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An *in silico* investigation and introduction of some secondary metabolites of medicinal plants with antiviral activity and effective vitamins for the treatment of MPox

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Abstract

Unfortunately, the world today is facing the dangers of bioterrorism. Bioterrorism has a long history, and contaminated and infectious materials, corpses, and animal carcasses have been used since ancient times. Therefore, we must be prepared to deal with them. After the eradication of smallpox through vaccination, vaccination was stopped worldwide, and this caused the next and enlarged generation of orthopoxviruses, including Mpox, to be of great concern. Again today, while we have very preliminary research, we are faced with a widespread outbreak of the MPox virus around the world. One of the important and available medicinal resources for the public in all countries is the native medicinal plants of each country. In addition to the independent use of medicinal plants, they can be good medicinal supplements along with the use of approved drugs. In many studies, functional compounds derived from medicinal plants called secondary metabolites have been proven to treat various chronic diseases with anti-cancer, antibacterial, antifungal, antiviral, anti-inflammatory, and allergy activities. Because smallpox and MPox have genetically similar conserved regions, this study was planned with the approach of investigating the inhibitory mechanism of drugs that are used to treat smallpox and is approved by the FDA (Tecovirimat, Brincidofovir, and Cidofovir). Additionally, to investigate the effect of plant metabolites and vitamins on the MPox virus' cell surface protein on preventing virus entry into the cell and causing infection. So far, no studies have been reported on vitamins and plant metabolites in the inhibition of the MPox virus. Some of the valuable candidate plant metabolites in this study such as gingerol in Ginger (*Zingiber officinale* Roscoe), Rosmarinic acid in Selfheal (*Prunella vulgaris* L.), Rosemary (*Salvia rosmarinus*), and Oregano (*Origanum vulgare*), Gallotannin in Aleppo oak (*Quercus infectoria*) and in Chinese nutgall (*Rhus chinensis*) can be potential inhibitors to inhibit MPox virus.

Key Word: Monkeypox, Plant metabolites, Vitamins, Molecular Dynamics

Introduction:

Bioterrorism is generally defined as the intentional use of any microorganism, virus, infection, or biological product as a result of biotechnology or any natural or biologically engineered product of any microorganism is done. Bioterrorism has a long history, and contaminated and infectious materials, corpses, and animal carcasses have been used since ancient times. Unfortunately, the world today is also facing the dangers of bioterrorism. Therefore, we must be prepared to deal with them. While the world is still not released from the nightmare of millions of deaths due to the Coronavirus, whispers are again heard about the imminent spread of another viral disease with a more frightening name than the Corona called MPox. In 1970, the first human case of Monkey-Pox (also called MPox by the WHO in 2022 [1]) was recorded in the Democratic Republic of Congo [2] during a period and Since then, MPox has been reported in humans in other Central and West African countries Before that, in the 1970s, smallpox spread in the world, which was eradicated with the discovery of the smallpox vaccine and vaccination of people in 1980 [3,4]. However, now in 2022, the MPox virus is still endemic in sub-Saharan Africa and has spread to non-native European, American, and Asian countries. Countries including Great Britain, Germany, France, Canada, Australia, Italy, Belgium, Spain, Holland, Portugal, Sweden, America, India, and Thailand [5,6]. The agents of both diseases, smallpox with the origin of Variola virus and MPox with the origin of MPox virus, are from the Orthopoxvirus family of double-stranded DNA viruses with a slight difference in their structure [7].

At first, with the spread of this disease in endemic areas of Africa, it was thought that the main source of disease transmission is through contact with infected animals in nature (zoonotic) until, in 2018, several cases of human-to-human transmission were confirmed in the UK and several other countries [8,9,10]. Symptoms of MPox appear like smallpox with clinical symptoms including fever, headache, back pain, skin rash, and flu symptoms [2]. According to the availability of tests, various methods are used to diagnose MPox, including PCR, culture, and immunohistochemistry such as ELISA or electron microscopy [11,12]. According to the report of Erez et al. in 2019, the detected viral particles have a size of $281 \pm 18 \text{ nm} \times 220 \pm 17 \text{ nm}$ ($n = 24$) [12].

After the eradication of smallpox through vaccination, vaccination was stopped in the world, which made the next-born and raised populations not safe from the dangers of orthopoxviruses, including smallpox. Therefore, a suitable opportunity was provided for the spread of common pathogenic viruses between humans and animals from the family of orthopoxviruses, including MPox, cow-pox, and camel-pox with adaptive mutations. In the meantime, Mpox was very worrying because the MPox virus was more similar in clinical manifestations to smallpox and led to more deaths [13]. As seen in Figure 1, bioinformatic studies also confirm the many similarities in the genetic sequences of different types of cowpox viruses, Buffalopox virus, Akhmeta virus, and Alaskapox virus, especially their similarity in conserved regions and their domain function. Again today, while we have very preliminary research, we are faced with a widespread outbreak of the MPox virus around the world. Currently, several experimental drugs used to treat smallpox are also used to treat MPox, such as Tecovirimat, which was approved by the US FDA. Of course, the drugs Cidofovir or Brincidofovir are also used to treat MPox, which have been somewhat effective [11].

Figure 1: Investigation of MPox 's conserved domain as calculated by the Consurf-DB server. A) In seven types of smallpox virus examined, the coloring scheme shows purple residues as conserved and turquoise as varied. B) 3D image of the MPox virus with conserved and variable regions. C) The common domain of carbonic anhydrase among the seven studied human pathogenic viruses was obtained from the Pfam site.

So far, extensive bioinformatic studies outside of experimental models have not been conducted on other drugs, studies that could increase our knowledge of the treatment of MPox. One of the important and available medicinal resources for the public in all countries is the native medicinal plants of each country. In addition to the independent use of medicinal plants, they can be good medicinal supplements along with the use of approved drugs. In many studies, functional compounds derived from medicinal plants called secondary metabolites have been proven to treat various chronic diseases with anti-cancer, antibacterial, antifungal, antiviral, anti-inflammatory, and allergy activities [14,15]. Secondary metabolites include a large group of active compounds such as flavonoids, polyphenols, terpenoids, coumarins, organosulfur compounds, saponins, lignans, proteins, and peptides that can have a positive effect on membrane permeability, virus replication, and cellular function [14,16,17]. Most of the antiviral activities of drugs or herbal compounds are through inhibition of virus entry by surface proteins, synthesis, and replication of the virus genome, including DNA or RNA. Therefore, for the design of antiviral drugs, it is very important to pay attention to the structure of the virus and its replication cycle [14,18]. The aim of this study is the bioinformatic investigation into different types of antiviral secondary metabolites to inhibit MPox virus entry through surface protein in comparison with existing drugs. According to the NCBI database, the E8L protein is a cell surface protein of the MPox virus that plays an important role in virus entry and infection [19,20]. Considering the availability of medicinal plants worldwide, we intend to introduce new auxiliary substances for treating MPox using secondary metabolites of different plants. These bioinformatic and in silico studies can open new doors for experts to conduct more experimental experiments.

To support the immune system's normal functioning, several trace elements and vitamins have been shown to significantly impact enhancing immunity. The metabolic machinery that is involved in biosynthesis and energy generation includes a wide range of minerals and vitamins [21,22]. According to the literature, some viral diseases, such as Coronavirus, may benefit from vitamin treatment [23]. COVID-19 disease severity was independently associated with both vitamin K and vitamin D deficiency in acute COVID-19, suggesting that these two vitamins may work together as a potential synergistic interplay [24]. Hepatitis C infection increases oxidative stress and decreases the level of group B vitamins in the blood circulation, therefore, to prevent further damage, you can benefit from food supplements and vitamin B consumption to prevent the spread of the disease [25]. Vitamin B17 (amygdalin) has anti-cancer properties because, according to hypotheses, its deficiency causes cancer [26,27]. Traditionally, it has been used to treat asthma, bronchitis, diabetes, and vaginal infections [28]. In general, more detailed research on the antiviral properties of vitamins is still unavailable. There is a need for more research on the antiviral, antibacterial, and antifungal properties of vitamins as supplements.

Methods

Molecular docking studies

-Preparation of Ligands:

In this study, 61 plant metabolites (provided as **a supplementary Table 1**) that have antiviral properties according to traditional claims and new research, and 10 vitamins were candidates as ligands [14,29,30,31,32,33,34,35]. These metabolites' 2D and 3D structures were saved from the PubChem chemical database at (<https://pubchem.ncbi.nlm.nih.gov>). First, ligands had to be prepared for binding and simulation studies. Therefore, 2D structures were transformed into 3D ones by ChemDraw v. Ultra 7.0 software, and then energy minimization was performed using the same software through the MM2 force field. At the same time, the 3D structure of the standard and

approved drugs used for MPox, including Tecovirimat, Cidofovir, and Brincidofovir, was stored as a control from the drug bank at the address (<https://go.drugbank.com>). Finally, the docking scores of antiviral metabolites were compared with standard drugs.

- Preparation of receptor:

Since the main goal of this study was the inhibition of the surface protein of the MPox virus, "MPox virus cell surface binding protein" was searched in the NCBI database. The amino acid FASTA sequence with accession number Q8V4Y0 as the cell surface binding protein from the E8L gene was selected (isolated from the Zaire-96-I-16 strain of MPox virus) [19]. The 3D structure of this amino acid sequence was not available in the protein data bank. Therefore, I-TASSER server, which is based on protein structures prediction and structure-based function annotation, was used for proper modeling and folding of this protein and creating its 3D structure (<https://zhanggroup.org/I-TASSER/>). Among the predicted models, the model with the highest C-score was saved in PDB file format. Now the E8L protein was considered as the receptor in this study and preliminary preparations were made for docking, including the addition of polar hydrogens, charges, and the minimization of structural energy.

-Docking with Molegro Virtual Docker (MVD):

Docking studies of our candidate ligands and receptor were performed by Molegro Virtual Docker v.6.0 (MVD) software, which is a fast and flexible docking program. Based on a new heuristic search algorithm, MolDock software predicts with a high confidence coefficient the most probable ligand-to-macromolecule binding combination through the combination of differential evolution with a cavity prediction algorithm [36]. Before docking, the possible binding sites of the ligand to the receptor must be identified in the form of cubic holes. Using the data obtained from the Coach server, approximately 16 residues including Asn158, Tyr265, Tyr155, Ile281, Ile26, Ile279, Val282, Phe283, Ile290, Leu291, Asp25, His27, Tyr28, Asn29, Leu24, Asp157 were identified as binding sites (active site) of E8L receptor. These results were also confirmed by docking 3 approved drugs Tecovirimat, Cidofovir, and Brincidofovir to determine the receptor binding site. According to Figure 2, all three drugs were placed in a junction box. In the first step, the protein as receptor was entered into the MVD software to reconstruct the residues with structural errors, and the ligands were all prepared by the default setting. For the performance of the docking process was selected MolDock SE algorithm for the scoring function. This program determined five different binding sites (cavities) of the E8L protein as a receptor. For the performance of the docking process was selected MolDock SE algorithm for the scoring function. Also, a spherical region of radius 23 Å with structural coordinates values X=62.96, Y=64.64, and Z=62.02 as defining the binding site of ligands was selected. To ignore atoms far away from the binding site we chose the ignore-distant-atoms option and hydrogen bonding between potential donors and acceptors was investigated. Ligand-receptor (protein) interaction energy calculated, indicate Docking scores thus, better binding bias is identified with more negative scores [37]. Also, according to experimental docking studies, for rating, the inhibitor poses the MolDock, re-rank scores for all ligands and drugs with better-chosen poses were elected. The re-ranking scoring functions can calculate chemical properties using molecular models created and predicted. In ranking different poses of a particular ligand, re-rank scores are outstanding. It is therefore recommended that virtual screening results are ranked using the re-rank score [38].

-Molecular Dynamics (MD) Simulations:

Molecular dynamics simulations for the ligands with minimal binding energy (stronger binding) were performed with the NAMD program (model: Git_2022_05_28), and the files were generated with Visual Molecular Dynamics (VMD) [39,40]. As a result of the structural coordinates of x=51, y=55, and

z=62, the protein was solved with a TIP3P water box and CHARMM 22 parameter files; phi and psi cross-term map correction were applied to force fields for proteins whose chemical structures are similar [41,42]. For minimizing and balancing the protein in the water box, we assumed force field parameters without scaling of 1.0 Å and a cutoff of Coulomb forces with a switching function that starts at 12 Å, goes to zero at a distance of 10 Å, and ends at 13.5 Å with a margin of 3.0 Å, and all atoms, including hydrogen atoms, were explicitly represented. The coordinates of the hydrogen atoms of the protein were generated using the VMD Tk-Console salvation command [39]. Additionally, integrator parameters covered 2 fs/step for all inflexible bonds and nonbonded frequencies have been decided on for 1 Å and complete electrostatic reviews for 2 Å have been used, with twenty steps for every cycle. The periodic boundary conditions with grid dimensions of 1.5 Å for electrostatic interactions of protein via particle mesh Ewald technique were executed. The 3D structure of E8L protein receptor includes 304 amino acids and the number of water molecules inside the simulation box is 4500. So, to remove the bad water constraints, the preliminary energy of the protein was minimized through 5,000 stages of Powell's algorithm at constant temperature (310 K). The simulation was done with Langevin dynamics to examine the kinetic energy, temperature, and/or pressure of the system without a binding pocket, none of the desired parameters change the protein structure during ligand dissociation. Following the performance of primitive simulations of the protein, the protein-ligand complexes were chosen, and via the SwissParam server was parameterization [42,43]. After parametrizing the ligands, they were embedded in the protein and stored as a protein-ligand complex by VMD with the binding pocket residues and immersed in the center of the box of water molecules [42,44]. Ultimately, simulation with solvated protein-ligand complex was balanced with 5,000 minimization steps, and 25,000,000 runs for 50 ns. At the end of the simulation, with the use of VMD the results by calculating the RMSD, root means square fluctuation (RMSF) trajectories, hydrogen bonds distance, and Radius of gyration (Rg) were analyzed and were generated by Matplotlib 3.6.3 library of Python.

- Study of pharmacokinetic indicators:

Computational technology has become a vital tool in drug candidate recognition because it has reduced experimental drug trials and increased the probability of success. For drug discovery, the pkCSM online web server (<http://structure.bioc.cam.ac.uk/pkcsml>) was used to investigate these compounds' pharmacokinetic/ADMET properties to generate predictive models of central ADMET properties using graph-based signatures. Simultaneously, the pharmacological similarity between these compounds was checked with another online server tool called SWISSADME (<http://www.swissadme.ch/index.php>). Among the many existing rules, Lipinski's rule of five (RO5) [45,46] was used to guide the selection of compounds in the early stages of drug discovery.

Results and discussion

-Molecular Docking:

Primarily, based on the literature review on the antiviral properties of medicinal plants and some vitamins, 71 compounds (provided as **a supplementary Table 1**) was chosen as ligand. After docking, ligands with lower MolDock scores rather than approved drugs were ignored. Thus, 28 compounds including medicinal plant compounds and vitamins were selected for the next steps. With the use of MVD software, all remaining compounds were categorized by their binding energy. Finally, five compounds including three medicinal plant compounds and two vitamins were selected due to higher MolDock scores (more negative), fewer side effects, more appropriate dosage, and more accessibility to people, and they were chosen for the molecular simulation stage. (Table1&2).

Table 1: *In-silico* docking analysis of approved drug ranking based on MolDock Score.

Table 2: *In-silico* docking analysis of candidate compounds ranking based on MolDock Score.

Based on the *in-silico* docking of three approved drugs with the MVD inspector tool, it was found that the binding patterns of candidate compounds are similar to existing approved drugs. Since the stability of structures and functions is due to the role of hydrogen bonding, thus the type of connecting a ligand in a receptor active site can best be described via the analysis of hydrogen bonds. Using the Coach server, approximately 16 residues including Asn158, Tyr265, Tyr155, Ile281, Ile26, Ile279, Val282, Phe283, Ile290, Leu291, Asp25, His27, Tyr28, Asn29, Leu24, Asp157 were displayed as binding sites (active site) of the receptor. Results obtained with blind docking with three approved drugs (Tecovirimat, Cidofovir, and Brincidofovir) were confirmed too.

Table 3: Comparative evaluation of the active sites and other binding site residues for receptor-ligand complexed.

According to table 3, some amino acids of ligands created more stable interactions in the receptor's active site by establishing more hydrogen bonds. To validate hydrogen bonds and steric interaction of candidate ligands in the receptor active site, the connections of the drug-receptor complex were investigated. As shown in figure 2, these interactions were completely consistent with drug-receptor complexes.

Figure 2: 3D visualizations of approved drugs and candidate ligands in the active site of E8L receptor with Pymol.

Among the 3 approved drugs as controls, Tecovirimat with one, Cidofovir with six, and Brincidofovir with four hydrogen bonds contain binding energy of -98/73 (Re-rank: -80/98), -118/57 (Re-rank: -91/21), and -144/74 (Re-rank: -102/63) (kcal/ mol). Based on these results, Brincidofovir showed higher binding energy compared to Cidofovir despite the lower number of hydrogen bonds. It may be argued that Brincidofovir, although it does not establish an extensive network of hydrogen bonds and steric interactions in the binding cavity, creates more effective hydrogen bonds than Cidofovir (Table 1,3 and Figure 3).

Figure 3: 3D and 2D molecular interaction of hydrogen and steric bonds with functional residues of the drug-receptor complex by Protein-ligand Interaction Profiler (PLIP) server and Molegro Molecular Viewer (MMV).: A) Tecovirimat (pink) with one hydrogen-bond B) Cidofovir (white) with six hydrogen-bond C) Brincidofovir (red) with four hydrogen-bond. (Notes: blue lines show hydrogen-bond, dotted lines show steric bonds, The type, and the number of involved residues are reviewed in table 2 completely).

Vital studies illustrated good preservation from fatality on some animal models of orthopoxviruses such as MPox virus in prairie dogs, and macaque monkeys [47]. In 2022, Desai et al reported all

patients with MPox infection tolerated tecovirimat well with minimal adverse effects during the clinical trial and showed a desirable clinical safety profile [48]. Another drug that displays good results against the MPox in rodent models is a nucleotide analog FDA-approved called Brincidofovir [49,50]. Cidofovir has also been shown to prevent lesions in non-human primates for up to 48 hours after exposure to MPox and infection [51]. According to Siegrist et al.'s 2022 report, three antiviral drugs, cidofovir, brincidofovir, and tecovirimat showed good activity against MPox, although tecovirimat and brincidofovir presented more promising tolerability profiles for treatment options. It seems more clinical trials should be done for a more accurate understanding [51].

According to the binding pattern of the drug-receptor complex, the candidate ligands showed interesting results. The binding energy of molecular docking for Gingerol with five hydrogen bonds, Rosmarinic acid, and Gallotannin with six hydrogen bonds were estimated to be -133.34 (Re-rank: -100/85), -156.51 (Re-rank: -122/37), and -19.19 (Re-rank: -125/89) (kcal/mol), respectively.

Figure 4: Molecular interaction of hydrogen and steric bonds with functional residues of the ligand-receptor complex by Protein-ligand Interaction Profiler (PLIP) server: A) Gingerol (yellow) with five hydrogen-bond B) Rosmarinic acid (green) with six hydrogen-bond C) Gallotannin (brown) with six hydrogen-bond D) Vitamin K (cyan) with one hydrogen-bond E) Vitamin B17 (purple) with eight hydrogen-bond (Notes: blue lines show hydrogen-bond, dotted lines show steric bonds, The type, and the number of involved residues are reviewed in table 2 completely).

Among vitamins, vitamin K with one and vitamin B17 with eight hydrogen bonds showed binding energy of -130.34 (Re-rank: -99/13) and -161.60 (Re-rank: -118/34) (kcal/mol), respectively. Based on the obtained results, the binding pattern of the residues of the ligand-receptor complex and their hydrogen bonds connections were observed for Gingerol according to Cidofovir, for Gallotannin according to Brincidofovir and for Rosmarinic acid according to both Cidofovir and Brincidofovir. Tecovirimat and vitamin K form one hydrogen bond, but vitamin K has a higher binding energy, perhaps because it binds with a more effective residue. Vitamin B17 also has eight hydrogen bonds and higher binding energy than cidofovir, but its hydrogen bond pattern is similar to Cidofovir and Brincidofovir (Table 1,3 and Figure 4).

-Molecular dynamics (MD) simulations:

We calculated the root mean square deviations (RMSD) of the atomic positions of the drug-receptor complexes as inhibitors of viral protein to examine conformational variations.

Figure 5: Investigation of 50 ns performance of molecular dynamics simulations. A) The plot of RMSD vs. time of all the Control and Candidates complexes. B) The plot of radiation of gyration (Rg) of all the Control and Candidates complexes. C) Evaluation of ligand-receptor interaction by the number of hydrogen bonds at a function of time. D) The plot of RMSF of the complexes obtained during 50 ns MD simulations.

RMSD for the ligands and atoms of the protein is plotted in Figure 5 (A) as a function of simulation time (50 ns for the final molecular dynamics). For each complex, RMSD values were calculated for a box with structural coordinates of x=51, y=55, and z=62 and they showed stability after 20 ns. Tecovirimat was shown to be more stable than Cidofovir and Brincidofovir among the 3 drugs investigated. According to them, Rosmarinic acid, Gingerol, and Vitamin K showed a similar stability pattern to Tecovirimat, Vitamin B17 showed a similar stability pattern to Cidofovir, and Gallotannin showed a similar stability pattern to Brincidofovir. However, all 5 candidate ligands showed to be more stable than drugs (Figure 5(A)).

The plot of the radius of gyration (R_g) shows the overall stability of the complexes. Figure 5(B) shows that R_g plots don't illustrate vigorous changes during the simulation after 20 ns. Although two separate patterns, one for Brincidofovir, Gallotannin, Vitamin B17, and another for Cidofovir, Rosmarinic acid, Gingerol, Vitamin K, and Tecovirimat, were obtained.

But it was shown that the overall compression of the systems had very few changes after 20 ns and was relatively stable. What is evident is the compatibility of the R_g pattern of Gallotannin and Vitamin B17 with Brincidofovir and Rosmarinic acid, Gingerol, and Vitamin K with Cidofovir. Tecovirimat has a larger radius of gyration than others. As mentioned earlier, hydrogen bonds play a very important role in the stability of complexes. So, in molecular simulation, checking the plot of hydrogen bonds is important to evaluate the stability of the complexes. In figure 5 (C), the results showed that all complexes follow a single and similar pattern for hydrogen bonds during the simulation time. Of course, as expected based on the results obtained from molecular docking, the pattern of hydrogen bonds in Brincidofovir and Cidofovir showed more vigorous changes during the simulation than in Tecovirimat. Unlike vitamin K, other ligands also showed more hydrogen bonds during molecular simulation.

To evaluate the vibration of each residue during the simulation, drew and analyzed the plot of root mean square fluctuation (RMSF). In the whole system, we observed three patterns of behavior based on approved drugs. Gallotannin and Vitamin B17 with Brincidofovir and Rosmarinic acid, and Gingerol with Cidofovir showed similar patterns in most of the residues. Also, vitamin K with few differences showed similar patterns with Tecovirimat (Figure 5(D)).

-Drug likeness and In-silico ADMET prediction Analysis:

Basically, indicators such as Log P, TPSA, MW, HBA, and HBD are calculated to evaluate the good permeability of the membrane and hydrophobicity properties of drug molecules. As is well shown in Tables 3 and 4, based on results of SWISSADME and pkCSM server, the pharmacokinetic parameters ADMET and drug-likeness of all three drugs to confirm the viability of the drugs, satisfy all derivatives of the Lipinski rule ($MW \leq 500$ Da, $\text{LogP} < 5$, $n\text{HBD} \leq 5$, $n\text{HBA} \leq 10$, and $\text{TPSA} < 140$ Å). Although Brincidofovir shows a higher molecular weight than 500 and this factor plays a vital role in the drug's oral bioavailability but the 500 Da cut-off mark does not seriously categorize compounds into poor or good oral bioavailability. While Brincidofovir is an oral antiviral drug and is used in the treatment of human smallpox infections. Nevertheless, almost most compounds that disregard two or more parameters of Lipinski rules can be considered non-bioavailable when taken orally [46].

Table 4: The ADMET properties of the approved drugs.

Also, based on the report in Table 5, all three drugs have a good human intestinal absorption percentage (minimum recommended values of 30%). It is recommended that blood-brain barriers (BBB) and central nervous system permeabilities have values of > 0.3 to < -1 Log BB and > -2 to < -3 Log PS, respectively. In the human body, the biotransformation of a drug is measured with the enzymatic metabolism of drugs and cytochrome P450 has a key role in drug metabolism. 1A2, 2C9, 2C19, 2D6, and 3A4 are CYP family indicators that attended in drug metabolism. Among all, 3A4 is a significant indicator because most of the compounds were reported to be substrates and inhibitors of it. Another indicator that explains the communication between the rate of exclusion of the drug and its concentration in the body is total clearance. This is a significant point that elimination and clearance have two different meanings. Elimination explains the rate of waste or damage (mg/h, amount per time) but clearance defines units of flow (L/h, volume per time). Therefore, the elimination of a drug than the drug concentration shows a linear function when the clearance is constant [52]. According to

the description provided, although Brincidofovir is an oral drug, it is not within the approved range for blood-brain barrier (BBB) (Log BB >-1) and central nervous system permeability (Log PS>-3).

Table 5: The predicted drug-likeness properties of the approved drugs.

As it has been reported in the review of the literature the drugs approved and available in the market also have different forms for consumption.

For example, cidofovir is better absorbed by intravenous infusion than by oral administration. Cidofovir in plasma is quickly filtered and excreted by the kidney and has a short half-life in cells [53]. The active form of Cidofovir, Cidofovir diphosphate, is obtained by phosphorylation of the prodrug by cellular enzymes. The intracellular half-life of Cidofovir diphosphate is prolonged once it has been phosphorylated [54].

Brincidofovir is a lipid-conjugated analog of cidofovir but has better oral absorption. In fact, by cellular phospholipases, it is hydrolyzed into cidofovir and converted into cidofovir diphosphate, in this case, it passes through the cell membranes more effectively and the level of Brincidofovir in the cells reaches a high concentration. As a result, unlike cidofovir, Brincidofovir has less permeability and accumulation in the kidneys and shows a lower risk of poisoning the kidneys [55]. Tecovirimat is formulated both orally and intravenously, but it is better absorbed orally. Seems co-administration of Brincidofovir and Tecovirimat seems to have a synergistic effect [56].

After examining the affinity of the ligands to the MPox virus protein during docking and molecular simulation, their drug-likeness properties and ADMET were also examined. As shown in Table 6, all ligands except Gallotannin showed suitable molecular weight. Of course, according to the available documentation and Brincidofovir as a control, poor or good oral bioavailability for a molecular weight > 500 is not a definitive classification criterion for pharmaceutical similarity. All compounds are fat-soluble (LogP<5), even vitamin K is fat-soluble despite showing LogP=5/64. This hydrophobicity has an important task in drug absorption, transport, and distribution. According to Table 6, Gallotannin and Vitamin B17 violated more than two out of five of Lipinski's rules and are not drugs. While Vitamin B17 is sold as a commercial drug in pharmacies. The data in Table 7 also show that despite the non-toxicity of all compounds, Gallotannin and Vitamin B17 do not have proper intestinal absorption (minimum recommended amounts of 30%). The central nervous system permeability (LogPS) indicator should be >-2 to <-3, that is -5/183 for Gallotannin. All compounds except Gingerol and Vitamin B17 showed acceptable total clearance. Based on review studies, vitamin B17 (Amygdalin) under the brand name Laetrile®, is artificially prepared from the natural amygdalin found in the kernels of apricots, peaches, apples, almonds, and cherries, and can be taken orally and intravenously [26]. Of course, oral consumption of amygdalin causes slight poisoning due to the inhibition of cytochrome oxidase of the electron transfer chain in mitochondria, and for this reason, it should be consumed with the advice of a consultant. Therefore, it is more appropriate to use it by intravenous injection (the highest dose of amygdalin in the human body is approximately 0.07 g/kg) [57,58].

Table 6: The ADMET properties of the candidate ligands.

Therefore, it can be argued that although some compounds do not get the necessary score for drug-likeness properties, they can be formulated as drugs by changing their administration form, for example, instead of oral administration by injection, topical creams, gels Transdermal, suppositories or nanoliposome drugs [59].

Table 7: The predicted drug-likeness properties of the candidate ligands

Also, some traditional techniques such as the use of co-solvents or surfactants, variation of pH of solvent, use of hydrates or solvates, inclusion complex, or change in the dielectric constant of the solvent are proposed as a solution to increase bioavailability [60]. Therefore, it seems that the general ADMET properties of these compounds represent their good pharmacokinetics properties and they can have a good ability as a drug supplement in the inhibition of the MPox virus.

-Conclusion:

Historically, MPox infections were treated with supportive care and management of complications, but new antivirals, such as tecovirimat, Cidofovir, and brincidofovir, have led to new therapeutic opportunities. However, more experimental tests are still needed to investigate their effectiveness in the treatment of MPox. What has been mentioned based on previous studies about the mechanism of effectiveness and inhibition of these drugs, in the case of Cidofovir and Brincidofovir is the inhibition of DNA polymerase through the entry of Cidofovir diphosphate into the DNA strand during its replication and the slowing down of DNA synthesis. In the case of the inhibitory mechanism of Ticovirimate, inhibition of extracellular virus production and reduction of virus transmission to distant sites have also been reported. Because smallpox and MPox have genetically similar conserved regions, this study was planned with the approach of investigating the inhibitory mechanism of drugs approved by the FDA (Tecovirimat, Brincidofovir, and Cidofovir), plant metabolites, and vitamins, on the protein of the cell surface of the MPox virus in preventing the virus from entering the cell and causing infection.

So far, no studies have been reported on vitamins and plant metabolites in the inhibition of the MPox virus. Since the covid-19 pandemic and infectious viral diseases spread in the new century, it has become increasingly important to examine medicinal supplements such as vitamins as well as local herbal products in every country at this time of widespread disease and drug shortages. In this study, by examining various vitamins against MPox, vitamins K and B17 showed a good inhibitory effect on the MPox virus. Also, valuable candidate plant metabolites in this study such as gingerol in Ginger (*Zingiber officinale Roscoe*), Rosmarinic acid in Selfheal (*Prunella vulgaris L.*), Rosemary (*Salvia rosmarinus*), and Oregano (*Origanum vulgare*), Gallotannin in Aleppo oak (*Quercus infectoria*) and in Chinese nutgall (*Rhus chinensis*) can be potential inhibitors to inhibit MPox virus. Obviously, these bioinformatics studies to introduce more candidates in the inhibition of the MPox virus are still in the beginning and there is a long way to their clinical effectiveness by other researchers.

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-Author Contributions:

DP and MT have prepared the manuscript of the article. DP collaborated on data collection and content and data analysis with MT's assistance. MT revised the manuscript. All authors endorsed the final version and are accountable for all aspects of this study.

-Data availability :

All of the data generated or analyzed during this study are included in this published article and its supplementary information files. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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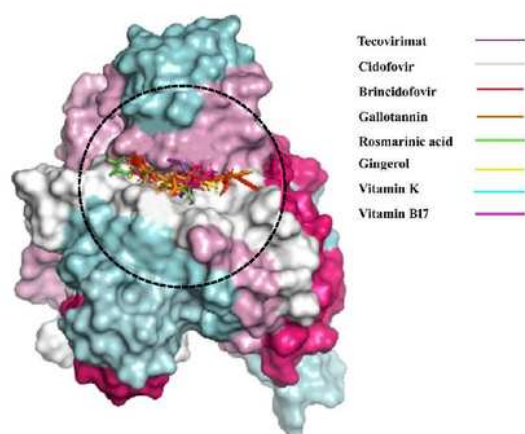


Figure 2: 3D visualizations of approved drugs and candidate ligands in the active site of E8L receptor with Pymol.

Figure 2

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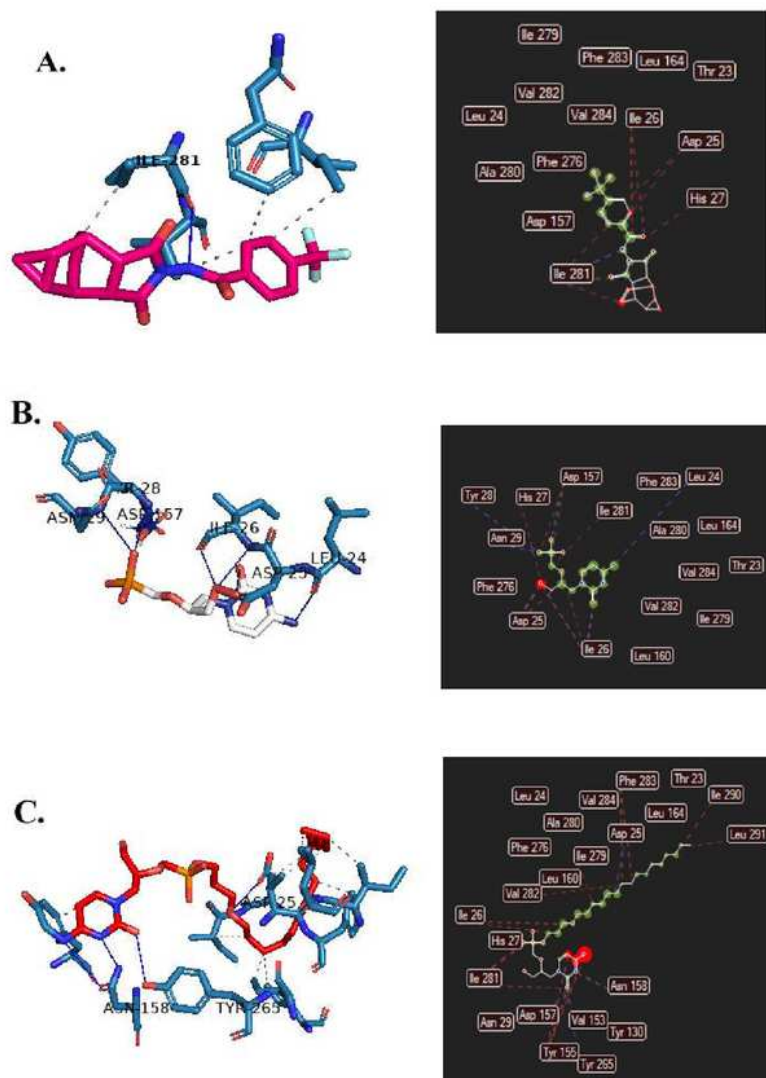


Figure 3: 3D and 2D molecular interaction of hydrogen and steric bonds with functional residues of the drug-receptor complex by Protein-ligand Interaction Profiler (PLIP) server and Molegro Molecular Viewer (MMV).: A) Tecovirimat (pink) with one hydrogen-bond B) Cidofovir (white) with six hydrogen-bond C) Brincidofovir (red) with four hydrogen-bond. (Notes: blue lines show hydrogen-bond, dotted lines show steric bonds, The type, and the number of involved residues are reviewed in table 2 completely).

Figure 3

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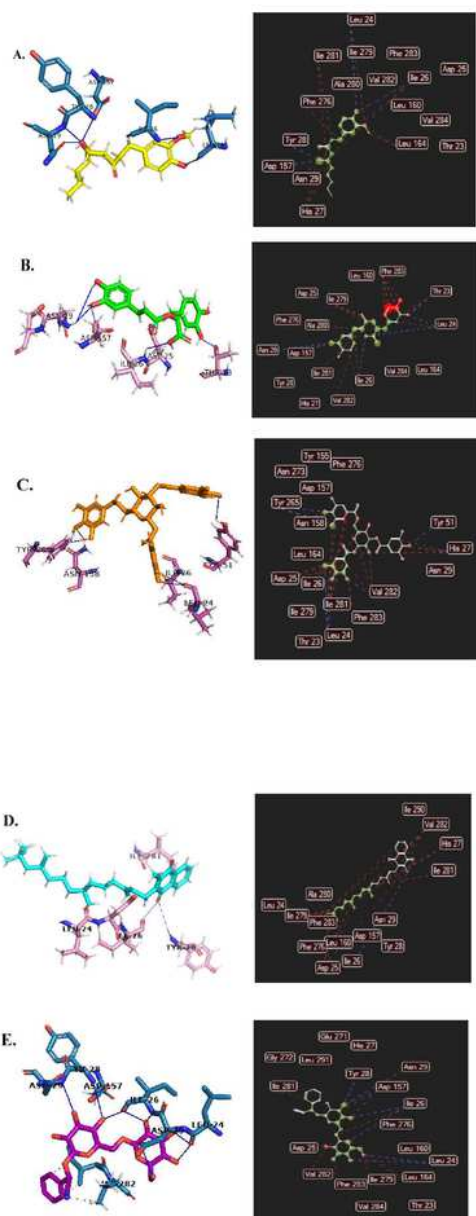


Figure 4: Molecular Interaction of hydrogen and steric bonds with functional residues of the ligand-receptor complex by Protein-ligand Interaction Profiler (PLIP) server: A) Gingerol (yellow) with five hydrogen-bond B) Rosmarinic acid (green) with six hydrogen-bond C) Gallotannin (brown) with six hydrogen-bond D) Vitamin K (cyan) with one hydrogen-bond E) Vitamin B17 (purple) with eight hydrogen-bond (Notes: blue lines show hydrogen-bond, dotted lines show steric bonds, The type, and the number of involved residues are reviewed in table 2 completely).

Figure 4

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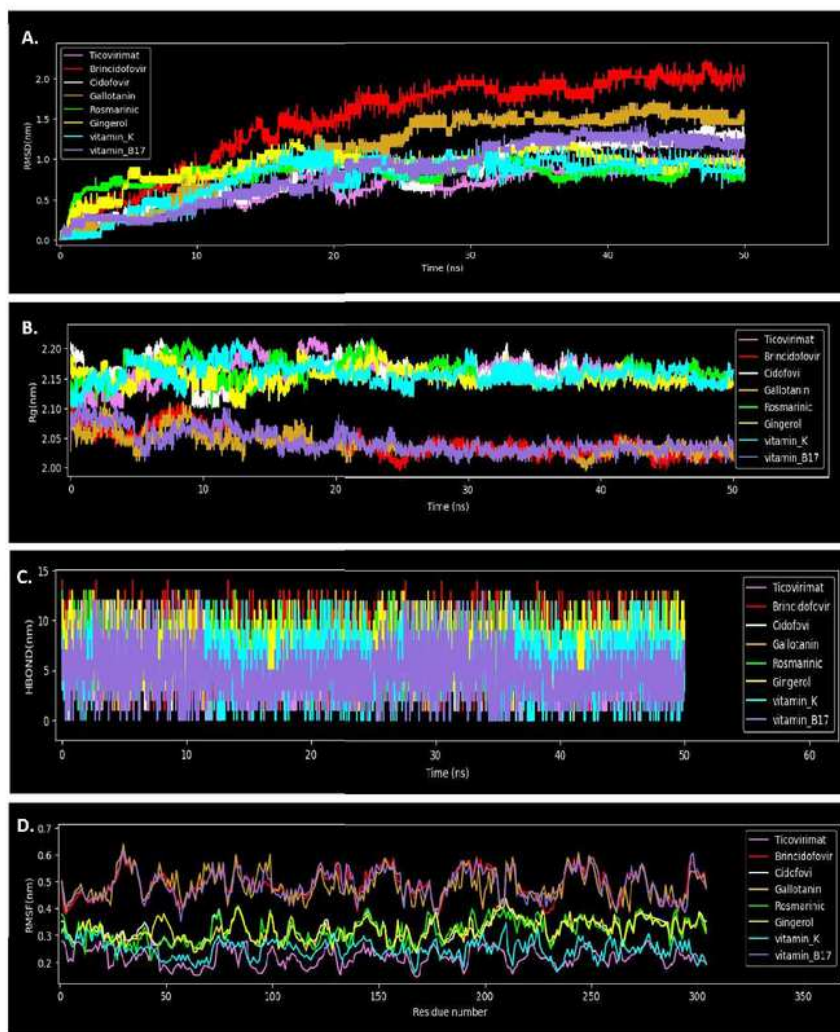


Figure 5: Investigation of 50 ns performance of molecular dynamics simulations. A) The plot of RMSD vs. time of all the Control and Candidates complexes. B) The plot of radiation of gyration (Rg) of all the Control and Candidates complexes. C) Evaluation of ligand-receptor interaction by the number of hydrogen bonds at a function of time. D) The plot of RMSF of the complexes obtained during 50 ns MD simulations.

Figure 5

See image above for figure legend

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