ACTA ABP BIOCHIMICA POLONICA

Vol. 70, No 3/2023
599–608
https://doi.org/10.18388/abp.2020_6667

Regular paper

Design and development of new inhibitors against breast cancer, Monkeypox and Marburg virus by modification of natural Fisetin *via in silico* and SAR studies

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The natural Fisetin and its derivatives have been shown to have effective bioactivity and strong pharmacological profile, which is continuously drawing the interest of therapeutic applications to the development of new biomolecules against Breast cancer and Monkeypox, and Marburg viral infection, while computational approaches and the study of their structure-activity relationship (SAR) are the most eloquent and reliable platform for performing their hypothetical profile renovation. So, the main perspective of this investigation is to evaluate dual function of Fisetin and its derivatives against both virus and cancerous target. First and foremost, the prediction of activity spectra for materials (PASS) valuation has provided preliminary data on the antiviral, antibacterial, antiparasitic, and anticancer possibilities of the mentioned compounds. According to the evidence, PASS predicted scores were shown to perform better in antineoplastic and antiviral than antibacterial, and antiparasitic efficiency; as evidenced by their higher PASS scores in antineoplastic and antiviral drug tests. Breast cancer, Monkeypox, and Marburg virus have been selected as targeted pathogens, and different *in silico* studies were conducted to determine the dual function of mention derivatives. The "Lipinski five rules," on the other hand, has been subjected to extensive testing for drug-like characteristics. Molecular docking against Breast cancer, Monkeypox, and Marburg virus have been accomplished after confirmation of their bioactivity. The molecular docking evaluation against targeted disease displayed re-markable binding affinity and non-bonding engagement, with most of the results indicating that derivatives are more effective than the FDA approved standard antiviral, and antineoplastic drugs. Finally, the ADMET characteristics have been computed, and they indicate that the substance is suitable to use and did not have any chance to produce adverse effects on aquatic or non-aquatic environment, as well as having a highly soluble capacity in water medium, high G.I absorption rate, with outstanding bioavailability index. Therefore, these mentioned Fisetin derivatives could be suggested as potential medication against Breast cancer and newly reported Monkeypox, and Marburg virus, and may further proceed for laboratory experiment, synthesis, and clinical trials to evaluate their practical value.

Keywords: ADMET, molecular docking, Lipinski rule and pharmacokinetics, pass prediction

Received: 13 February, 2023; revised: 14 March, 2023; accepted: 17 March, 2023; available on-line: 07 September, 2023

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Acknowledgments of Financial Support: The authors greatly acknowledge and express their gratitude to the Researchers Supporting Project number (RSP2023R335), King Saud University, Riyadh, Saudi Arabia.

Abbreviations: CADD, computer-aided drug design; PASS, prediction of activity spectra for materials; SAR, structure-activity relationship

INTRODUCTION

Breast cancer is the most frequent cancer in women globally, where it is accompanied with a devastating impact on life among females (Bhattacharyya *et al*., 2020). Every year, many patients have been identified by Breast cancer globally. Among them, many patients cannot survive due to limitation of proper treatment. Currently, finding on literature review, chemotherapeutics drugs, radiation therapy, surgery, hormone therapy, targeted therapy, and immune therapy seem to be the treatment options for Breast cancer that applies, which is very expensive with numerous side effects like killing healthy cells (Eniu *et al*., 2008; Pilla *et al*., 2018; Schirrmaker, 2003). Recently, it has been seen that several cancer-fighting medications (chemotherapeutic agent) are becoming increasingly ineffective or cancerous cells gain resistance against them. As a result, alternative options for Breast cancer treatment should be found for the future generation (Naveed *et al*., 2022a; Naveed *et al*., 2023b; Afshari *et al*., 2022; Farkona *et al*., 2016; Poojan *et al*., 2020).

One the other side, human Monkeypox seems to be a *zoonotic orthopoxvirus* and composed of double stranded DNA, transmitted by Monkey to human, which is particularly reported in tropical Western and Central African areas. It was first reported in 1958 when during the out-breaks of a pox-like infection (Naveed *et al*., 2023c; Mileto *et al*., 2022; Pal *et al*., 2017). Previously, tropical Western and Central African areas were a major region of Monkeypox virus (MPXV), but recently the MPXV resurfacing and expanding throughout the world is causing a major threat to human life and it especially affected most of the European countries, as well as North and South America (Hatmal *et al*., 2022; Majie *et al*., 2023). About 4900 infected of human Monkeypox were reported in more than 50 countries at the end of June 2022, and one infected person has died (Mucker *et al*., 2022). So, it is a reminder that another pandemic might happen around the globe, which make concern to the global policymaker, and healthcare system. For more

Table 1. Data of PASS prediction data

S/N	Antiviral (Herpes)		Antibacterial		Antiparasitic		Antineoplastic	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
01	0.471	0.014	0.388	0.033	0.404	0.031	0.783	0.014
02	0.447	0.019	0.420	0.026	0.309	0.053	0.818	0.010
03	0.427	0.025	0.376	0.036	0.240	0.078	0.849	0.007
04	0.428	0.025	0.298	0.061	0.358	0.040	0.556	0.055
05	0.419	0.028	0.279	0.068	0.340	0.045	0.508	0.069
06	0.442	0.020	0.336	0.047	0.410	0.019	0.735	0.020
07	0.421	0.027	0.299	0.060	0.401	0.031	0.727	0.022
08	0.405	0.033	0.364	0.039	0.342	0.044	0.775	0.015
09	0.392	0.039	0.327	0.050	0.301	0.056	0.754	0.018

than couple of decades, scientists have worked to enhance Smallpox vaccinations and find medicines to assure immunity against Smallpox or Smallpox-like illnesses. But investigation reported that there is no authorized medication against MPXV till now (Gong *et al*., 2022). Besides, following corona virus epidemic, another pandemic is knocking at the door, which might be caused by Marburg virus (MARV). The Marburg virus (MARV) has been considered as the deadly hemorrhagic infection that may produce a fatal condition. MARV is suspected to be a zoonotic infection spread by animals (Albaqami *et al*., 2023; Reuben & Abunike, 2023). The virus may spread from bats to people by extended exposure to bat colonies' tunnels and caves, and by interaction with bat saliva, excrement, and infected fruits (Asad *et al*., 2020; Mortlock, 2013). Recently, it was in the headlines in mid-July 2022 due to an epidemic in Ghana, an African country, where two affected people have died. MARV is an enclosed single-stranded RNA virus of the *Filovirus* genus, which composed to the *Filoviridae* family, like the Ebola virus. Although, the MARV is happening consciously and infects the patients, Scientists did not find any suitable treatment for the inhibition of MARV (Chakraborty *et al*., 2022; Sah *et al*., 2022). The natural bioactive compounds of Fisetin should be an alternative approach for the treatment of Breast cancer, and Monkeypox, and Marburg virus. So, in this research, the natural compounds of Fisetin have been counted as primary compounds and we modified its structure by different functional groups to develop a potential medication, which might have better efficacy, lower toxicity, and capability to inhibit Breast cancer, Monkeypox, and Marburg virus.

In these circumstances, computational drug design tool is used, which is the most efficient approach of finding potential therapeutic candidates and implementing them into the therapy regimen in short period of time (Aziz *et al*., 2023; Moingeon *et al*., 2022; Patel *et al*., 2022; Aziz *et al*., 2022). In comparison to traditional drug discovery procedures, computational drug design offers many benefits, including substantially lower costs, faster drug development durations, and possibility to eliminate phase 1 clinical trial. Thus, this approach of computer-aided drug design (CADD) could be a helpful method.

RESULTS AND DISCUSSION

PASS prediction analysis

It seems that a substantial proportion of investigations should not go to the end of the process due to significant harmful side effects and toxicity that are unclear. These undesirable effects are discovered or manifest much too late in the development. In today's high-tech, possibility to fail or reject any compounds has been min-

Table 2. Data of Lipinski rule, and pharmacokinetics.

Ligand No	Hydrogen bond acceptor	Hydrogen bond donor	Topological polar surface area Å^2	Lipinski rule		Molecular weight	Bioavailability Score	G.I. absorption
				Result	Violation			
01	06	04	111.13	Yes	00	286.24	0.55	High
02	08	05	132.39	Yes	00	331.28	0.55	High
03	10	06	153.65	Yes	01	376.32	0.55	Low
04	07	03	109.37	Yes	00	316.26	0.55	High
05	08	02	107.59	Yes	00	346.29	0.55	High
06	06	03	100.13	Yes	00	362.33	0.55	High
07	06	02	89.13	Yes	00	438.43	0.55	Low
08	08	04	137.43	Yes	00	330.25	0.56	High
09	10	04	163.73	Yes	00	374.26	0.11	Low

Table 3. Binding affinity against Breast cancer protein

Drug molecules No	Breast cancer protein (PDB: 3HB5)	Breast cancer protein (PDB: 7KCD)	Breast cancer protein (PDB 6NLV)
	Binding affinity (kcal/mol)	Binding affinity (kcal/mol)	Binding affinity (kcal/mol)
01	–8.7	–7.0	–7.6
02	–9.7	–8.5	–7.5
03	–9.3	–7.4	–7.3
04	–8.8	–7.2	–7.3
05	–8.0	–8.1	–7.2
06	–9.6	–9.3	–8.0
07	–11.0	–9.6	–9.1
08	–9.3	–8.8	–7.8
09	–9.0	–7.2	–7.5
Epirubicin hydrochloride	–9.1	–7.0	–8.0

imized since the probability to be active and probability to be inactive for any molecules could be identified as early stages (Filimonov *et al*., 2014). In Table 1 below, probability to be active (Pa) and probability to be inactive (Pi) has been listed and it has been shown that the mentioned bioactive molecules are most potent against antineoplastic and antiviral effects compared to antibacterial and antiparasitic effects. In antiviral, the range of Pa is reported from 0.392–0.471 while the Pa score against antineoplastic is found between 0.508–0.849. So, based on the score, the Breast cancer and Monkeypox, and Marburg virus has been chosen and completed the investigation.

Lipinski rule, and pharmacokinetics

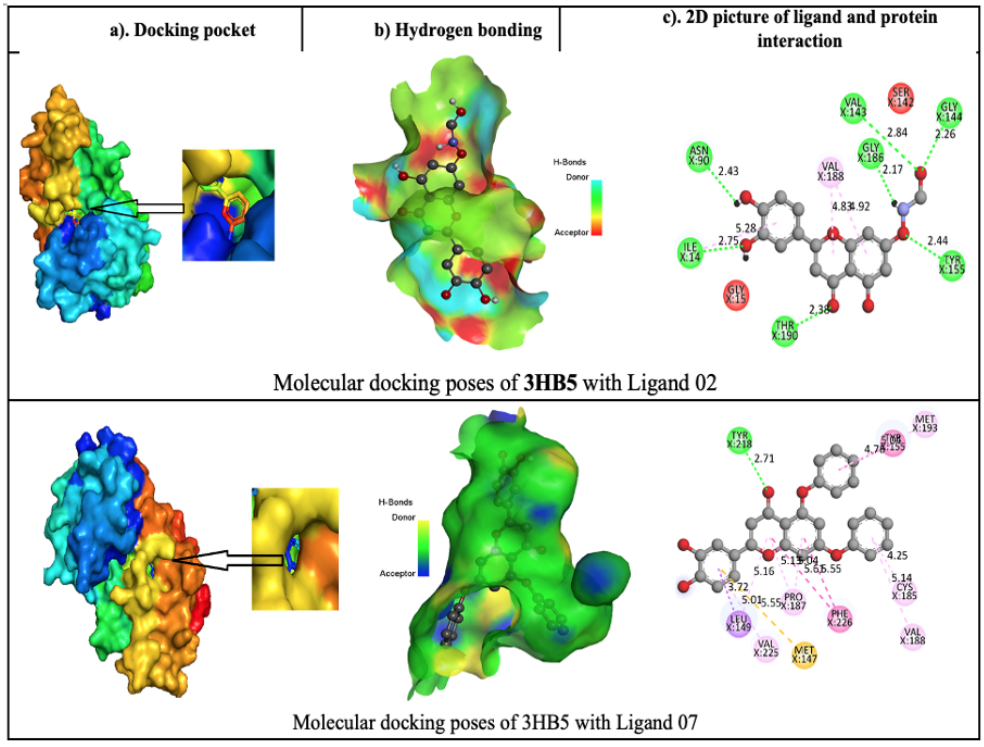
Lipinski rule is a potential assessment of any pharmacological or bioactive molecules which makes them to be a potential oral medication based on different parameters. So, in view of Lipinski rule, number of hydrogen bond acceptor 06-10, hydrogen bond donor 02–06, topological polar surface area 89.13 Å² to 163.73 Å², which has shown that all the medications are fully accepted and followed Lipinski rule by all Fisetin derivatives (Santos *et al*., 2016; Walters, 2012). For any oral medication, bioavailability is the most essential parameter, and it is noticed that almost all the drugs are highly effective and have a similar score and that only Ligand 09 has poor bioavailability. On the other portion, six ligands out of nine molecules have higher G.I absorption rate, which is another important parameter to make them as oral medication. Finally, it is said that these mentioned molecules could be effective against the Breast cancer, Monkeypox, and Marburg virus. Data of Lipinski rule, and pharmacokinetics are displayed in Table 2.

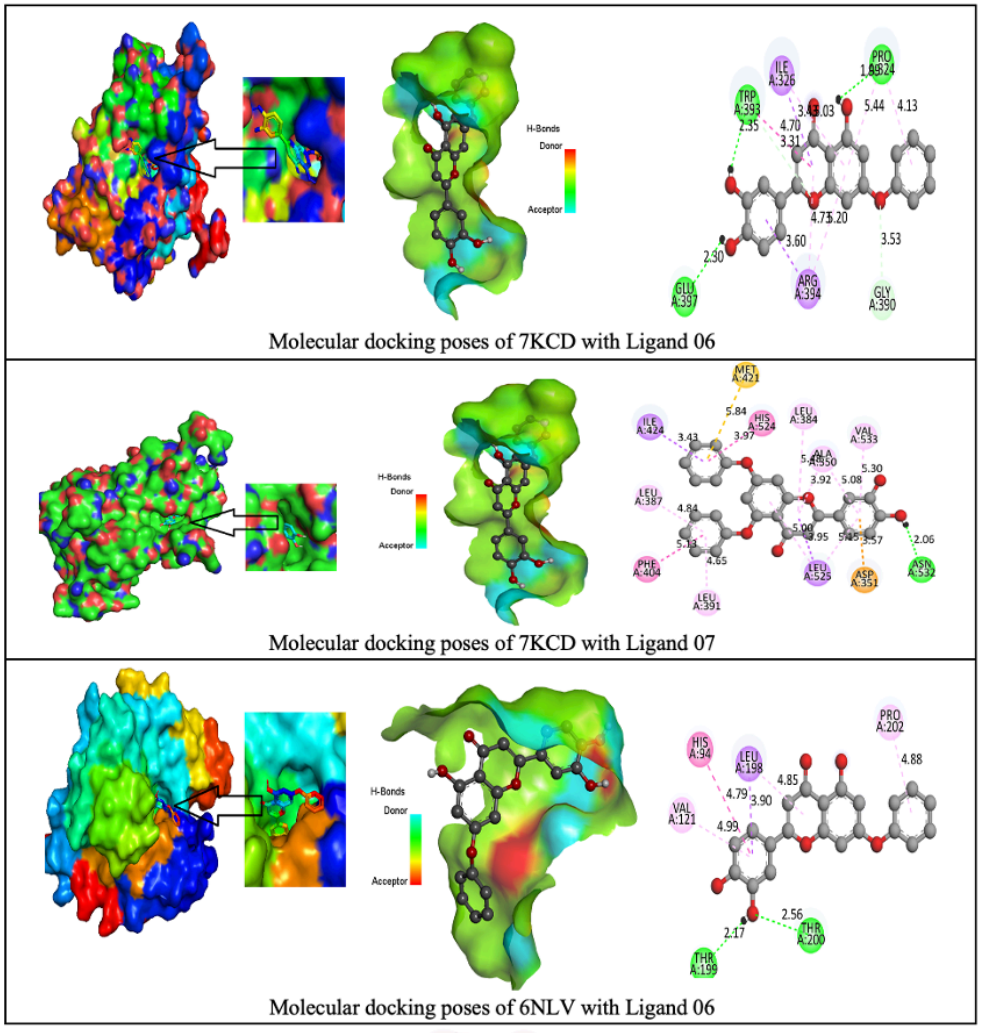
Molecular docking against Breast cancer

Molecular docking is an established and effective method for explaining how two molecules interact and make the optimal ligand arrangement to produce a complex. Any molecules could be active and produce biological response if their minimum binding energy is –6.0 kcal/mol and considered as a potential drug (Nath *et al*., 2021). In view of these studies, all the bioactive Fisetin derivatives have been documented that they have much better binding affinity than the standard and FDA approved Epirubicin hydrochloride. The maximum docking energy has been obtained in ligand 07 (–11.00 kcal/mol) against PDB: 3HB5, in protein PDB: 7KCD, the maximal score is found to be –9.6 kcal/mol, and the last one PDB: 6NLV has obtained –9.1 kcal/mol maximum in the same ligand (Table 3). In the overall analysis, it is clear that all the ligands have crossed the binding affini-

Table 4. Binding affinity for bacteria against Monkeypox and Marburg virus

Drug molecules No	Monkeypox virus (PDB ID 4QWO)	Marburg virus (PDB 4OR8)
	Binding affinity (kcal/mol)	Binding affinity (kcal/mol)
01	–7.8	–7.2
02	–8.2	–7.0
03	–7.9	–7.3
04	–7.7	–7.0
05	–7.6	–6.5
06	–9.0	–8.5
07	–9.4	–10.1
08	–8.2	–7.4
09	–8.0	–7.1
Standard (acyclovir)	–6.3	–5.8


a). Docking pocket
b) Hydrogen bonding
c). 2D picture of ligand and protein interaction
H-Bonds
Donor
Acceptor
Molecular docking poses of 3HB5 with Ligand 02
Molecular docking poses of 3HB5 with Ligand 07


H-Bonds
Donor
Acceptor
Molecular docking poses of 7KCD with Ligand 06
Molecular docking poses of 7KCD with Ligand 07
Molecular docking poses of 6NLV with Ligand 06

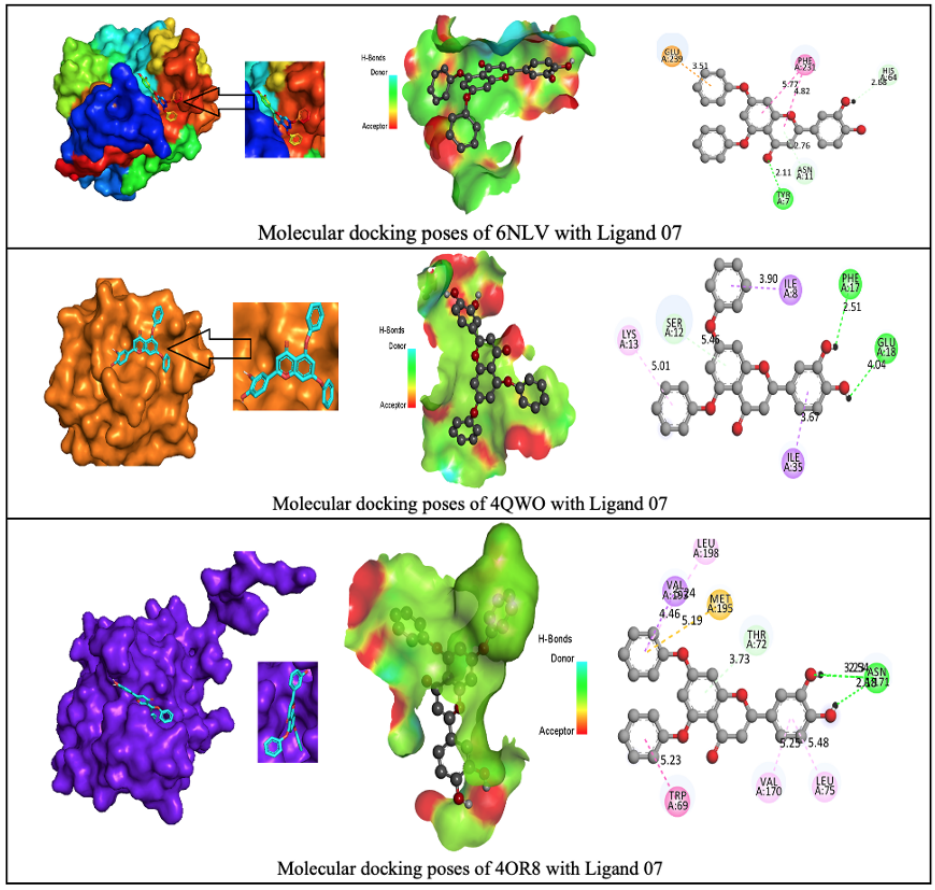


Figure 1. Molecular docking poses breast cancer, Monkeypox, and Marburg virus.

ties and compared much better to standard drugs, which turn into them as oral medication against breast cancer protein.

Binding affinities against pathogenic Monkeypox and Marburg virus

According to the result of pass prediction value, it was shown that these mentioned ligands could be effective against viral pathogens, followed by antibacterial and antiparasitic, since the antiviral score is higher than the antibacterial and antiparasitic. So, the Monkeypox and Marburg virus are also included in this investigation, and it is found that the reported ligand may also act as a potential inhibitor against Monkeypox and Marburg virus. In given Table 4, it is notable that the maximum affinities for Monkeypox virus (PDB ID 4QWO) is –9.0 kcal/mol, –9.4 kcal/mol, where –10.1 kcal/mol has been obtained against Marburg virus (PDB 4OR8), and it has also significantly better binding affinities. As, there is no documented or authorized medication against Monkeypox and Marburg virus, a common antiviral medication (acyclovir) is also compared with our development drug, where the standard acyclovir has provided –6.3 kcal/mol and –5.8 kcal/mol, which is much lower than the reported ligands. So, it is understood that all these may be possible therapeutic approaches as inhibitors against Monkeypox and Marburg virus.

Ligand-protein interaction and molecular docking poses

The interactions between the inhibitor and the targeted protein active side, docking pocket drug-protein are graphically represented in Figs 1a, 1b and 1c. In the 2D configuration, the active side of amino acid residue with bond angle has been seen and in most cases the number of hydrophobic bond residue is higher than the other bonds, such as hydrogen, electrostatic, Van der Waals interactions and Halogen bond. This result has been obtained by importing protein ligand complex file into the Discovery Studio Visualizer (Balasubramaniam & Reis, 2020; Wang *et al.*, 2015). This figure has been configured based on maximum binding energy. The first illustration (Fig. 1a) determined drug-protein pocket, or how a drug attached to protein during the formation of the complex. It has been designed after molecular docking, by using Pymol application. Then, (Fig. 1b) represented hydrogen bonding donor or acceptor region, where the sky blue indicates donor region, and red hue indicates acceptor region. Finally; (c). 2D picture of ligand and protein interaction, where X: TYR-218, X: LEU-149, X: MET-147: X: TYR-155, X: PHE-226, X: PHE-226, X:PRO-187, X: LEU-149, X:PRO-187, X: VAL-225, X: MET-193, X: CYS-185.X: VAL1-88, against breast cancer, A: GLU-18, A: GLU-18, A: PHE-17, A: SER-12, A: SER-12, A: ILE-8, A: ILE-35, A: LYS-13, against Monkeypox virus, and A: ASN-171, A: THR-72, A: VAL-193, A: MET-195, A: TRP-69, A: LEU-75. A:VA-L170, A: LEU-198, against Marburg virus are seen in most of the cases.

Absorption, Distribution, Metabolism and Excretion. (ADME) studies

It was possible to forecast the ADMET features of drugs or chemical compounds by utilizing the free PkCSM online web tool, which was developed by machine

Table 5. ADME Properties summary

S/N	Absorption		Distribution		Metabolism		Excretion	
	Water solubility Log S	Caco–2 permeability (10^{-6} cm/s)	VDss (human)	BBB permeability	CYP450 1A2 Inhibitor	CYP450 2C9 Inhibitor	Total Clearance (ml/min/kg)	Renal OCT2 substrate
01	–3.207	0.86	–0.103	No	Yes	No	0.662	No
02	–3.665	–0.293	–0.041	No	Yes	No	0.802	No
03	–3.767	0.40	–0.12	No	Yes	No	0.912	No
04	–4.157	0.928	–1.364	No	Yes	No	0.732	No
05	–4.196	0.893	–0.539	No	No	Yes	0.791	No
06	–4.083	0.928	–0.756	No	Yes	Yes	0.450	No
07	–3.442	1.076	–1.169	No	No	Yes	0.513	No
08	–4.036	–0.061	–0.484	No	Yes	No	0.653	No
09	–3.317	–0.621	–0.788	No	Yes	No	0.621	No

Table 6. Aquatic and non-aquatic toxicity

Aquatic and non-aquatic Toxicity different parameter							
S/N	AMES toxicity	Max. tolerated dose (human) mg/kg/day	Oral Rat Acute Toxicity (LD50) (mol/kg	Oral Rat Chronic Toxicity (mg/kg/day)	Hepatotoxicity	Skin Sensitization	T. Pyriformis toxicity (log ug/L)
01	No	0.982	2.178	2.259	No	No	0.352
02	No	1.046	2.162	1.947	No	No	0.305
03	No	1.211	2.291	1.785	No	No	0.292
04	No	0.913	2.24	2.221	No	No	0.294
05	No	0.731	2.507	2.768	No	No	0.86
06	No	0.329	2.675	1.56	Yes	No	0.288
07	No	0.432	3.163	0.698	Yes	No	0.285
08	No	0.983	2.13	2.21	No	No	0.289
09	No	0.963	2.471	2.50	No	No	0.285

learning (Pires *et al.*, 2015). ADME is the key factor of any drug molecules to establish them as safe and usable medication. In listed data, it is observed that the drugs are moderately soluble in water and the Caco-2 permeability range is –0.621 to 1.076. VDss (human) level is –0.041 to –1.364 and no drugs can penetrate the BBB (Table 5). All the drugs can inhibit the CYP450 1A2 inhibitor except 05 and 07 and only ligands 05, 06, and 07 can inhibit the CYP450 2C9 inhibitor. Finally, almost all the ligands have better Total clearance rate, and no drugs can substrate through Renal OCT2 substrate. Above all discussion, the Table 5 data for ADME parameters might suggest them as a suitable medication.

Aquatic and non-aquatic toxicity

Aquatic and non-aquatic toxicity studies are performed to analyze the drug safety of animals and the environment, because during the production of drugs they might be mixed with environment, which may have an impact on surrounding animals (Kar & Roy, 2012). Our findings on the aquatic and non-aquatic toxicity of the examined substances have shown that all of the medications investigated are non-cancerogenic and non-AMES poisonous and only 06 and 07 may be responsible for hepatotoxicity. So, patients with liver disease may use these two medications with caution. Secondly, the max. tolerated daily dose could be between 0.329 mg/kg/day to 1.211 mg/kg/day. The Oral Rat Acute Toxicity and Oral rat chronic toxicity level is also lower compared to standard drugs and no drugs can produce skin sensitization. These findings give insight into these new modified Fisetin derivatives that are safer to use (Table 6).

Experimental methodology

Preparation of Ligand and Structural Activity relationship (SAR) studies

Firstly, we have collected the chemical structure of Fisetin from the PubChem database. After that, we have observed how it is antineoplastic and antiviral properties change if the side chain is substituted by adding different functional group. So, all the derivatives of Fisetin have been generated using ChemBioDraw 12.0 and in each case, two -OH functional groups have been substituted by four functional groups such as Benzene ring, NH-CH2-OH, OCH_3 and -COOH(Milne, 2010). Finally, geometry optimization has been conducted by using density functional theory (DFT) in material studio at the DFT/B3LYP/6-31G and after optimization has been done, all the atoms of molecule have been reached at the most stable state with the optimum ground state energy and saved as PBD format for molecular docking, ADMET, and other computational experiment (Eno *et al.*, 2022; Oyeneyin *et al.*, 2022). The optimization technique is utilized in the

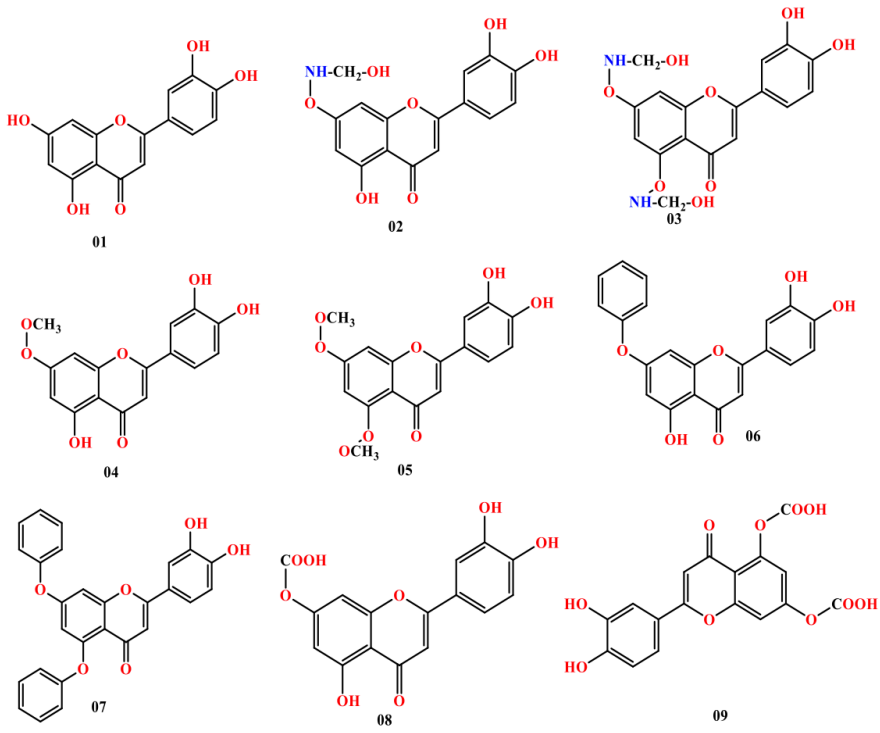


Figure 2. Chemical structure of Genistein and its derivatives

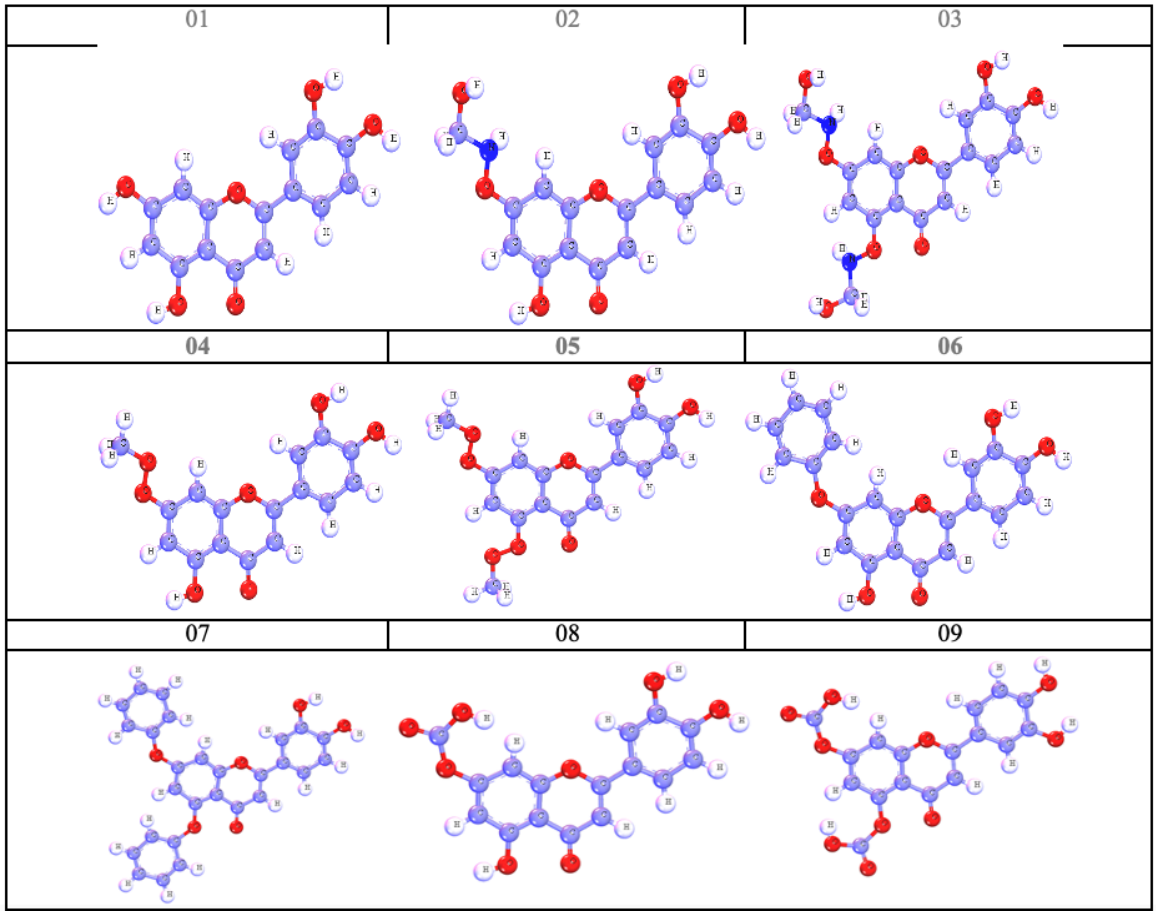


Figure 3. Optimized molecular structure of Fisetin derivatives.

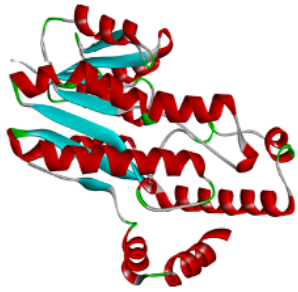
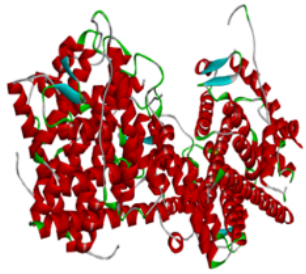
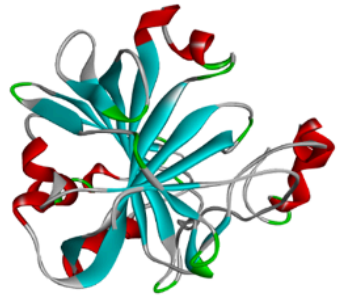
Breast cancer protein PDB: 3HB5	Breast cancer protein PDB: 5KCD	Breast cancer protein PDB: 6NLV
Organism: Homo sapiens	Organism: Homo sapiens	Organism: Homo sapiens
Resolution: 2.00 Å	Resolution: 1.80 Å	Resolution: 1.79 Å
		
Ref. (Mazumdar et al., 2009)	Ref. (Srinivasan et al., 2017)	Ref. (Mboge et al., 2021)

Figure 4. Three-dimensional protein structure of Breast cancer

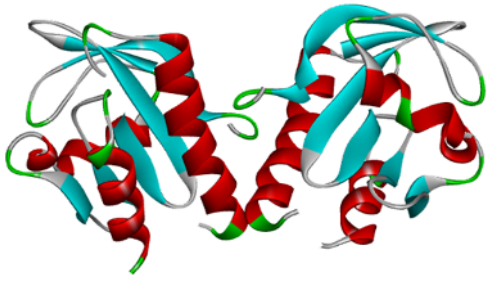
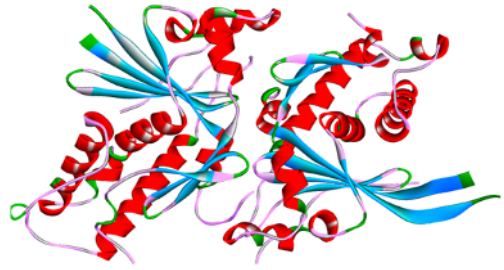
Monkeypox Virus (PDB ID 4QWO)	Marburg virus (PDB 4OR8)
Organism: Monkeypox virus Zaire-96-I-16	Organism: Marburg virus - Musoke, Kenya, 1980
Method: X-ray diffraction	Method: X-ray diffraction
Resolution: 1.52 Å	Resolution: Resolution 2.65 Å
	
Ref. (Minasov, Inniss, Shuvalova, Anderson, & Satchell, 2022)	Ref.(Oda et al., 2016)

Figure 5. Three-dimensional protein structure of Monkeypox, and Marburg virus

context of protein-ligand docking investigation to determine the optimal binding posture of a ligand against a bioreceptor. Optimization is the fundamental and important parameter for an accurate design of the ligands (Kobir *et al.*, 2022). The modified structures, and the optimized figures are given in Fig. 2 and Fig. 3.

Pass prediction

The pass prediction is an important feature for computer-based drug design, which is described by Pa and Pi ratio, where Pa means probability to be active and Pi means probability to be inactive. It is possible to separate most active molecules by screening pass prediction values which reduce the time and cost for developing new drugs (Pa>Pi value) (Filimonov *et al.*, 2014; Poroikov & Filimonov, 2005). The pass prediction data has been collected from the PASS online website "http://way2drug.com/PassOnline/predict.php". First enter the PASS online then the Pa>Pi value has been collected for the selected molecule and all the values are shown in Table 1.

Determination of ADMET, Lipinski rule and pharmacokinetics

With the help of pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction), and SwissADME, (http://www.swissadme.ch/index.php) we investigated the overall pharmacokinetic parameter of Fisetin and its derivatives. This section mostly investigated human intestinal absorption, distribution, metabolism, excretion, water solubility, bioavailability, toxicity, carcinogenicity, and drug likeliness (Azzam, 2023). The Lipinski Rule and drug likeness are important features for oral medication development (Tian *et al.*, 2015). Once the drugs have satisfied the Lipinski Rule, they should be considered as oral drug candidates.

Protein preparation and Molecular docking study and visualization

The crystal structure of Monkeypox virus (PDB ID 4QWO), Marburg virus (PDB ID 4OR8), and Breast Cancer (PDB: 3HB5, PDB: 5KCD and 6NLV) (Figs. 4

and 5) have been collected from the databank of RCSB protein (http://www.rcsb.org). Inadequate bonds, omitted hydrogens and side chain defects, access water have then been investigated and rectified, as necessary. Once all these issues have been resolved, they were saved as pdbqt file format. Then, the structure file has been loaded into PyRx AutoDock Tools, followed by usual processes to obtain binding affinities (Dallakyan & Olson, 2015). Finally, BIOVIA Discovery Studio Visualizer was used to investigate the interaction between the ligands and the protein (Zothantluanga, 2021).

CONCLUSIONS

This investigation has been designed to identify the dual mode of function of the ligands against virus and cancerous proteins. Our computational investigation has found that all the evaluated natural Fisetin derivatives demonstrated adequate reactivity with excellent binding affinity to be a viable therapeutic target for Breast cancer, Monkeypox, and Marburg virus. The biological characteristics of reported compounds such as toxicity, carcinogenicity, and Lipinski rule are good enough for human usage of the selected drug. We ran their various parameters *in silico* to verify their durability as a highly potential drug candidate, and these results assessed their acceptability as a potential new drug candidate. Following the investigation of protein-ligand (drug) interactions, several outstanding binding affinities were discovered, which will effectively assist in the discovery of the ideal natural medication or a novel drug. The highest value of docking energy has been found in Ligand 07 (–11.00 kcal/mol) against PDB: 3HB5 for breast cancer and the highest docking energy for Monkeypox virus (PDB ID 4QWO) is –9.0 kcal/mol, –9.4 kcal/mol, where -10.1 kcal/mol has been obtained against Marburg virus (PDB 4OR8). Besides, the results of pharmacokinetics, drug likeness and aquatic toxicity meet the requirements of the newly developed molecules. All the parameters are recorded as significant and better than standard. Concluding, the reported drug can be a candidate for further use.

Declarations

Author Contributions. Conceptualization, S.A, M.R, SS, C.M.L and T.B.E; methodology, T.A., A.S, and G.N; software, M.A; validation, A.A.S; formal analysis, T.A.; investigation, S.A, M.R, SS, C.M.L and T.B.E; resources, M.A and A.A.S.; data curation, A.S.; writing – original draft preparation, T.A and S.N.; writing – review and editing, A.S and S.N; visualization, A.F.A, A.S; supervision, T.A and S.N.; project administration, A.A.S and M.A ; funding acquisition, T.A

Data Availability statement. The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Conflicts of Interest. The authors declare no conflict of interest.

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