can lead to rapid drug discovery in response to new infectious diseases. The Docking results with PDB Id (6LUT) receptor showed that many phytoconstituents screening compounds isolated from medicinal plant such as; Luteolin (− 3.244), Luteolin-7-o-β-glucoside (− 2.357), Vernodalol (− 2.089), Vernolepin (− 1.757), Vernodalin (-1.534) when compared with antiviral drug Tecovirimat whose docking score (− 0.162) these compounds results might be used to inhibit *Monkeypox* infection an important source for novel antiviral drugs targeting *Monkeypox* virus.

Keywords: Zoonosis; Monkeypox; *Vernonia amygdalina*; Phytoconstituents; Molecular docking; Docking score; Glide energy

1. Introduction

The first human case of the zoonotic orthodox DNA virus known as *Monkeypox* virus was reported in the Democratic Republic of the Congo in 1970. (Formerly Zaire) [1]. Africa has had sporadic outbreaks of illness, usually brought on by contact with wildlife reservoirs (particularly rodents) [2]. Due to the limited secondary spread of such epidemics and travel-related cases outside of Africa, human-to-human transmission has been labelled as ineffective [3-9]. Although the *Monkeypox* virus has been present in areas where it has historically been common for decades, research into the disease has been neglected and underfunded. The World Health Organization declared *Monkeypox* a "evolving danger of moderate public health concern" on June 23, 2022, as a result of more than 3000 infections with the *Monkeypox* virus being reported since early May 2022 in more than 50 nations across five regions [10-11].

Large respiratory droplets, close or direct touch with skin lesions, and possibly contaminated fomites are all ways that the *Monkeypox* virus is spread [12].

* Corresponding author: Sudhanshu Kumar Jha

1.1. *Vernonia amygdalina* Del

Mostly found in tropical Africa, *Vernonia amygdalina Del* (Asteraceae) is a tiny shrub with dark green leaves and rough bark that has been domesticated in various regions of West Africa. [13]. It is a perennial plant with a height range of one to six meters [14]. Soft-wooded *Vernonia amygdalina Del* is a versatile shrub with a quick regeneration rate. Due to its bitter flavor, it has earned the nickname "bitter leaf," and it is also known by a number of other local names in other local languages. The bitter flavor is caused by antinutritional compounds in the plants [15]. One of the medicinal plants used around the world to treat a variety of disorders is Vernonia amygdalina Del. This plant is occasionally grown for medicinal purposes in Bihar, Madhya Pradesh, Odisha, and West Bengal in India, where it is thought to have only recently arrived [16-17].

In eastern Bihar, it was occasionally discovered being grown in the herb gardens of local healers and herbalists, who recommend it as a treatment for diabetes, a blood purifier, a cough and fever, intestinal parasite infections, hepatic problems, and other ailments [16]. There are rumors that the *Vernonia amygdalina Del* plant is used in Africa and Asia to treat stomachaches, diabetes, yellow fever, dysentery, constipation, and dysentery. One of the medicinal plants used around the world to treat a variety of disorders is Vernonia amygdalina Del. According to reports, *Vernonia amygdalina Del* plant is used in Africa and Asia to cure diabetes, yellow fever, dysentery, constipation, malaria, and stomachaches [18-19]. A qualitative phytochemical analysis of *Vernonia amygdalina Del* found that polyphenols were heavily present, whereas alkaloids, saponins, flavonoids, and steroids were somewhat present [20]. Two sesquiterpene lactones, vernolide and vernodalol, were discovered in the plant during a phytochemical analysis of the leaves of V. amygdalina Del. [21]. The leaves of *Vernonia amygdalina Del* were separated for Vernoniosides D and E [22].

2. Research and Methodology

2.1. Molecular docking

The molecular docking method allows us to characterize how small molecules behave in the binding site of target proteins and to better understand basic biological processes by simulating the interaction between a small molecule and a protein at the atomic level [23]. There are more and more new therapeutic targets available for drug discovery as a result of the completion of the human genome project. The development of nuclear magnetic resonance spectroscopy, crystallography, and high-throughput protein purification methods has also led to the understanding of several structural features of proteins and protein-ligand complexes. These developments now make it possible for computational methods to be used in all phases of drug discovery [24-28]. Prediction of the ligand structure as well as its placement and orientation within these sites (often referred to as pose) and evaluation of the binding affinity are the two fundamental processes in the docking process. These two actions have an impact on sample techniques and scoring systems, which will be covered in the theory section.

The efficiency of docking procedures is greatly improved by knowing the location of the binding site prior to docking actions. Before docking ligands into the binding site, the binding site is frequently known; the efficiency of docking procedures is greatly improved by knowing the location of the binding site prior to docking actions. Before docking ligands into the binding site, the binding site is frequently known. Additionally, by contrasting the target protein with a family of proteins that perform a comparable function or with proteins that have been co-crystallized with different ligands, one can learn more about the sites. Additionally, by contrasting the target protein with a family of proteins that perform a comparable function or with proteins that have been co-crystallized with different ligands, one can learn more about the sites. Without knowing the binding sites, cavity detecting software or internet services, such GRID [29-30], POCKET [31], Surf Net [32-33], PASS [34] and MMC [35].

2.2. Examples of how molecular docking is used in drug discovery

The method that has been used the most frequently is molecular docking. Though its primary use is in structure-based virtual screening to find new compounds that are active against a specific target protein, there have been some notable successes in this area [36].

2.2.1. Docking studies using Maestro 12.8

The method that has been used the most frequently is molecular docking. Though its primary use is in structure-based virtual screening to find new compounds that are active against a specific target protein, there have been some notable successes in this area [37]. In reality, it is not a stand-alone procedure but is typically incorporated into a workflow comprising several *in silico* and experimental techniques [38].
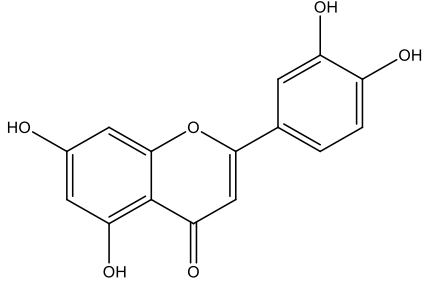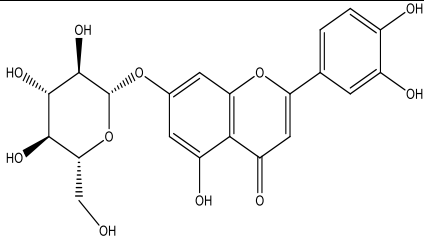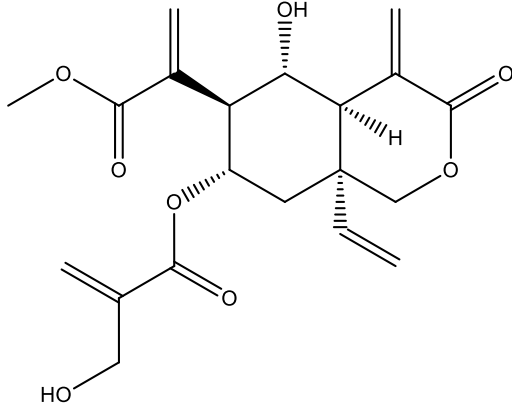
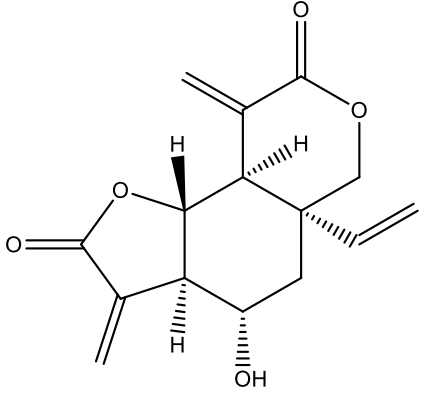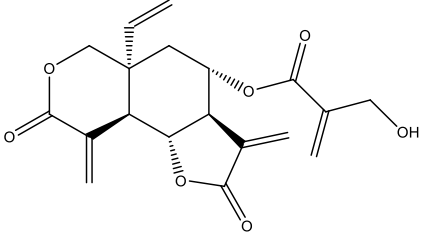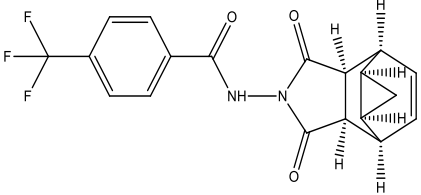### 2.2.2. Docking preparation of predicted TPP and 5 ligands

The Maestro 12.8 software includes tools for both protein and ligand optimization, such as assigning atomic charges to make proteins more polar, modifying ligands by assigning charge and rotatable bonds, calculating the energy contribution of de-solvation during ligand-binding on proteins, and assigning grid maps on protein surfaces in advance of ligand interaction by auto grid. The aforementioned facilities enhance molecular docking's speed, accuracy, and docking with a new scoring mechanism, effective optimization, and multithreading [39].

2.2.3. Protein docking with ligand (phytochemicals) molecules in a modelled TPP

In the current study, we have calculated the binding-free energy or docking, which reflects the binding affinity of 5 ligands and 1 prescription medicine (Standard drug Tecovirimat) to model TPP. According to the aforementioned docking research, out of five phytochemicals. Among the five phytochemicals, luteolin has the highest binding affinity, the highest docking score (-3.244 kcal/mole), and the least interaction with the medication Tecovirimat. The majority of the phytochemical ligands tested had higher binding energies than the prescription medications, according to reports. As a result, we chose a phytochemical ligand from each plant that exhibits superior docking energy. Table 1 lists the ligands that have the greatest affinity for the model TPP for further research [40]. As an alternative to AutoDock Vina in the current investigation, the Schrodinger program's Glide energy (Maestro 12.8) drug discovery tool was used in the study. When docking calcineurin with inhibitors, Maestro 12.8 predicts binding affinity energy between -3.244 to -1.534 kcal/mole, which is nearly identical to the findings of the current investigation [41].

Table 1 *In-silico* screening of *Vernonia amygdalina del.* phytoconstituents derivatives

S. No	Name of Phytoconstituents	Chemical Structure	Docking score	Glide energy
1.	Luteolin		-3.244	-0.154
2.	Luteolin-7-o- β-glucoside		-2.357	-0.074
3.	Vernodalol		-2.089	-0.075

4.	Vernolepin		-1.757	-0.088
5.	Vernodalin		-1.534	-0.083
6.	Tecovirimatat		0.162	0.001

2.2.4. Vernonia amygdalina Del.'s phytoconstituents' chemical composiztion [42]

Vernodalin

(3aR,4S,5aR,9aR,9bR)-3,9-dimethylene-2,8-dioxo-5a-vinyldecahydro-2H-furo[2,3-f]isochromen-4-yl 2-(hydroxymethyl)acrylate
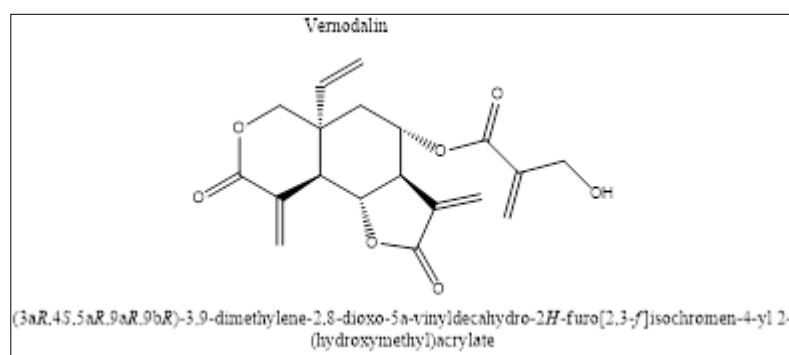
Figure 1 Chemical structure of Vernodalin

Luteolin

2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one
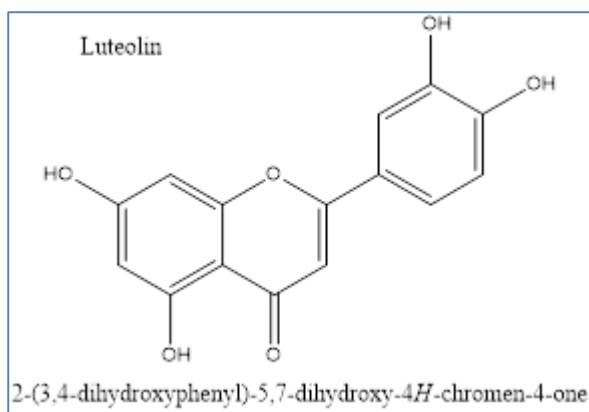
Figure 2 Chemical structure of Luteolin

Vernolepin

(3aR,4S,5aR,9aR,9bR)-4-hydroxy-3,9-dimethylene-5a-vinyloctahydro-2H-furo[2,3-f]isochromene-2,8(9bH)-dione
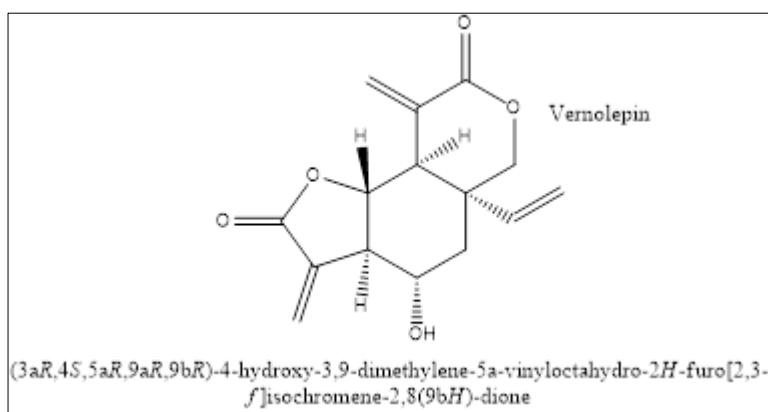
Figure 3 Chemical structure of Vernolepin

Vernodalol

(4aR,5R,6S,7S,8aR)-5-hydroxy-6-(3-methoxy-3-oxoprop-1-en-2-yl)-4-methylene-3-oxo-8a-vinyloctahydro-1H-isochromen-7-yl 2-(hydroxymethyl)acrylate
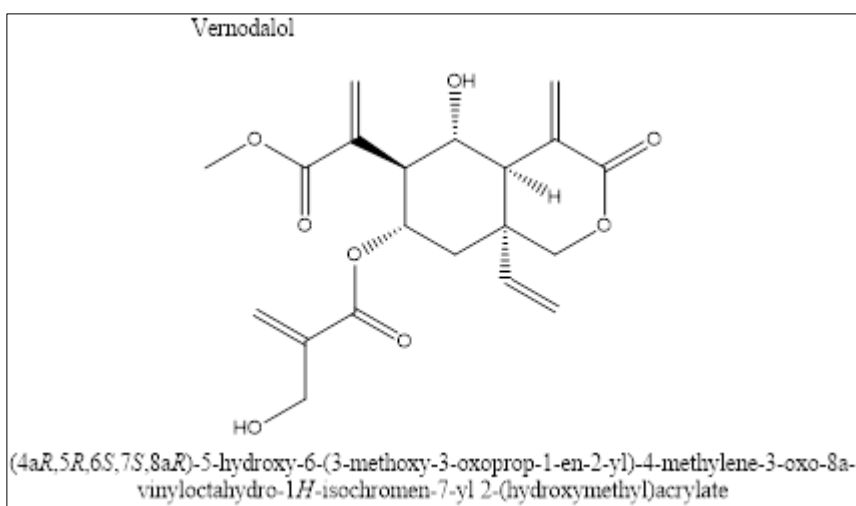
Figure 4 Chemical structure of Vernodalol

Luteolin 7-O- beta-glucoside

2-(3,4-dihydroxyphenyl)-5-hydroxy-7-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one
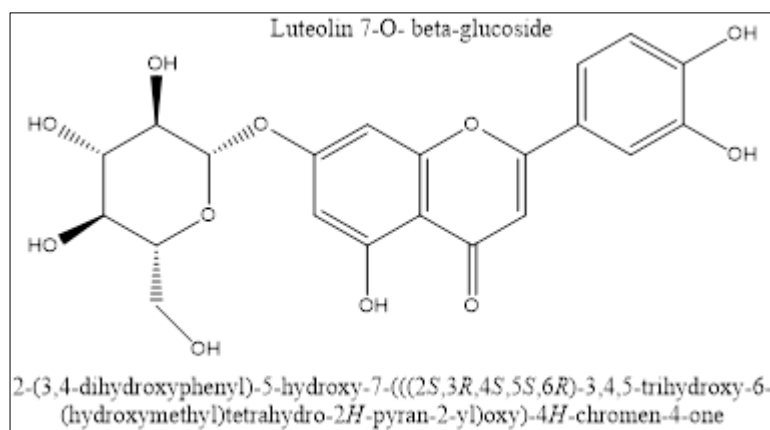
Figure 5 Chemical structure of Luteolin-7-o-beta-glucoside

Tecovirimat

N-((3aR,4R,4aR,5aS,6S,6aS)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[f]isoindol-2(1H)-yl)-4-(trifluoromethyl)benzamide
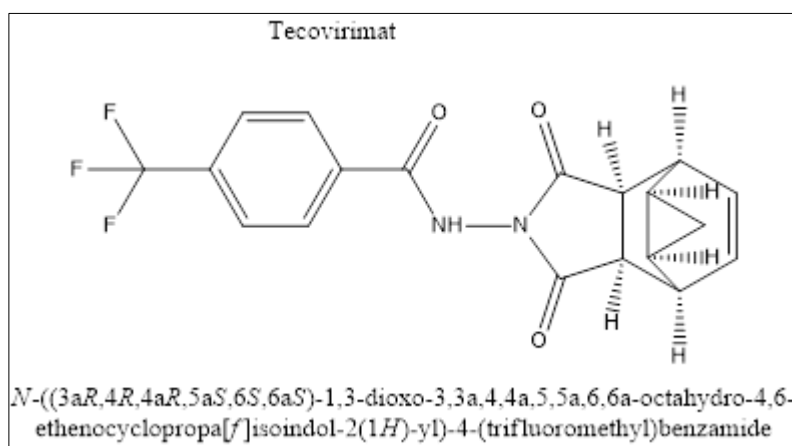
Figure 6 Chemical structure of Tecovirimatat

3. Result and Discussion

The above *in silico* study experimental evaluation data shows that Luteolin phytoconstituent present in Vernonia amygdalina del. medicinal plant shows the highest binding affinity and docking score (-3.244) with receptor having PDB id (6LUT) and Tecovirimatat international formulated antiviral drug shows docking score of (0.162) which is the least among all phytoconstituents present in Vernonia amygdalina del. plant this result prove that luteolin phytoconstituent shows tremendous result not only in treatment of *Monkeypox* virus but also for various viral diseases.

6LUT: Crystal structure of Serine Racemase from Dictyostellium disodium [43].

Classification: Isomerase

Organism(s): Dictyostellium discoideum

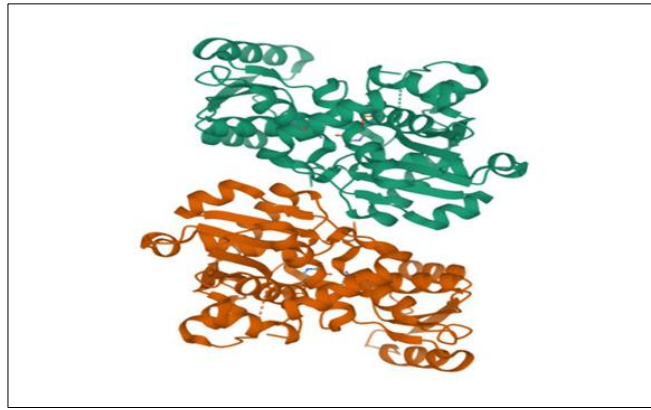Expression system: Escherichia coli

Mutation(s): No

Resolution: 1.35 Å
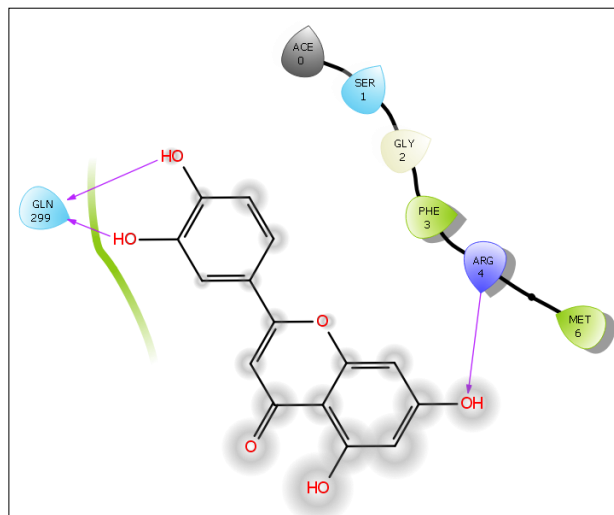
Figure 7 3D- Structure of protein (6LUT)

Figure 8 Luteolin 2D diagrams of docked conformation compound
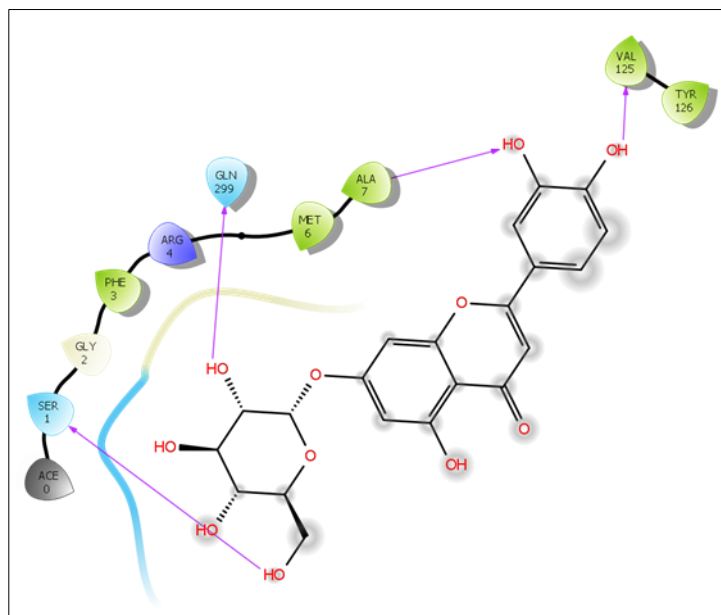

Figure 9 Luteolin-7-o- β-glucoside 2D diagrams of docked conformation compound
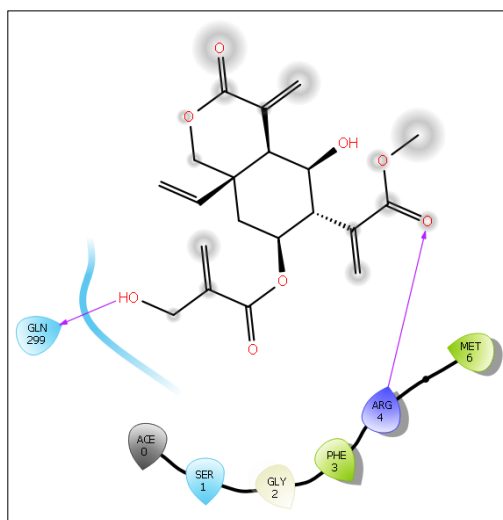
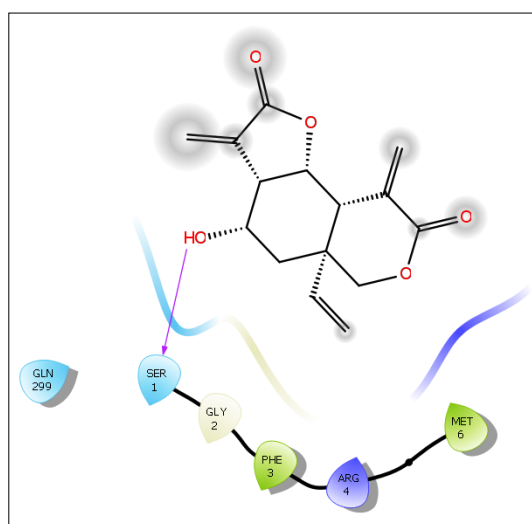**Figure 10** Vernodalol 2D diagrams of docked conformation compound

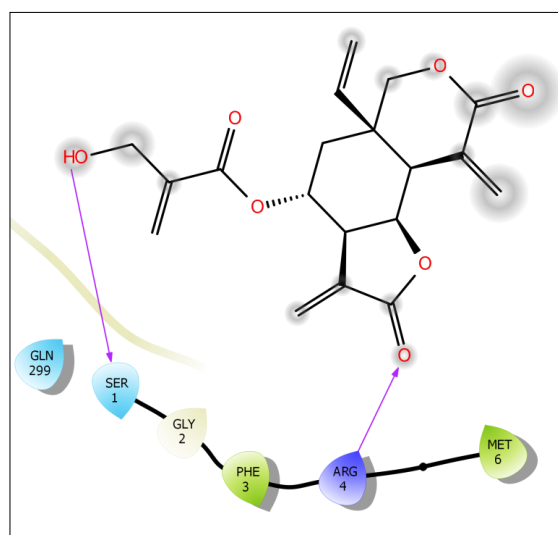**Figure 11** Vernolepin 2D diagrams of docked conformation compound

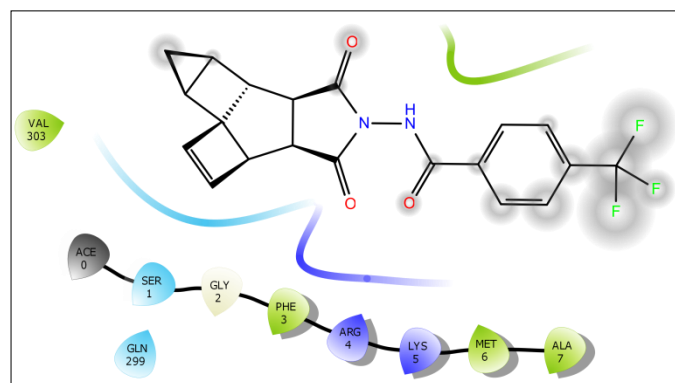**Figure 12** Vernodalin 2D diagrams of docked conformation compound

Figure 13 Tecovirimatat 2D diagrams of docked conformation compound

4. Conclusion

Our research which is based on in-silico study evaluation of *Vernonia amygdalina del.* conclude that phytoconstituents present in *Vernonia amygdalina del.* leaves show effective property and potent record against virus group of animal kingdom although our work is based on computational molecular docking but with great importance of this scientific tool which is known as Maestro 12.8 used for molecular docking analysis prove its authenticity.

Compliance with ethical standards

Acknowledgments

The authors thank the reviewers for their insightful suggestions.

Disclosure of conflict of interest

The authors declare there is no conflict of interest in this study.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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