Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 15 July 2026
Revised 27 Aug 2026
Accepted 11 Sep 2026

Natural Resources for Human Health 2026, Vol. 6 (21s): 50–64

KEYWORDS:
Aloe vera; monkeypox virus; molecular docking; ADMET; molecular dynamics simulation; flavonoids; Lipinski's rule of five; drug discovery

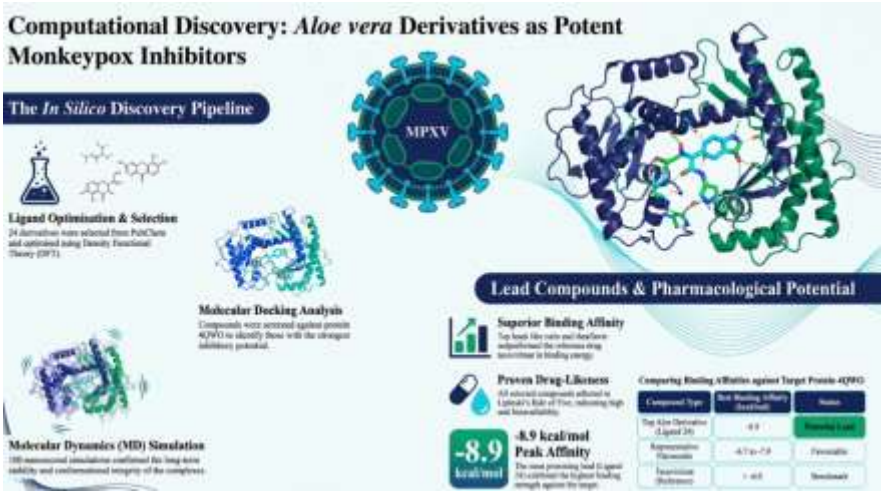
Natural Derivatives of Aloe Vera in Antiviral Drug Discovery: Targeting Monkeypox via Computational Approaches

Yasmeen A. Albalawi[1]

[1]Department of Biology, College of Science, Jouf University, Sakaka, Al-Jouf, Saudi Arabia;Yaalbalawi@ju.edu.sa, https://orcid.org/0000-0001-8497-5240

ABSTRACT: Monkeypox has gained increasing global attention as an important public health issue, posing a high risk to vulnerable groups such as young children and pregnant women. Effective therapeutic agents remain limited. In this study, natural flavonoid compounds derived from Aloe vera were evaluated in silico as potential inhibitors of the monkeypox virus. Twenty-four Aloe vera-derived compounds were assessed for binding affinity to the monkeypox virus protein target, 4QWO. The most promising leads, rutin, theaflavin, and hesperidin, showed favorable binding energies against the target protein, suggesting potential efficacy. Molecular docking analysis elucidated specific interactions between these compounds and the target protein, with particular emphasis on residues like Arg119. Furthermore, comprehensive evaluations including ADMET profiling, adherence to Lipinski's rule, and drug-likeness assessments were conducted to gauge their pharmacological potential. Molecular dynamics simulations provided insights into the stability of selected compounds, revealing minimal conformational changes over time. These results attest to the promise of natural agents, especially derivatives of Aloe vera, in the treatment of monkeypox. There are, however, also notable regional and national regulatory differences with regard to plant-based agents. Further research is therefore required to identify and describe the antiviral properties of various plant species to maximally exploit the plant-based antivirals. Botanists, virologists, and pharmacologists should consult each other and invest in newer technologies by using genomics and high-throughput screening. More research is necessary to create non-toxic safe and long-lasting antiviral medicines from plants.

Graphical Abstract



Natural Resources for Human Health
eISSN: 2583-1194

INTRODUCTION

Plant-derived vaccines, also known as plant-based vaccines, are gaining increasing importance in the field of biotechnology. The potential of plant-derived vaccines is their cost-effectiveness for mass-scale production while being safer in the human environment. These efforts significantly play a vital role toward vaccination against pathogens, especially regarding newly emerging infectious diseases [1]. Viral infections are a leading cause of infectious disease and are commonly transmitted by either direct or indirect contact. These infections spread via airborne droplet or direct and indirect contact transmittance (Figure 1). The emergence of new viral agents, as well as viral resistance mutations, has created a growing demand for antiviral agents from various sources. Ancient ethnobotanical uses for a wide variety of plants are now being applied as a powerful tool to combat such ailments. Roughly 35% of the pharmaceutical market and 20% of drugs come from plants. Native plants are used regularly for food and herbal medication by rural populations in certain regions, and traditional practices have informed today's more advanced methods of plant processing and use [2]. Biologically active compounds isolated from medicinal plants are envisaged as new safe drugs and can be a key to find low-cost treatments with fewer complications to cure many diseases [3].

These traditional systems, including Unani, Traditional Chinese, and Ayurvedic medicine, are supported by long-standing evidence for their use in disease treatment and in restoring physiological balance [4]. Egyptian physicians relied on medicinal plants together with basic anatomical knowledge to treat disease, and such practices have been shown to be effective. Plant-based medicines continue to serve as a complementary option in modern treatment, reflecting a long history of reliance on medicinal-plant-derived drugs [5].

Monkeypox virus is a DNA virus most closely related to the smallpox virus and forms the Orthopoxvirus genus of the Poxviridae family, responsible for the emerging zoonosis, monkeypox [6]. In Central and West Africa, sickness is recognised to be caused by two distinct genetic subgroups. In contrast to the Central African (Congo Basin) subtype, the West African subtype causes a milder form of the disease. The West African subtype of the virus is currently the most prevalent and widely dispersed form, according to preliminary data from the current outbreak. Rather of affecting monkeys, this disease affects rodents including squirrels, rats, and mice and is spread from them to people. Because it first produced a smallpox-like illness in monkeys in 1958, it is known as monkeypox [6, 7]. It is unknown exactly where the virus lives in nature or how it cycles naturally. Two wild animal isolates of the virus have been made thus far; the first was from an African squirrel in the Democratic Republic of the Congo's Equatorial area in 1985. The second was isolated in 2012 from a deceased newborn primate belonging to the "mangabey" monkey species in the Ivory Coast's rainforests [8]. The rash of monkeypox might be confused with herpes, shingles, or chickenpox. However, a board-certified dermatologist can identify the specific condition causing the rash by examining the skin's pattern and the area where the rash first emerges. The dermatologist will take a sample of the rash and send it to a lab if monkeypox is the most likely culprit. A polymerase chain reaction (PCR) test will be conducted in the laboratory. If the swab has the monkeypox virus, it will be revealed by the PCR test findings. The number of cases of human monkeypox that appear to have increased recently over a large geographic area and the possibility of additional transmission have increased concerns about this developing zoonosis [8, 9].

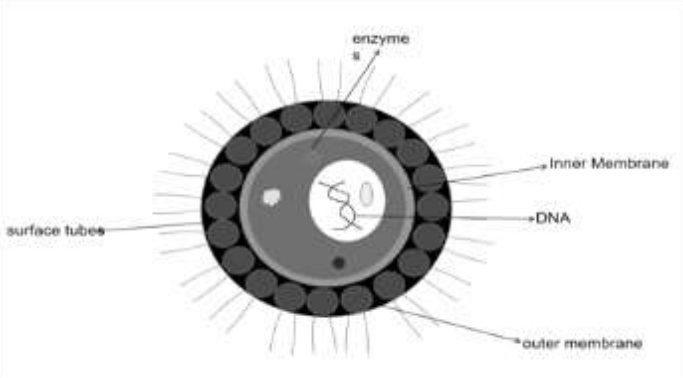


Figure 1. Schematic structure of the monkeypox virus (MPXV), an Orthopoxvirus of the Poxviridae family, illustrating its overall virion architecture.

Monkeypox has become a major global health concern, posing a higher threat to children under one year of age and to pregnant women, particularly since the 2021 outbreak began to escalate. Unlike several other viral infections, such as influenza or measles, few therapeutic options exist for monkeypox; tecovirimat remains the major treatment option [10]. Given the therapeutic potentials of natural products, we therefore used computational approaches to assess some potential novel and existing nature-based compounds that could target MPV for therapy in this study [11]. The research findings confirm that as a natural compound, flavonoids have various pharmacological properties, including antiviral effects. In this study, according to literature review 24 natural compounds were chosen. The investigation further emphasized on the binding affinity of these ligands with target protein (4QWO, monkeypox virus) which is responsible for their possible efficiency against the virus. These results indicate that several compounds, including rutin, theaflavin, and hesperidin, show favorable binding energies against the 4QWO target that are comparable to or more favorable than the reference antiviral tecovirimat [12]. Detailed investigation revealed unique interactions between the chemicals and the target protein, such as hydrogen bonding and other molecular interactions, which contribute to their binding affinity [6].

There are five clinical stages of monkeypox:

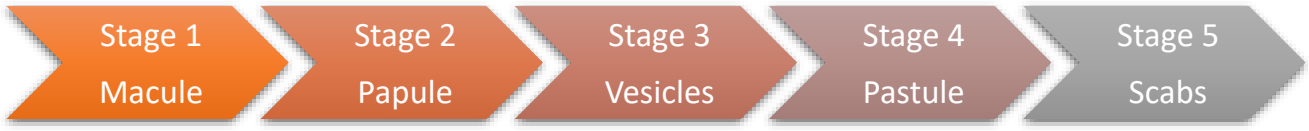


Figure 2. The five clinical stages of monkeypox skin lesions, from macule to scab formation.

Regions affected by monkeypox where indigenous tribes have vital knowledge regarding the native flora and its medicinal properties used traditional medicine against this virus. Plants are a rich source of pharmacologically active antiviral agents. Biochemical and bioactive substances that are extractable from medicinal plants are used to target particular viruses and help to treat or prevent a wide range of viral diseases and infections [13]. Traditional healers are skilled in using plant-based solutions for a range of illnesses, including monkeypox. Because they have transmitted their expertise orally over time, traditional medicine is useful in places lacking access to modern medical care. Natural plant synthesis of medicinal chemicals has resulted in the development of novel medicines with powerful therapeutic benefits. Nearly 80% of the world's population still receives their primary care from traditional medicine, which has been using plants and plant products to treat illnesses for millennia long before the active ingredients were discovered. It is worth noting that almost half of all prescription drugs come from plants or plant derivatives. It has been demonstrated that using plants for medicinal purposes in combination therapy is beneficial against a variety of viruses, such as influenza and herpes viruses. Furthermore, a variety of plant extracts, including those derived from Aloe vera, have proven to be antiviral against a wide spectrum of viruses [14].

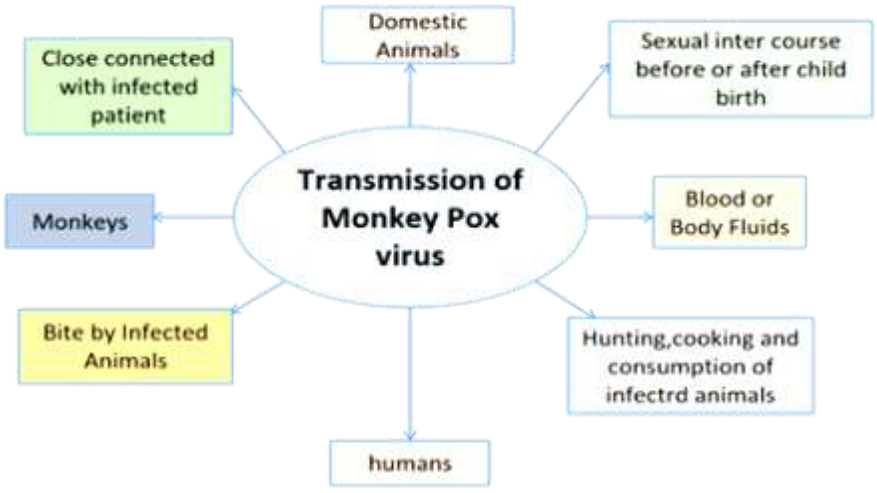


Figure 3. Transmission routes of the monkeypox virus, including direct contact, respiratory droplets, and fomite transmission.

The family Liliaceae consists of the genus Aloe as well as a vast range of succulent plant species. Most important of these is the ornamental and medicinal plant referred to as Aloe vera. It thrives in the entire Mediterranean area of Southern Europe, Asia, and Africa. This extract is present all over the globe but for its origin, it can be abundantly found especially dry areas. Aloe vera naturally possess many biological and pharmacological characteristics, such as anti-inflammatory, immunostimulatory, cell growth stimulatory, antiviral, antibacterial, and antifungal effects. This study, therefore, used an in silico method to predict the bioactive compounds present within the Aloe vera leaves [15].

Flavonoids are natural chemicals with a variety of pharmacological actions, including antiviral, antioxidant, anti-inflammatory, antibacterial, and antifungal characteristics. In light of this, we set out to identify potentially beneficial natural substances for treating monkeypox by drawing on the results of earlier studies. Twenty-four naturally occurring Aloe vera-derived substances were selected, and their capacity to bind to the target protein (4QWO, monkeypox virus) was investigated [16]. Research findings similarly showed that rutin, theaflavin, and hesperidin exhibited favorable binding energies against the 4QWO target, consistent with the docking results reported in Section 3.3, suggesting their potential effectiveness [17]. Tecovirimat, used here as the reference antiviral, formed hydrogen bonds with four residues of 4QWO (Arg119, Glu77, Tyr80, and Arg127) when the precise interactions between these compounds and the target protein were examined. Theaflavin had the highest binding energy among the tested compounds and formed three conventional hydrogen bonds with three residues of 4qwo [18]. Because no specific medications are available, the Centres for Disease Control and Prevention (CDC) states that supportive care is frequently adequate for patients infected with the monkeypox virus. The development of a safe medication to prevent monkeypox infections is done by computational methods. Since creating a medication requires more than ten to twelve years, a significant amount of money, time, and resources, this new computational technique ushers in a new era in which new biological substances and effective medications may be created quickly, saving money and time. For almost thirty years, computer-aided drug discovery and design methods have been a major asset in the search for clinically relevant molecules [14, 19]. While computer-aided drug design and discovery has many benefits and can save time, money, and resources in the process of developing a new medication, it is not without its drawbacks. Interestingly, Arg119 turned out to be an important amino acid for 4qwo interaction and binding affinity. Furthermore, we discovered other interaction types that can improve binding affinity and boost the biological efficacy of these compounds, including pi-donor hydrogen bonds, pi-alkyl, alkyl, halogen, and pi-cation interactions [20].

Drug target discovery can yield better results with in silico investigations. As demonstrated during the recent COVID-19 pandemic, in silico research is crucial during unanticipated outbreaks, since drug targets cannot be identified quickly by conventional methods alone. Addressing such large numbers of potential targets requires considerably faster methods. Using in silico techniques, the process of screening natural medicinal plants for drug targets can be accelerated [21].

MATERIALS AND METHODS

2.1 Synthesis of ligand and optimizing its structure

Aloe vera is a medicinal plant whose leaves are a rich source of bioactive flavonoid polyphenols. Flavonoids are among the most widely occurring classes of phenolic compounds, with approximately 8000 distinct compounds discovered to date [22]. These compounds are often used as nutritional supplements due to their potential health benefits, including boosting immunity and protecting against infections [23]. Numerous studies have highlighted the various biological effects of Aloe vera, suggesting its potential in preventing a wide range of diseases. To explore its potential further, we selected 24 derivatives of Aloe vera from the PubChem database. The canonical SMILES (Simplified Molecular Input Line Entry System) of these molecules were obtained from the database, and their 2D structures were generated using the ChemBioOffice program. To better understand the molecular structure of these derivatives, we employed a method called density functional theory (DFT) for molecular optimization. This involved optimizing the 3D structures of the molecules and minimizing their energy using the B3LYP functional unit DFT procedure within the DMol3 code from Material Studio 08. Following optimization, we calculated the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) expressions for each molecule [24].

2.2 Prediction of ADMET profile

Such advancement of computer technology has led to the discovery of drug to such an extent that novel targets can be developed, and experimental trials throughout this process can be reduced with higher success rates. In this regard, ADMET

pharmacokinetic properties like absorption, distribution, metabolism, excretion, and toxicity, besides drug-likeness evaluation, assume great significance in the perspective of making preliminary assessments during drug discovery as well as drug development processes [25]. For instance, web-based tools, for example, pkCSM and SwissADME, are being widely used for the evaluation of ADMET properties, Lipinski's Rule observance, and drug-likeness. Therefore, in this work, due to the use of online resources pkCSM and SwissADME, it is possible to assess the ADMET properties, Lipinski's Rule, and drug-likeness of the investigated compounds. By providing access to these computational tools, screening could now efficiently prioritize candidate compounds as having favorable pharmacokinetic profiles with drug-like properties, thus accelerating the efficiency of a drug discovery and development process.

2.3 Selection of target structure and synthesis

The 3D crystal structures of the Monkeypox virus (PDB ID 4QWO) were obtained from the RCSB PDB database as it holds the potential receptor for drug design because of their role in pathogenic effects. Target proteins can be inhibited thus slowing down replication inside host cells impeding pathogenicity [25]. To facilitate precise drug binding akin to a lock-and-key mechanism, it is imperative to ensure a clean receptor environment devoid of excess molecules such as water and non-protein components. Thus, the obtained crystal structures underwent preparation steps using Discovery Studio v16.1.0.15350 and Pymol version 2021 programs. This preparation involved the removal of ligands, non-protein components, and water molecules to create an optimized receptor environment for molecular docking experiments. Prior to molecular docking, the energy of the target proteins was minimized using SwissPDBViewer, a step crucial for achieving stable and accurate docking results. This process ensures that the target proteins are in an energetically favorable conformation for interaction with potential drug molecules [26]. The optimized 3D structures of the target receptors serve as the foundation for subsequent computational analyses aimed at identifying potential drug candidates for inhibiting viral replication and mitigating pathogenic effects.

2.4 Analysis of molecular docking

Molecular docking studies were performed to identify the molecular interactions and assess the efficacy of ligand binding along with their corresponding binding affinities in the inhibition of target proteins. As referred, the molecular docking analysis for the study was done using a version 4.2 of PyRx Auto Dock tools software [27]. During molecular docking, the 3D grid for ligand-receptor interactions was generated using the automatic maximized function. For the monkeypox virus, the grid box parameters were set at a center coordinate with dimensions of (x= 35.14496, y= 37.645, z=36.966). Following the completion of docking analysis, the BIOVIA Discovery Studio Visualizer v16.1.0.15350 was utilized to monitor the docked residues, and ligand-protein complex structures, and generate 2D and 3D representations. This software facilitated the comprehensive analysis and interpretation of the docking results, providing insights into the potential interactions between the ligands and target proteins.

2.5 Simulations of molecular dynamics

The YASARA v21.6.17 software was employed to conduct molecular dynamics (MD) simulations investigating the interaction between Aloe vera and the 4QWO viral protein. The simulations utilized the aided model construction approach, employing the AMBER 14 force field to accurately represent molecular interactions [28]. To simulate the physiological environment, a combination of Cl- and Na+ ions was introduced, along with the exchangeable TIP3P water model. Each system underwent energy minimization with the most effective gradient strategy, comprising 5000 cycles. Additionally, a periodic boundary condition was applied, with the cell size maintained at ten times larger than the protein size [29]. The MD simulations incorporated particle-mesh Ewald (PME) methods to account for long-range electrostatic interactions, ensuring an accurate representation of molecular behavior. Physiological conditions were simulated, with the simulations conducted at a temperature of 298 K, a NaCl concentration of 0.9%, and a pH of 7.4. The simulation temperature was controlled using a Berendsen thermostat, maintaining constant pressure throughout the simulation. Subsequently, MD simulations were conducted for a duration of 100 nanoseconds under constant pressure conditions. Analysis of the simulation trajectories and interaction dynamics was performed using the built-in YASARA MACRO scrip, providing insights into the Aloe vera-4QWO protein interaction.

RESULTS

3.1 Preparing ligand

The molecular structures of the Aloe vera derivatives selected for this study contain a range of functional groups characteristic of anthraquinone and phenolic compound classes, including hydroxyl and carbonyl moieties, as shown in Figure 4 [30]. Additional structural attributes relevant to the bioactivity of the Aloe vera derivatives include hydroxyl and carbonyl substituents contributing to their polarity and reactivity. The optimized chemical structures of the Aloe vera derivatives are depicted in Figure 4, and these optimized structures form the basis for the subsequent docking and dynamics analyses described below. Consistent with the general pharmacology of flavonoid polyphenols discussed above, numerous studies have shown that Aloe vera derivatives exhibit a broad spectrum of biological effects, supporting their potential in the prevention of a range of disorders. A total of 24 Aloe vera derivatives were selected from the PubChem database for this study [22].

3.2 ADMET analysis and Lipinski rule, pharmacokinetics

When different substitutions are introduced, generating various analogs, they serve as potential drug candidates, offering enhanced pharmacological efficacy. The analyzed analogs of Aloe vera are depicted in Figure 4 [31]. The Lipinski rule, also known as the rule of five, is pivotal in determining drug-likeness and pharmacokinetics [32]. It delineates essential criteria for evaluating drug similarity characteristics, including consensus (Log P) values and molecular weight [4]. According to Lipinski's criteria, the molecular weight should fall within the range of 150 to 500 g/mol, with fewer than five hydrogen bond donors and ten or fewer hydrogen bond acceptors. The TPSA value should range between 20 and 130 Å², while the Log P value should not exceed 6.00 [33]. In our study, the Aloe vera derivatives exhibited molecular weights ranging from 294.34 to 492.49 Dalton, with two compounds (02 and 27) showing a molecular weight of 502.51 Dalton. The number of hydrogen bond donors and acceptors, TPSA, and Log P values all fell within standard ranges. Utilizing the Lipinski rule accurately predicted drug-likeness, with all chosen compounds adhering to Lipinski's criteria, indicating their potential utility as drugs [34]. The in silico prediction of druglike properties was compiled in Table 2 using the online program SwissADME.

3.3 Molecular docking analysis against monkeypox

Molecular docking is a key strategy in computational chemistry for innovative drug development, facilitating the elucidation of molecular interaction strategies and the assessment of ligand effectiveness in inhibiting targeted proteins. Docking values are computed to ascertain the extent to which ligand molecules bind to the active site of specific receptors [35]. A more negative binding energy value indicates a stronger binding preference and the formation of a more persistent ligand-receptor complex structure. To qualify as a potential drug candidate, the docking score should exceed -6.0 kcal/mol. In our current study, binding affinities ranged from -6.7 kcal/mol to -7.9 kcal/mol against the monkeypox virus target protein (PDB ID 4QWO) [36]. Notably, all binding energies surpassed -6.00 kcal/mol, exceeding the docking score of the reference antiviral tecovirimat. Among the derivatives, the highest binding affinity was -8.9 kcal/mol against the monkeypox virus target protein (PDB ID 4QWO), reported for ligand 24, suggesting the potential effectiveness of these Aloe vera derivatives against monkeypox [37]. The identification of significant sites in the monkeypox virus active site pocket revealed key residues crucial for ligand binding. These findings suggest that these ligands could potentially serve as effective therapeutic agents against monkeypox by impeding viral replication and expression.

3.4 Protein-ligand interaction analysis

Chemical descriptors were calculated to assess the reactivity and stability of the Aloe vera derivatives. The HOMO-LUMO energy gap, which influences biochemical reactions, was evaluated using density functional theory (DFT). A smaller energy gap suggests higher chemical reactivity, while a larger gap indicates greater kinetic stability. The calculated chemical descriptors indicated that all compounds maintain energy gaps within the acceptable range, suggesting favorable chemical stability and potential therapeutic efficacy. Frontier molecular orbitals (HOMO and LUMO) were analyzed to predict the physicochemical properties of the Aloe vera derivatives [38]. The proximity between HOMO and LUMO nodes indicates the regions where protein-ligand interactions occur, with LUMO regions being of particular interest.

3.5 Molecular dynamics simulations

Molecular dynamics simulations were conducted to evaluate the stability and conformational changes of the protein-ligand complexes over time. The analysis revealed that ligand 24, the top-ranked compound identified in Section 3.3, exhibited stable behavior, with minimal conformational changes observed in the protein structure. The evaluation of protein-ligand interactions, solvent accessibility, and structural changes provided insights into the compounds' efficacy as antiviral agents [39]. ADME and toxicity predictions were performed to assess the pharmacokinetic properties and safety profile of the Aloe vera derivatives [40]. The in silico ADMET predictions indicated favorable properties, suggesting the potential of these compounds as new drug candidates. The overall findings support further investigation of these Aloe vera derivatives for their therapeutic potential against viral infections.

3.6 Chemical descriptors calculation

To analyze biological reactions, LUMO and HOMO are found significant in terms of electrochemical resistance and kinetics. The drug molecule's stability, its chemical hardness and softness are correlated to get the separation energy gap in the HOMO-LUMO.

These characteristics are obtained by using the HOMO and LUMO frequencies. These reactivity's characteristics are derived using the HOMO and LUMO frequencies.
Significant kinetic stability but low electrochemical stability is indicated by a bigger energy gap, whereas higher polarity and chemical conductivity are observed by using a relatively small energy difference and improved softness. Additionally, a large HOMO-LUMO energy gap indicates a lower electron electronic transition, whereas a small gap indicates higher electrochemical stability level in both of which are closely related to binding with a targeted protein receptor. A high degree of dissolving capacity is indicated by the components' softness score [36]. For the Aloe vera derivatives examined, the predicted chemical hardness values ranged between 3.5 and 4.5, with corresponding softness values between 0.24 and 0.25, indicating favorable chemical stability.

Table 1. Docking binding affinities (kcal/mol) of Aloe vera-derived ligands (identified by PubChem CID) against the monkeypox virus target protein 4QWO.

Ligands	Binding affinity
102052685	-6.5
10207	-6.5
102445577	-6.1
12305761	-5.9
1488736	-6.3
14889737	-6.8
14989	-6.6
158096	-6.5
160190	-6.0
21582596	-6.6
3220	-6.3
46173997	-7.4
46173998	-7.2
5317657	-5.8

Natural Resources for Human Health
eISSN: 2583-1194

Table 2. ADMET (absorption, distribution, metabolism, excretion, and toxicity) profile of representative Aloe vera derivatives, predicted using SwissADME. BBB: blood-brain barrier; ESOL: estimated aqueous solubility class; Lipinski, Ghose, and Veber refer to compliance with each rule-based drug-likeness filter.

ADMET parameter	C15H20O5	C21H32O9	C21H45O9	C19H27O9
BBB permeant	no	no	yes	no
ESOL	-1.25 very soluble	-1.39 soluble	-1.39 very soluble	-0.43 soluble
Lipinski	yes	yes	yes; 1 violation	yes
Ghose	yes	yes	yes	no
Veber	yes	yes	yes	no

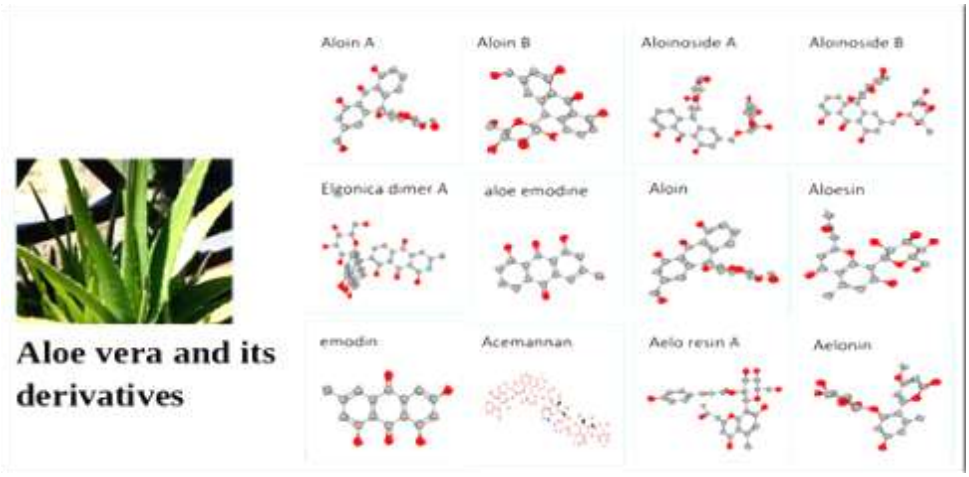


Figure 4. Chemical structures of the 24 Aloe vera derivatives selected from PubChem and optimized by density functional theory (B3LYP/DMol3) prior to molecular docking.

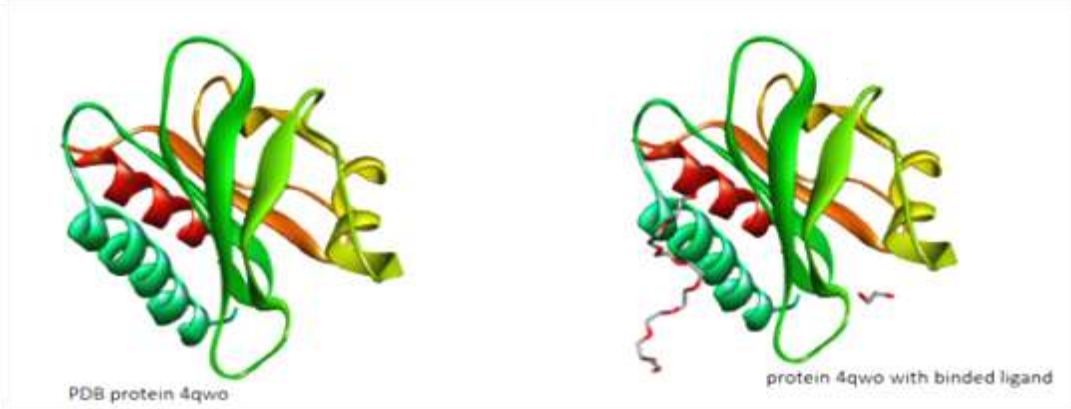


Figure 5. Three-dimensional structure of the monkeypox virus target protein (PDB ID: 4QWO) with a representative Aloe vera-derived ligand docked at the binding site.

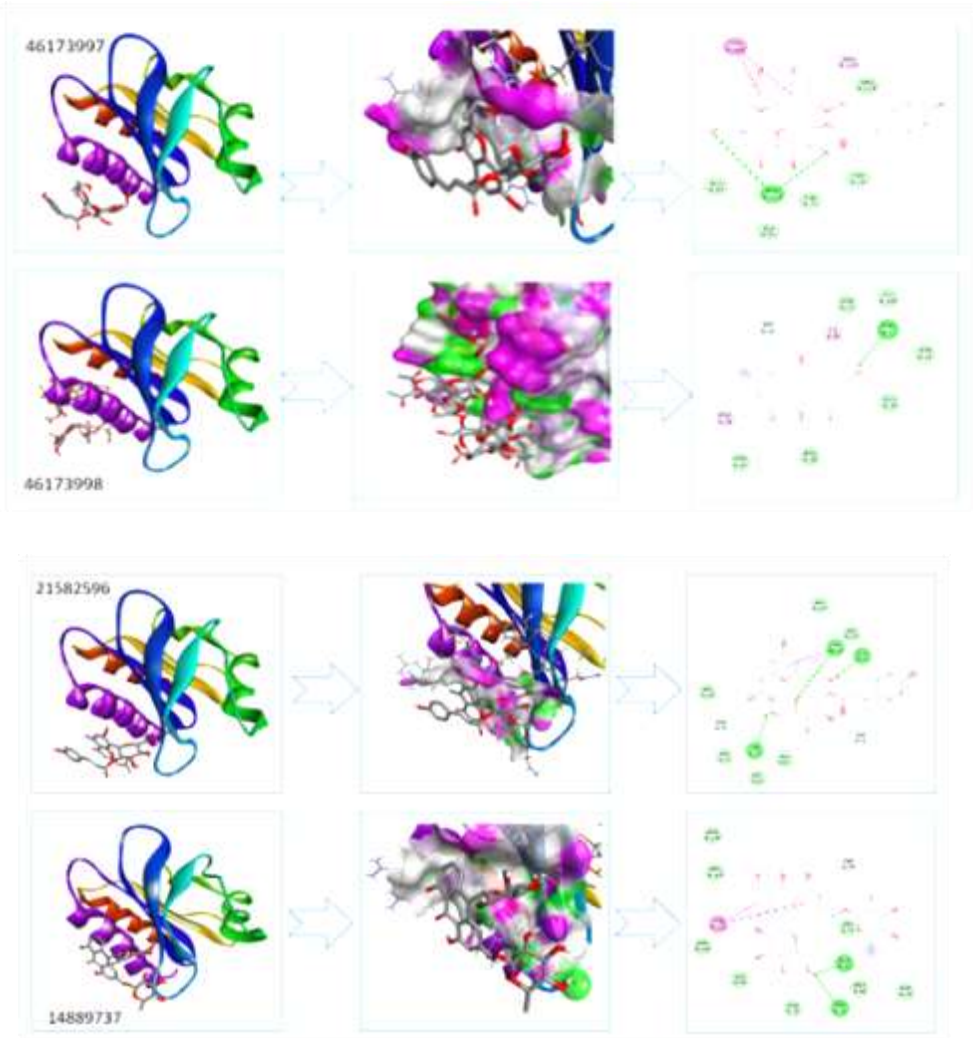


Figure 6. Two-dimensional docking interaction diagrams showing hydrogen bonds and other non-covalent contacts between the top-ranked Aloe vera derivatives and residues of the 4QWO binding pocket.

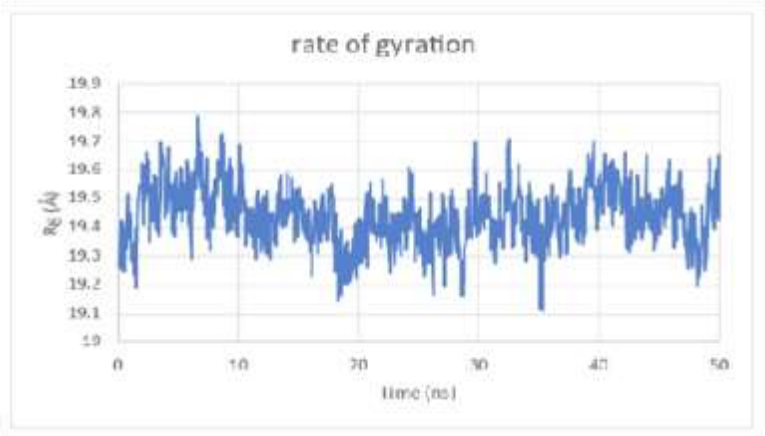


Figure 7. Radius of gyration (Rg) of the protein-ligand complexes over the 50-ns molecular dynamics simulation trajectory shown, indicating the compactness and structural stability of the complexes.

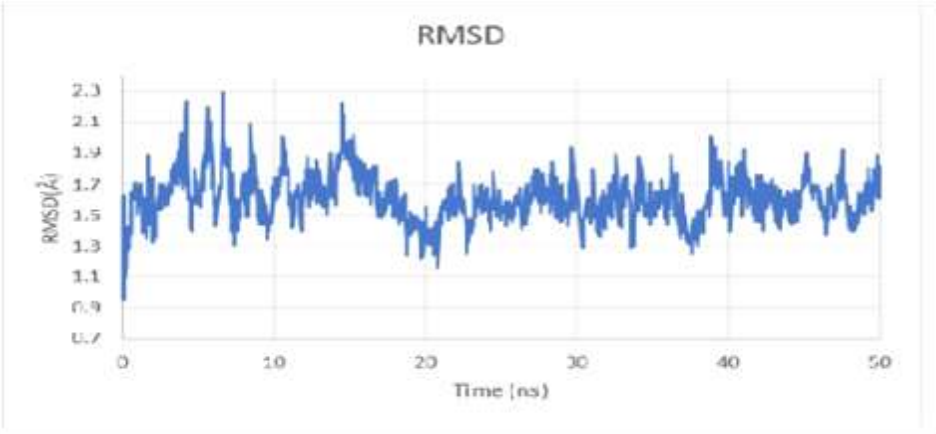


Figure 8. Root-mean-square deviation (RMSD) of the protein-ligand complexes over the 50-ns molecular dynamics simulation trajectory shown, reflecting overall structural stability.

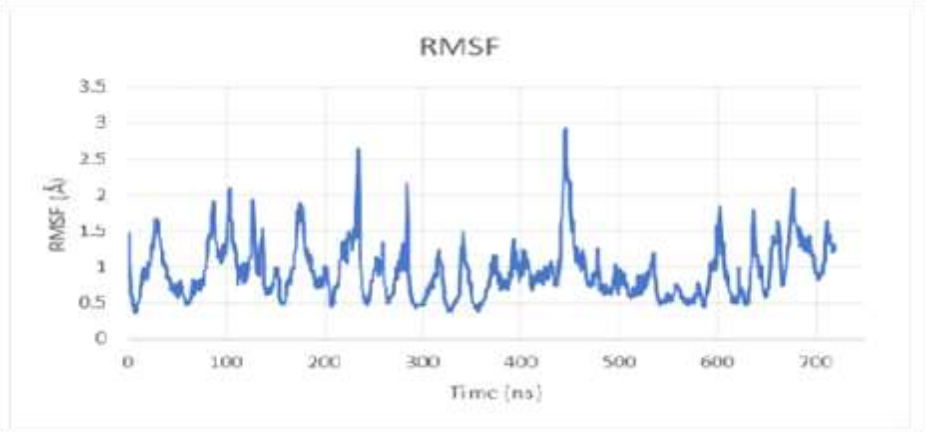


Figure 9. Root-mean-square fluctuation (RMSF) of the protein-ligand complexes over the simulation trajectory shown, indicating local flexibility.

DISCUSSION

The well-known medicinal plant Aloe vera has long been utilized for a variety of therapeutic applications. Its bioactive substances, mostly flavonoids, have a variety of pharmacological qualities, such as antibacterial, anti-inflammatory, and antioxidant capabilities [41]. A number of derivatives were created and assessed for their drug-like qualities and antiviral activity in order to investigate the possibility of Aloe vera as a source of antiviral medicines. There have been a number of discoveries over the years, most notably including the recent COVID-19 pandemic and various viral diseases, to drive forth the immediate necessity of novel antiviral drugs [42, 43]. In the modern world, plant-based natural chemicals have become very favorable as potential alternatives, particularly since they possess extensive pharmacological properties and resistance towards medication. This paper intends to examine the antiviral properties of Aloe vera derivatives against the monkeypox virus [44].

Derivatives of Aloe vera include compounds such as acemannan and aloe-emodin, that carry potential agents against different viruses. Acemannan, which is a polysaccharide from Aloe vera, reveals immunomodulatory activity that promote the induction of antiviral mechanisms in the human's body [45]. Aloe-emodin is one of the active principles of Aloe vera and has exhibited activity against several viruses, including herpes simplex and influenza viruses. These antiviral activities are supposed to be due to their interference with viral replication and the modulation of immune responses, hence, Aloe vera is considered as a candidate to be further explored against viral infections such as monkeypox [1, 6, 46]. In order to find molecules with appropriate pharmacokinetic properties for drug development, drug-likeness assessment is essential. The drug-likeness of the

Aloe vera derivatives was evaluated by applying Lipinski's rule of five [47] , which specifies requirements for molecular weight, hydrogen bond donors and acceptors, lipophilicity, and polar surface area. The findings showed that every chemical complied with these requirements, indicating that they may be used in drug development and oral bio-availability [48].

Furthermore, the favorable pharmacokinetic characteristics of these compounds were corroborated by in silico ADMET (absorption, distribution, metabolism, excretion, and toxicity) predictions [49]. ADMET evaluation is now considered an indispensable component of early-stage drug discovery, as it allows the safety and therapeutic potential of candidate compounds to be assessed before costly experimental validation [50]. This approach also helps optimize time and resource expenditure while improving the overall prospects for clinical success [51].

Using the monkeypox virus protein (4QWO), molecular docking studies were performed to assess the antiviral effectiveness of the Aloe vera derivatives. By simulating the interaction between a ligand—in this example, a derivative of Aloe vera—and a target protein, this computational method can provide light on binding affinity and possible inhibitory consequences [52].

The findings showed that every molecule had a considerable affinity for binding to the viral protein; in fact, some of the derivatives showed even higher binding affinities than the reference antiviral, tecovirimat. These results point to a promising possibility for these chemicals' ability to inhibit the virus that causes monkeypox [53]. Molecular dynamics simulations were carried out to provide additional understanding of the dynamic behaviour of the protein-ligand complexes. The picture of molecular interactions across time offered by these simulations is more accurate [54].

Chemical descriptors were computed in order to comprehend the electronic characteristics and reactivity of the Aloe vera derivatives [55]. These descriptors shed light on the chemical characteristics that may affect a compound's potential as a medicine and its biological activity. For every molecule, the HOMO-LUMO energy gap—a gauge of chemical reactivity—was computed. Higher chemical reactivity is often correlated with a lower energy gap, indicating a higher likelihood of interactions with biological targets [56].

The study's findings indicate that Aloe vera derivatives have the potential to be effective antiviral treatments for the monkeypox virus. In molecular dynamics simulations, the compounds demonstrated robust binding affinities to the viral protein, persistent interactions, and favorable drug-like features. These results add to the increasing amount of data that encourages the investigation of natural compounds as a potential source of innovative antiviral medications [57].

It is important to note that this study is based on in silico evaluations and computational simulations rather than laboratory experiments. The antiviral effectiveness and safety of these compounds need to be confirmed by additional experimental validation, including in vitro and in vivo studies [58]. To improve the potency and selectivity of the Aloe vera derivatives, more optimization would be necessary.
To sum up, this work lays the groundwork for future investigations into the creation of antiviral medications based on Aloe vera. Lead drugs for preclinical and clinical development can be found by combining computer modelling with experimental validation. The effective creation of antiviral medications made from natural ingredients may be a useful supplement to the medical toolkit for combating newly developing viral threats.

CONCLUSION

Plant-derived antivirals represent a promising complementary strategy for future outbreak preparedness, alongside traditional vaccine platforms. This paper explored the possibility that Aloe vera derivatives may represent a viable avenue for this purpose. The current study identified several Aloe vera derivatives as candidate therapeutic agents warranting further testing for their antiviral properties. Identification of molecules with a favorable pharmacokinetic profile is an essential step in drug discovery. The Aloe vera derivatives showed promise for oral bioavailability by meeting these requirements. Moreover, the viability of these bioactive compounds as therapeutic possibilities was reinforced by computerized forecasts of ADMET characteristics. The molecular docking simulations showed promising antiviral activity of these derivatives against the monkeypox virus protein, revealing favorable binding interactions between the compounds and the target protein. The results were encouraging, as some of the derivatives showed better binding affinities than tecovirimat. These findings seem to suggest that the molecules may prevent monkeypox virus replication. It is important to recognize, however, that this research represents only the beginning of the drug discovery process. It is necessary to move from computational investigations to experimental validation. To evaluate

these drugs' antiviral efficacy in a lab setting, in vitro research is required. Consequently, in vivo investigations will be necessary to assess their safety and effectiveness in animal models.

DECLARATIONS

Funding: The author received no specific funding for this work.

Conflicts of Interest: The author declares that there are no conflicts of interest regarding the publication of this paper.

Ethics Approval and Consent to Participate: Not applicable. This study did not involve human participants, human data, human tissues, or animals.

Consent for Publication: Not applicable.

Availability of Data and Materials: All data generated or analyzed during this study are included in this published article. Additional information supporting the findings of this study is available from the corresponding author upon reasonable request.

Authors' Contributions: Yasmeen A. Albalawi conceived and designed the study, performed the computational analyses, interpreted the results, prepared the figures and tables, wrote the manuscript, and approved the final version for publication.

Acknowledgements: The author would like to acknowledge Jouf University, Sakaka, Saudi Arabia, for providing institutional support and research facilities.

Code Availability: The software and online tools used in this study are publicly available and have been appropriately cited in the manuscript.

REFERENCES

[1] Franconi R, Demurtas OC, Massa S (2010) Plant-derived vaccines and other therapeutics produced in contained systems. Expert Rev Vaccines 9:877–892

[2] Yusibov V, Rabindran S (2008) Recent progress in the development of plant derived vaccines. Expert Rev Vaccines 7:1173–1183

[3] Guan Z, Guo B, Huo Y, et al (2013) Recent advances and safety issues of transgenic plant-derived vaccines. Appl Microbiol Biotechnol 97:2817–2840

[4] Zou M, Lei C, Huang D, et al (2024) Application of plant-derived products as adjuvants for immune activation and vaccine development. Vaccine

[5] Streatfield SJ (2005) Delivery of plant-derived vaccines. Expert Opin Drug Deliv 2:719–728

[6] Altindis M, Puca E, Shapo L (2022) Diagnosis of monkeypox virus–An overview. Travel Med Infect Dis 50:102459

[7] Sklenovská N (2020) Monkeypox virus. In: Animal-origin viral zoonoses. Springer, pp 39–68

[8] Thornhill JP, Barkati S, Walmsley S, et al (2022) Monkeypox virus infection in humans across 16 countries—April–June 2022. N Engl J Med 387:679–691

[9] Mailhe M, Beaumont A-L, Thy M, et al (2023) Clinical characteristics of ambulatory and hospitalized patients with monkeypox virus infection: an observational cohort study. Clin Microbiol Infect 29:233–239

[10] Peng Q, Xie Y, Kuai L, et al (2023) Structure of monkeypox virus DNA polymerase holoenzyme. Science 379:100–105

[11] Letafati A, Sakhavarz T (2023) Monkeypox virus: A review. Microb Pathog 176:106027

[12] Shchelkunov SN, Totmenin A V, Safronov PF, et al (2002) Analysis of the monkeypox virus genome. Virology 297:172–194

[13] Sah R, Abdelaal A, Reda A, et al (2022) Monkeypox and its possible sexual transmission: where are we now with its evidence? Pathogens 11:924

[14] Karagoz A, Tombuloglu H, Alsaeed M, et al (2023) Monkeypox (mpox) virus: Classification, origin, transmission, genome organization, antiviral drugs, and molecular diagnosis. J Infect Public Health 16:531–541

[15] Walker M (2022) Monkeypox virus hosts and transmission routes: a systematic review of a zoonotic pathogen

[16] Beeson A, Styczynski A, Hutson CL, et al (2023) Mpox respiratory transmission: the state of the evidence. Lancet Microbe 4:e277–e283

[17] Velavan TP, Meyer CG (2022) Monkeypox 2022 outbreak: an update. Trop Med Int Health 27:604–605

[18] Yu Z, Zou X, Deng Z, et al (2024) Genome analysis of the mpox (formerly monkeypox) virus and characterization of core/variable regions. Genomics 116:110763

[19] Wang L, Shang J, Weng S, et al (2023) Genomic annotation and molecular evolution of monkeypox virus outbreak in 2022. J Med Virol 95:e28036

[20] Licheri M, Licheri MF, Probst L, et al (2024) A novel isothermal whole genome sequencing approach for Monkeypox Virus. Sci Rep 14:22333

[21] Pastula DM, Tyler KL (2022) An overview of monkeypox virus and its neuroinvasive potential. Ann Neurol 92:527–531

[22] Akash S, Hossain A, Hossain MS, et al (2023) Anti-viral drug discovery against monkeypox and smallpox infection by natural curcumin derivatives: A Computational drug design approach. Front Cell Infect Microbiol 13:1157627

[23] Zeghbib W, Boudjouan F, Bachir-bey M (2022) Optimization of phenolic compounds recovery and antioxidant activity evaluation from Opuntia Ficus indica using response surface methodology. J Food Meas Charact 1–13

[24] Binoy J, Marchewka MK, Jayakumar VS (2013) The 'partial resonance'of the ring in the NLO crystal melaminium formate: Study using vibrational spectra, DFT, HOMO–LUMO and MESP mapping. Spectrochim Acta A Mol Biomol Spectrosc 104:97–109

[25] Kumer A, Chakma U, Matin MM (2022) Bilastine based drugs as SARS-CoV-2 protease inhibitors: molecular docking, dynamics, and ADMET related studies. Orbital Electron J Chem 15–23

[26] Rangisetty PT, Kilaparthi A, Akula S, et al (2023) RSAD2: An exclusive target protein for Zika virus comparative modeling, characterization, energy minimization and stabilization. Int J Health Sci 17:12

[27] Rizvi SMD, Shakil S, Haneef M (2013) A simple click by click protocol to perform docking: AutoDock 4.2 made easy for non-bioinformaticians. EXCLI J 12:831

[28] Krieger E, Nielsen JE, Spronk CAEM, Vriend G (2006) Fast empirical pKa prediction by Ewald summation. J Mol Graph Model 25:481–486

[29] Zhang D, Wu K, Zhang X, et al (2020) In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. J Integr Med 18:152–158

[30] Akash SR, Hossain MI, Ali MS (2023) Developing a multiepitope vaccine against dengue virus in Bangladesh using immunoinformatics approach

[31] de Oliveira MR, Jardim FR, Setzer WN, et al (2016) Curcumin, mitochondrial biogenesis, and mitophagy: Exploring recent data and indicating future needs. Biotechnol Adv 34:813–826

[32] Xiong P, Zhang F, Liu F, et al (2023) Metaflammation in glucolipid metabolic disorders: Pathogenesis and treatment. Biomed Pharmacother 161:114545

[33] Liu X, Chen T, Yu F, et al (2020) AIE-active random conjugated copolymers synthesized by ADMET polymerization as a fluorescent probe specific for palladium detection. Macromolecules 53:1224–1232

[34] Kobir ME, Ahmed A, Roni MAH, et al (2023) Anti-lung cancer drug discovery approaches by polysaccharides: an in silico study, quantum calculation and molecular dynamics study. J Biomol Struct Dyn 41:6616–6632

[35] Hoque MM, Hussen MS, Kumer A, Khan MW (2020) Synthesis of 5, 6-diaroylisoindoline-1, 3-dione and computational approaches for investigation on structural and mechanistic insights by DFT. Mol Simul 46:1298–1307

[36] Kawsar SMA, Kumer A, Munia NS, et al (2022) Chemical descriptors, PASS, molecular docking, molecular dynamics and ADMET predictions of glucopyranoside derivatives as inhibitors to bacteria and fungi growth. Org Commun 15:203

[37] Prasasty VD, Istyastono EP (2020) Structure-based design and molecular dynamics simulations of pentapeptide AEYTR as a potential acetylcholinesterase inhibitor. Indones J Chem 20:953–959

[38] Pullakhandam R, Srinivas P, Nair MK, Reddy GB (2009) Binding and stabilization of transthyretin by curcumin. Arch Biochem Biophys 485:115–119

[39] Al Mashud MA, Kumer A, Mukerjee N, et al (2023) Mechanistic inhibition of Monkeypox and Marburg virus infection by O-rhamnosides and Kaempferol-o-rhamnosides derivatives: a new-fangled computational approach. Front Cell Infect Microbiol 13:1188763

[40] Kumer A, Sarker MN, Paul S (2019) The simulating study of HOMO, LUMO, thermo physical and quantitative structure of activity relationship (QSAR) of some anticancer active ionic liquids. Eurasian J Environ Res 3:1–10

[41] Datta S (2024) Bio-Engineered Plant-produced Antigens, Self-Administered for Oral Vaccination: A Cottage Industry for Vaccines for Less Affluent Nations?

[42] Balke I, Zeltins A (2019) Use of plant viruses and virus-like particles for the creation of novel vaccines. Adv Drug Deliv Rev 145:119–129

[43] Kumar S (2018) Natural killer cell cytotoxicity and its regulation by inhibitory receptors. Immunology 154:383–393

[44] Esqueda A, Sun H, Bonner J, et al (2023) A monoclonal antibody produced in glycoengineered plants potently neutralizes monkeypox virus. Vaccines 11:1179

[45] Malabadi RB, Kolkar P, Chalannavar K (2022) Human Monkeypox detected first time In India: role of traditional herbal treatment. Int J Sci Res Rev 4:3686–3691

[46] Singh L, Arora MK, Kumar P, et al Medicinal Plants and Herbs in Viral Meningitis. In: Promising Antiviral Herbal and Medicinal Plants. CRC Press, pp 276–294

[47] Chen X, Li H, Tian L, et al (2020) Analysis of the physicochemical properties of acaricides based on Lipinski's rule of five. J Comput Biol 27:1397–1406

[48] Chagas CM, Moss S, Alisaraie L (2018) Drug metabolites and their effects on the development of adverse reactions: Revisiting Lipinski's Rule of Five. Int J Pharm 549:133–149

[49] Cheng F, Li W, Zhou Y, et al (2012) admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties

[50] Chandrasekaran B, Abed SN, Al-Attraqchi O, et al (2018) Computer-aided prediction of pharmacokinetic (ADMET) properties. In: Dosage form design parameters. Elsevier, pp 731–755

[51] Dearden JC (2007) In silico prediction of ADMET properties: how far have we come? Expert Opin Drug Metab Toxicol 3:635–639

[52] Raen R, Islam MM, Islam R, et al (2024) Functional characterization and structural prediction of hypothetical proteins in monkeypox virus and identification of potential inhibitors. Mol Divers 1–29

[53] Hosen MI, Mia ME, Islam MN, et al (2024) In silico approach to characterize the structure and function of a hypothetical protein of Monkeypox virus exploring Chordopox-A20R domain-containing protein activity. Antivir Ther 29:13596535241255199

[54] Suleman M, Rashid F, Ali S, et al (2022) Immunoinformatic-based design of immune-boosting multiepitope subunit vaccines against monkeypox virus and validation through molecular dynamics and immune simulation. Front Immunol 13:1042997

[55] Raies AB, Bajic VB (2016) In silico toxicology: computational methods for the prediction of chemical toxicity. Wiley Interdiscip Rev Comput Mol Sci 6:147–172

[56] C Basak S (2013) Mathematical descriptors for the prediction of property, bioactivity, and toxicity of chemicals from their structure: a chemical-cum-biochemical approach. Curr Comput Aided Drug Des 9:449–462

[57] Mpiana PT, Ngbolua K-T-N, Tshibangu DST, et al (2020) Aloe vera (L.) Burm. F. as a potential anti-COVID-19 plant: a mini-review of its antiviral activity. Eur J Med Plants 31:86–93

[58] Warner BM, Klassen L, Sloan A, et al (2022) In vitro and in vivo efficacy of tecovirimat against a recently emerged 2022 monkeypox virus isolate. Sci Transl Med 14:eade7646