Exploring the Drug Potential of Phytochemicals as a Novel Therapeutic Drug Candidate for Herpesvirus: An In-silico Evaluation

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Abstract
Generally, the herpes virus is categorized into HSV-1 and HSV-2, with HSV-1 being transmitted through oral contacts. In contrast, HSV-2 is transmitted during sexual intercourse; hence known as genital herpes. In the infected individual, the majority of HSV infections are asymptomatic, although herpes can cause painful blisters or ulcers. On the other hand, HSV-2 infection increases the possibility of both transmission and contraction of HIV. In order to eradicate these viral infection complications and avoid the possibility of contracting HIV, few drugs have been prescribed for decades when infected with this viral infection. However, the prescribed drugs are not effective in eradicating this virus from infected individuals, which means few virus particles are latent after treatment with these drugs. Therefore, to investigate the novel anti-herpes potential of phytochemicals, the Maestro V13.3 was run with LigPrep, Grid Generation, SiteMap, Glide XP Docking, Pharmacophores and MM-GBSA. Ultimately, the docking result showed that all examined phytocomponents except ellagic acid had good docking values of −8.321 (epicatechin), −8.001 (rac 8-prenylnaringenin), −7.531 (apigenin) and −7.252 (−D-(+)-catechin) exhibited. In this in-silico assessment, we confirmed that the phytochemicals had more potential scores in docking scores, binding affinity, and MM-GBSA scores compared to the corresponding anti-herpes drugs. Apart from the molecular docking and MM-GBSA values, the phytochemicals were found to have good pharmacological potentials through pharmacophore and pharmacokinetic assessments. Moreover, we believe that compounds such as epicatechin, Rac 8-prenylnaringenin, apigenin and -D-(+) catechin would reveal possible therapeutic effects when tested in-vitro and in-vivo trials. Finally, the present research suggests that although these molecules have such therapeutic potential, a detailed toxicological study of these molecules should be performed in a dose-dependent manner prior to clinical trials.

Keywords Herpesvirus · Phytochemicals · Molecular docking · Pharmacophore · MM-GBSA

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1 Introduction

Herpesviruses belong to the double-stranded DNA family, which is divided into three subfamilies including α-herpesviruses, β-herpesviruses and γ-herpesviruses. According to a recent WHO report [1], almost 3.7 billion people under the age of 50 are living with HSV-1 infection; while nearly 491 million people aged 15–49 are living with HSV-2 infection. These viruses are responsible for causing neurotropic infections and lymphotropic diseases in host. They often adapt to their host system, and remain dormant until the immune system is weak. Later, the virus particles are activated in the host and cause diseases [2]. Despite their very different pathogenic properties and clinical manifestations, all herpesviruses have a set of core genes, most of which encode important core protein and replicate the viral particles [3]. Furthermore, the conserved herpesvirus protein kinases (CDPKs), which play a key role medically as drug targets and pro drug-activating enzymes, are also one of the few core genes with regulatory functions [4].

The conserved herpesvirus protein kinases (CHPKs) have been reported to be the primary target of cellular cycle independent kinase (CDK) phosphorylation sites. Particularly, there is significant structural and functional homology between CDKs and the kinases of human β- and γ-herpesviruses. Especially, the herpesvirus viruses such as Epstein-Barr virus and Kaposi’s sarcoma-associated herpesvirus are known as human herpesvirus-4 and human herpesvirus-8, which are considered to be the main causative agents of lymphomagenesis in immunocompromised people. Specifically, these viruses are responsible for causing numerous lymphoproliferative and neoplastic diseases in the human race [5]. These viruses have also been reported to be involved in a number of cellular signaling pathways involved in phosphorylation and dephosphorylation functions [5].

By hijacking phosphorylation and cellular signaling in the human body, the herpes viruses are responsible for the development of cancer. In addition, phosphorylation caused by viral infection has been shown to have a remarkable impact on viral invasion, proliferation, and cytotoxicity of host cells. In most cases, chronic viral infection is asymptomatic or accompanied by harmless cellular manifestations. However, chronic herpesvirus infection leads to the emergence of cancers including Burkitt’s lymphoma, nasopharyngeal carcinoma, Kaposi’s sarcoma, and B-cell lymphoproliferative syndromes. Most of these cancers appear years after the viral infection has subsided and are associated with viral reactivation [6].

In order to inhibit the DNA replication of the herpes viruses, the drugs aciclovir, valaciclovir, penciclovir and famciclovir are prescribed for more than a decade. Although the drugs are effective in the treatment of active infections, they are not effective in controlling the recurrence of a latent virus and they also lose effectiveness if resistance mutations develop [7]. Therefore, alternative anti-herpesvirus molecules are required to completely eradicate the virus even though it is latent in the human body. Accordingly, it is imperative to constantly search for novel antiviral drugs.

Since the phytochemical have a wide range of biomedical potential and minimal side effects, we sense that a molecule from the plant would be a better drug for herpes viruses as an anti-viral drug. Consistent with this statement, many studies have previously reported that plant products have been used primarily to cure a number of diseases, including viral infections, for many years. Many of the plants are considered reliable drug sources for research into novel antiviral drugs [7]. Furthermore, several extracts from plants have recently been reported to have a broad spectrum of antiviral activity against corona virus, dengue fever, influenza and so on. Therefore, the present research is looking for novel therapeutic molecules from natural sources to combat the herpesvirus.

2 Materials and Methods

2.1 Biological Data

The phytochemicals such as 8-rac-prenaylnaringin, apigenin, epicatechin, (+) catechin and ellagic acid were obtained from Chemspider in mol format to assess their anti-herpes viral potential through this computational biological research. Likewise, the herpes protein, human cyclin-dependent kinase 2, was taken from the protein database. The alphanumeric identity of the protein is 1F5Q.

2.2 Docking and Modeling Platform

This Insilico research was performed using Maestro V.12.7 module consisting of LigPrep, Grid Generation, SiteMap and Glide XP. In order to investigate the drug possibility of the proposed molecule, this module was run in the highly configured Centox Linux operating system.

2.3 Target Preparation

This protein consists of almost 298 residues. It was prepared by removing water molecules using the Protein Preparation Wizard module. This is because the protein that contains the intertwined water molecules is unsuitable for the docking process. During protein preparation, two passes such as preparation and refinement were used to uncover the missing
residues, which also served to update these missing residues in the protein. Ultimately, a few more gears such as optimization and minimization gears were employed to get the final structure of the protein for further exploration. As line with previous research, the whole process has also been carried out in this research [8].

2.4 Active Site Prediction

This site exploration plays an important role in docking as it helps to find the ligand binding pocket in the protein. It was analyzed on the prepared protein. Although the protein consists of an enormous number of binding sites, not all of them could be identified as suitable sites for docking without this investigation. Therefore, for the docking of the phytochemicals with this protein, it was thoroughly investigated and a suitable site was selected in the metrics including site rating and site volume for grid generation [8].

2.5 Grid Generation

The grid module was used to stabilize the ligand binding in this protein by constructing the grid box. Later, the phytochemicals were docked to the grid-fixed protein through grid-based ligand docking. With this approach, a lattice box was fashioned to dock the phytochemicals at the focal point of this herpes virus protein. The grid box of 1F5Q was built with X: 69.31, Y: 64.39 and Z: -14.86. After the lattice box was built; it was docked with the secondary metabolites of medicinal plants. In accordance with previous research, this was accomplished [8].

2.6 Ligand Preparation

The mol format of the phytochemicals was prepared using the LigPrep (2.4) module before they were docked. In order to optimize the geometry of the obtained ligand, the force field Optimized Potentials for Liquid Simulations 2005 (OPLS2005) was also employed. With this module all phytochemicals were constructed as 3D structures from the 1D (Smiles) and 2D (SDF) representations of the ligand; where, the two gears such as tautomers and stereoisomers was also applied to reduce the geometric complexity of the ligand. Finally, for each successfully processed input structure, a ligand molecule with a certain molecular weight or a specific amount and kind of functional groups with correct chirality was docked with herpes virus protein [8].

2.7 Molecular Docking

This was performed using the Maestro V.12.7 Glide docking module, after taking the ligands out of the Ligprep tools and the protein out of the grid generation, which were used to determine the binding affinities between them. The present study was used for two docking modes, Standard Precision (SP) and Xtra Precision (XP), to predict the inhibition constants and binding affinities of the ligand to the herpesvirus protein. The drug potential of ligands was confirmed by docking metrics such as docking scores and contacts [8].

2.8 Pharmacophore Analysis

The energetic (e)-pharmacophore approach combined ligand and structure-based approaches. The docking post-processing option in Maestro version 13.2 was made possible by the E-Pharmacophore scripting tool that was created to investigate the E-Pharmacophore hypothesis. Then, the uncorrected phase v 3.4 detection application (Schrödinger, LLC, NY) creates pharmacophore sites using a set of six chemical properties: hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), positively ionizable (P), negatively ionizable (N) and aromatic ring (R). The most energetically positive site was then selected for pharmacophore generation after these sites were ranked according to their energies [9].

2.9 Drug Probability of Phytochemicals

With the help of the pass server, the drug potential of the explored phytochemicals was evaluated with regard to the probabilities of active and inactive against the enzymes [10].

2.10 Pharmacokinetics Analysis

In order to evaluate the various physicochemical and pharmacokinetic features of the phytochemicals employed in this study, a pkCSM portal was used [11].

3 Results and Discussion

3.1 Plants as a Source of Immune-Stimulant and Antiviral Agents

A recent study has highlighted that plants are used as first aid by 80% of people around the world. Plants and their products are primarily used by humans to strengthen the immune system [12]. According to a report by Shukla et al. [13], the WHO lists almost 21,000 species that are underlined as valuable from a therapeutic and commercial point of view. Of the plants listed, almost 2500 plants exist in India. These plants are used to treat disease either as polyherbs or alone by a variety of traditional medicinal systems including Ayurveda, Siddha, and Unani. Consistent with this statement, the plants and their products have been recommended for two decades to inhibit viral replication and
resulting health complications; where it primarily boosts the immune system of the viral host [12]. For instance, the two Siddha based chooranams namely Nilavembu Kudineer Chooranam (nilavembu kudineer chooranam) and Kabasura Kudineer Chooranam (kabasura kudineer chooranam) have been prescribed by the AYUSH Department of the Government of India to boost the immune of the viral host [14]. These chooranams were recommended by the Ministry of AYUSH during the dengue and corona outbreaks after a thorough immune system assessment [14]. These chooranams are reported to perform as immunostimulants and immunomodulators of the body’s defense mechanisms to prevent viral infections and their associated consequences. There are valuable health benefits in the use of natural remedies. Therefore, the current study is looking for nature-based medicines from plants to avoid the consequences of side effects.

### 3.2 Computational Biology and Its Significance

At present, this computational biology has been widely used by scientists to find the exact drug molecule for specific diseases, specifically to evaluate the potential geometry of a target-ligand binding affinities. By showing the drug potential of ligand molecules at the binding site of proteins and highlighting the ligand associated with the biological process, it is being employed to delve a little deeper into ligand–protein interactions at the atomic level [15].

### 3.3 Active Site

In this binding pocket detection, nearly five drug grade pockets were identified as suitable ligand binding sites. Later, only one location was chosen to generate the grid, which was chosen based on the metrics of the site values (Fig. 1 and Table 1).

### 3.4 Molecular Docking

The present research has shown that this herpes protein is successfully inhibited by all bound phenolic substances. The finest docking values and most impressive hydrogen bonding with the amino acid residues of this viral herpes protein were first discovered to be with epicatechin. After epicatechin, other phytochemicals such as Rac 8-prenylnaringenin, api-genin, -D-(+)-catechin and ellagic acid possessed notable docking scores, specifically, Rac 8-prenylnaringenin was found to be similar to that of epicatechin in terms of docking scores and binding affinities (Table 2). We eventually found that the hydroxyl groups of these phytochemicals showed hydrogen bonding contacts in the binding site of the docked

![Fig. 1 Ligand binding pocket in the herpesvirus protein (1F5Q)](image)

| S. No. | Sites   | Score  | Volume  | Ligand binding pocket residues within 3 Å                                                                 |
|-------|---------|--------|---------|----------------------------------------------------------------------------------------------------------|
| 1     | Sitemap-1 | 1.015  | 287.777 | Chain A: 9,18,19,20,31,33,51,55,64,80,81,82,83,85,86,89,134,144,145,146                                |
| 2     | Sitemap-2 | 0.9    | 262.395 | Chain A: 218,219,220,221,222,223,226,236,238,240,242,244,245,246,247,248,264,267,268,269,270        |
| 3     | Sitemap-3 | 0.846  | 220.892 | Chain A: 91,95,96,97,98,99,100,101,104,194,196,197,198,199,200,201,202,203,204,214,217,218,246,251,253,254,255|
| 4     | Sitemap-5 | 0.668  | 78.89   | Chain A: 85,89,90,93,94,98,99,100,103,294,295,296,297                                                    |
| 5     | Sitemap-4 | 0.66   | 140.63  | Chain A: 166,169,173,174,208,209,212,213,235,237,240                                                   |
proteins with a range of 3 Å. The contacts between these two molecules were known to have possible drug effects.

3.4.1 Epicatechin

Epicatechin has a prime docking score of -8.321 with the glide energy values of -42.595 (Table 2). Almost five lines were found as binding contacts in the docked complex of epicatechin and herpesvirus. Among the contacts, the residues such as LYS33, GLU51, VAL64 and LEU83 were found as hydrogen bond contacts with epicatechin; whereas, PHE80 was found as π–π contact with it. Accordingly, the distances of the hydrogen bonding contacts of LYS33, GLU51, VAL64 and LEU83 were found to be 1.79, 1.83, 2.57 and 1.72, respectively (Fig. 2a). In order to know the functional and ammonia groups of the phytochemicals contributed to the hydrogen bonding contacts, the docked complex was subjected to an examination of the two-dimensional diagram. In this interaction diagram, all residue contacts were found to be involved in the interactions of the hydroxyl group of epicatechin. Conversely, the residue PHE80 was found as a green line at the center of the main group of this molecule, known as pi-pi stacking. It was precisely shown in Fig. 2b.

Generally, the catechins are the group of polyphenolic compounds which are classified into esterified and non-esterified. The estified catechins are (+)—catechin, gallocatechin, epicatechin (EC) and epigallocatechin (EGC), while the non-esterified catechins are epigallocatechingallate (EGCG), epicatechingallate (ECG), gallocatechingallate (GCG) and catechingallate. These contain two aromatic rings with multiple hydroxyl groups that are similar in chemical structure to each other. Based on the similarity in chemical nature, two phytochemicals from the catechins were currently selected to evaluate their anti-herpes potential using the insilico strategy. With this molecular docking, these two phytochemicals were found to have remarkable docking scores and binding affinities with this protein. The antiviral potential of these phytochemicals has been attested to by many scientists from all over the world for decades. In accordance with this statement, the antiviral drug abilities of these phytochemicals have been discussed as follows. Consistent with this statement, previous phytochemical studies showed that the catechins were found in the aerial parts of Camellia sinensis L., Prunus dulcis L., Pseudocydonia sinensis Schneid, Malus domestica Mühle, Cydonia oblonga Mühle, Bauhinia racemosa Lam, Spondias mombin L., Ricinus communis and Rumex acetosa [16, 17]. Among these plants, Camellia sinensis has been found to have a higher content of catechins. Leaves from it are used to make green tea. Three types of teas have been made from the leaves of this plant, such as white tea, green tea, oolong tea and black tea, which have been classified based on the drying and fermentation processing, lightly fermented, unfermented,

Table 2  Docking scores, glide energy and GG/MMGBSA values of phytoconstituents with the gamma herpesvirus cyclin cdk complex

| S. No. | Name of the Phytochemicals | Docking Scores | Glide Energy | MM-GBSA |
|--------|-----------------------------|----------------|--------------|---------|
| 1      | Epicatechin                 | -8.321         | -42.595      | -52.65  |
| 2      | Rac 8-Prenylnaringenin      | -8.001         | -39.943      | -46.11  |
| 3      | Apigenin                    | -7.531         | -40.471      | -41.74  |
| 4      | D-(+)-Catechin              | -7.252         | -40.46       | -43.97  |
| 5      | Ellagic acid                | -6.815         | -24.069      | -38.77  |

Fig. 2  a Epicatechin: interactions and the values of the hydrogen bond distances, b 2D template plots showing contacts between the hydroxy and methoxy groups of epicatechin and the amino acids of the gamma herpesvirus cyclin cdk complex
partially fermented and fully fermented. In China, tea powders made from *C. sinensis* have been pursued by the Chinese since ancient times. Therefore, it is considered by them to be traditional Chinese medicine. Since then, it has cured a variety of human health complications, including cardiovascular protection, antidiabetic, immune regulation, and antiviral. Therefore, it has been used by them since ancient times to till now. Beside these health potential, it is reported to have antiviral potential for Herpes Simplex Types 1 Virus (HST-1) [18] and Influenza A Virus (IFV) [19]. It effectively suppressed these viral replications in a dose-dependent manner. A recent study by Bondonno et al. [20] reported that it was found to have the inhibitory potential of SARS-CoV-2, specifically the main protease thereof. Similar catechins including gallocatechin-3-gallate, epigallocatechin gallate and epicatechingallate are also claimed as active components in preventing SARs-CoV-2 Mpro; while, it has also been reported to have therapeutic potential in alleviating hyperinflammation in COVID-19 mediators due to its antiviral, antiseptic, antifibrotic and reduced oxidative stress synthesis and signaling [21, 22]. According to the research reports of previous findings, we believe that these may potentially act concert with other catechins to inhibit viral replication and also act individually as an antiviral agent. In general, it can be found in the blood plasma after ingestion of catechin-containing foods and has also been observed to be stable in solution at pH values around 4–6 [23].

### 3.4.2 Rac 8-Prenylnaringenin

It has a docking score -8.321 with the glide energy values of -42.595, which is close to epicatechin in terms of docking score and energy values (Table 2). Almost four lines were found as binding contacts in the docked complex of rac 8-Prenylnaringenin and herpesvirus. Among the contacts, the residues such as PHE146, GLU51 and LEU83 were found as hydrogen bond contacts with this molecule; whereas, PHE80 was found as \( \pi - \pi \) contact. Accordingly, the distances of the hydrogen bonding contacts of PHE146, GLU51 and LEU83 were found to be 1.74, 2.42 and 1.95 respectively (Fig. 3a and Table 3). In order to know the functional and ammoniac groups of the phytochemicals contributed to the hydrogen bonding contacts, the docked complex was subjected to an examination of the two-dimensional diagram. In this interaction diagram, all residue contacts were found to be involved in the interactions of the hydroxyl group (OH) of rac 8-Prenylnaringenin. Conversely, the residue PHE80 was found as a green line at the center of the main group of this molecule, known as \( \pi - \pi \) stacking. It was precisely shown in Fig. 3b.

Previous research by Eesolowska et al. [24] and Wolff et al. [25] have reported that the phytoestrogens exhibit high antiviral activity, particularly naringenin, which has been shown to be 10 times more active in antiviral potential through prenylation. They claimed that the antiviral potential of polyphenols was enhanced by prenylation; where it facilitates intracellular uptake and possibly cellular accumulation. According to the research by Hanada et al. [26] the glycosylation can render phytoestrogen flavonoids water soluble
and also result in reduced or lost antiviral activity due to in vitro membrane permeability issues. They also described that it has more potent antiviral activity than the aglycones, indicating there may be at least two groups with different signaling pathways. They discovered that 8-prenylnaringenin has potent antiviral potential against influenza viruses; its mode of growth inhibition during virus adsorption may differ from that of amantadine, however its mechanism of endocytosis and inhibition of late replication may be similar to that of the corresponding drug oseltamivir. Ultimately, the present results agree with those of [26].

3.4.3 Apigenin

It has a docking score -7.531 with the glide energy values of -40.471 (Table 2). Almost five lines were found as binding contacts in the docked complex of apigenin and herpesvirus protein. Among the contacts, the residues such as LYS33, GLU51, LEU83 and VAL64 were found as hydrogen bond contacts with this molecule; whereas, LYS33 was covalently bound with the functional groups of apigenin. Accordingly, the distances of the hydrogen bonding contacts of GLU51, LEU83 and VAL64 were found to be 1.61, 1.78 and 2.31 respectively (Fig. 4a). Furthermore, the distances of the contact lines of the covalent bond residue LYS33 were measured to be 2.32 and 2.64 respectively. In order to know the functional and ammoniac groups of the phytochemicals contributed to the hydrogen bonding contacts, the docked complex was subjected to an examination of the two-dimensional diagram. The interaction plot revealed that the residue such as GLU51, LEU83 and VAL64 were found to be involved in the interactions of the hydroxyl group (OH) of apigenin. Conversely, the covalently bound LYS33 showed that one end of the contact lines was connected to the hydroxyl group and the other end was connected to the oxygen group of this ligand molecule. It was precisely shown in Fig. 4b.

It is an important source of foods such as fruits and vegetables, especially humans consume these foods for their diet. It is quite similar to naringin in that it varies some functional groups between these molecules. Spectrally, it is classified as 4,5,7-dihydroxyflavone, which structurally possesses a compound with hydroxyl groups at the C-5 and C-7 positions of the A ring and C-4 of the B ring. Previous studies have reported high concentrations in barley, chamomile, celery, vine spinach, artichokes and oregano. In particular, it can be so rich in these when consumed in dried form [27]. Consistent with this statement, a research in 2016 has been claimed that there were 45,035 g/g in dried parsley, 3000 to 5000 g/g in chamomile, 786.5 g/g in celery, and 622 g/g and 240.2 g/g in vine spinach and Chinese celery respectively [28].

Apigenin is also found in the aerial parts and roots of Carum carvi Linn, Dichrostachys drupifera Mill, Digitalis purpurea L, Enicostemma littorale Blume, Eryngium campestrum L, Kaempferia galanga L, Lonicera japonica L, Matricaria arcoreita L, Mentha piperita Wild, Petroselinum sativum Fuss, Passiflora speciesism L, Ruellia tuberosa L, Tanacetum vulgare L and Verbaseum Thapsus L [11]. Conversely, in southern India, the apigenin-containing Carica papaya L extract is used to treat dengue to strengthen the immune system. A study by Jasso-Miranda et al. [29] reported that apigenin has demonstrated its antiviral and immunomodulatory potential while treated on macrophages infected with dengue virus serotypes 2 and 3. They reported that interleukin 10 was significantly down regulated in dengue-infected BHK-21 cell lines and also showed potent antiviral activity in dengue serotype 3.

3.4.4 −D +(+ )-Catechin

It has a docking score -7.252 with the glide energy values of -40.46 (Table 2). Almost four lines were found as binding contacts in the docked complex of −d-(+)-catechin and herpesvirus protein. Among the contacts, the residues such as

![Fig. 4 a Apigenin: interactions and the values of the hydrogen bond distances, b 2D template plots showing contacts between the hydroxy and methoxy groups of Apigenin and the amino acids of the gamma herpesvirus cyclin cdk complex](https://example.com/fig4.png)
LYS33, GLU51, LEU83 and VAL64 were found as hydrogen bond contacts with this molecule. Accordingly, the distances of the hydrogen bonding contacts of GLU51, LEU83 and VAL64 were found to be 1.88, 1.73, 1.83 and 2.47 respectively (Fig. 5a). In order to know the functional and ammoniagroups of the phytochemicals contributed to the hydrogen bonding contacts, the docked complex was subjected to an examination of the two-dimensional diagram. The interaction plot reveals that the residue such as LYS33, GLU51 and VAL64 were found to be engaged in the interactions of the hydroxyl group (OH) of −d-(+)-catechin. Conversely, residue LEU83 was in contact with the oxygen group (O) of this phytoconstituent. It was precisely shown in Fig. 5b.

3.4.5 Ellagic Acid

It has a docking score -6.815 with the glide energy values of −24.069 (Table 2). Almost four lines were found as binding contacts in the docked complex of ellagic acid and herpesvirus. Among the contacts, the residues such as LYS33 and LEU83 were found as hydrogen bond contacts with this molecule; whereas, PHE80 was found as π–π contact. Accordingly, the distance of the hydrogen bonding contacts of LYS33 was found to be 2.05. Furthermore, the residue LEU83 was found be covalent hydrogen bond contacts with ellagic acid. Covalent bond distances were measured to be 1.96 and 2.56 (Fig. 6a). In order to know the functional and ammoniagroups of the phytochemicals contributed to the hydrogen bonding contacts, the docked complex was subjected to an examination of the two-dimensional diagram. It has been identified that all residual contacts are involved in the interactions of the hydroxyl group (OH) of ellagic acid in this interaction diagram. Conversely, the residue PHE80 was found as a green line at the center of the main group of this molecule, known as π–π stacking. It was precisely shown in Fig. 6b.

It is a polyphenol found primarily as ellagitannin in woody dicotyledonous plants such as grapes, strawberries, blackcurrants and raspberries. It has previously been found to have a range of biological activities including antioxidant,
anti-inflammatory and anti-fibrotic activities. A recent review by Javad Sharifi-Rad et al. [30] documented that the ellagic acid is present in a variety of food plants such as Car- yallino inensis (Wangenh.) K. Koch, Castanea sativa Mill, Hippophae rhamnoides L, Juglans nigra L, Myrciaria dubia (Kunth) McVaugh, Psidium guajava L, Punica granatum L, Rosa rugosa Thunb, Rubus arcticus L, Rubus chamaemorus L, Rubus idaeus L, Rubus ursinus Cham. & Schltldl, Terminalia ferdinandiana Exell and Vitis rotundifolia Michx. In 2019, a study by Wang et al. [31] reported that it is also found in the medicinal mushrooms Phellinus linteus and Myriophyllum spicatum.

In general, ellagic acid has been ascribed a diverse therapeutic potential, including antiviral activity. Consistent with this statement, it has been found to have the potential to inhibit alpha papillomavirus, which is known to be the causative agent of widespread viral diseases that are sexually transmitted. Regardless of geography, it affects a large proportion of the population worldwide. In many cases this only leads to benign lesions, but in other cases it can also lead to cause of tumors and even cancer. In particular, it is considered the main cause of cervical cancer [32–34]. For instance, Morosetti et al. [35] reported that the tablet of 16 mg ellagic acid with 100 mg cherimoya pulp significantly reduced the cell progression of cervical cancer after consumption in people with cervical cancer caused by alphapapillovirus. Based on their findings, they hypothesized that the substance has an antiviral effect that could help prevent infection and potentially treat the infection successfully. Similarly, prior to Mattoscio et al. [34], Park et al. [36] isolated ellagic acid from the leaves of Lagerstroemia speciosa to study its antiviral potential on viral cell lines; where it has shown strong HRV-4 RNA replication in the HeLa system, ultimately suggested that ellagic acid suppresses viral replication by targeting cellular components rather than the viral molecules.

### 3.6 Pharmacophore

The data set was divided into active, moderately active and inactive areas by keeping the activity threshold in the range of 6.5–7.9. As shown in Fig. 8A–D, the entire phytochemical binding domain was defined in terms of five traits that included generic pharmacophore hypotheses due to their high survival value. Figure 8e shows that the phytochemicals have 80% of the active regions in pharmacophore explorations.

### 3.7 Drug Likeness

The drug-likeliness of docked molecules was examined based on their physico-chemical properties, which are clearly shown in Table 4 and Fig. 9.

### 3.8 Pharmacokinetics Properties of Docked Molecules

The pharmacological profiles of the docked phytochemicals were clearly presented in Table 5. In addition, the prediction also showed how the explored phytochemicals act in the body in the following ways: absorption, distribution, metabolism, excretion and toxicity (ADMET). As reported by Alamri et al. [37] this prediction helps to understand the state of drug molecules in the biological mechanism, as revealed in Table 5. Only a handful of drugs have been withdrawn from the market in the past two decades due to significant side effects. This could be due to a lack of relevant studies, such as drug likeness and ADMET properties.

### 4 Conclusion

Currently there are no fixed drugs against the viruses such as dengue, herpes virus, corona, H1N1, nipha and so on. On the other hand, the plant extracts are widely used by people all over the world to reduce the complications of viral diseases in the human body. Therefore, the present in-silico research was chosen phytochemicals such as epicatechin, Rac 8-prenylnaringenin, apigenin, − D-(+)-catechin and ellagic acid to study their anti-herpesvirus potential. Since the existing drugs are not able to properly eradicate the virus in the infected person, the present study was explored these phytochemicals as an alternative drug.
molecule for herpesviruses. Finally, we found that each docked phytochemical had remarkable docking values and binding affinities than the existing anti-herpes virus drugs. According to this docking result, the drug possibilities of these phytochemicals were further explored using pharmacokinetics and pharmachopore; where all phytochemicals, with the exception of ellagic acid, revealed possible drug potential. Although the phytochemicals showed the potential biological properties in this research, a more detailed study of the docked molecule in in-vitro and in-vivo model is needed to understand more about these biomedical drugs. Ultimately, based on the observation, the present research suggests that phytochemicals such as epicatechin, rac 8 prenylnaringenin and apigenin would have potential biomedical potential as antiviral agents if subjected to clinical trials.
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Fig. 8 a–e Pharmacophore hypothesis of phytochemicals: a denotes hydrogen bond acceptor in pink color, D denotes hydrogen bond donor in blue) and R denotes aromatic rings in brown color from docked phytochemicals; a–d showed the active site of docked phytochemicals developed by e-Pharmacophore and E Plot E reveals the percentage of active pharmacological properties of phytochemicals.

Fig. 9 The plot with boiled eggs shows the importance of the phytochemicals examined in this study for the blood–brain barrier, the gastrointestinal tract and the glycoproteins.
**Table 4** Drug likeness parameters of explored phytochemicals in this research

| S. No | Name of the Polyphenols | MW (g/mol) | Rotatable bonds | H-bond acceptors | H-bond donors | Log P | TPSA (Å²) | Bio availability |
|-------|--------------------------|------------|-----------------|------------------|--------------|-------|-----------|------------------|
| 1     | Epicatechin              | 290.27     | 1               | 6                | 5            | 1.5461| 110.38    | 0.55             |
| 2     | rac 8-Prenylnaringenin   | 340.37     | 3               | 5                | 3            | 4.0186| 86.99     | 0.55             |
| 3     | Apigenin                 | 270.24     | 1               | 5                | 3            | 0.52  | 90.9      | 0.55             |
| 4     | D-(+)-Catechin           | 290.27     | 1               | 6                | 5            | 1.5461| 110.38    | 0.55             |
| 5     | Ellagic acid             | 302.19     | 0               | 8                | 4            | 1.3128| 141.34    | 0.55             |

*MW* molecular weight, *HBD* hydrogen bond donors, *HBA* hydrogen bond acceptor, *RB* rotatable bond, *TPSA* topological polar surface area

**Table 5** ADMET profiling parameters of phytochemicals explored in this research

| Pharmacokinetic properties | Azadirachtin | Rax 8 prenylnaringenin | Apigenin | D-(+)-Catechin | Ellagic acid |
|----------------------------|--------------|------------------------|----------|----------------|--------------|
| Absorption                 |              |                        |          |                |              |
| Water solubility           | −0.376       | −3.91                  | −4.073   | −3.139         | −3.209       |
| Caco2 permeability         | 68.117       | 0.926                  | 0.035    | −0.371         | 0.466        |
| Intestinal absorption (human) | −2.735     | 90.768                 | 82.441   | 72.107         | 74.339       |
| Skin Permeability          | Yes          | −2.735                 | −2.768   | −2.735         | −2.735       |
| P-glycoprotein substrate   | No           | Yes                    | Yes      | Yes            | Yes          |
| P-glycoprotein I inhibitor | No           | Yes                    | Yes      | No             | No           |
| P-glycoprotein II inhibitor| −0.376       | Yes                    | Yes      | No             | No           |
| Distribution               |              |                        |          |                |              |
| VDss (human)               | 0.531        | 0.075                  | −0.258   | 0.869          | 0.46         |
| Fraction unbound (human)   | 0.12         | 0.019                  | 0        | 0.311          | 0.071        |
| Blood–Brain barrier permeability | −1.191   | −0.906                 | −0.51    | −1.232         | −1.338       |
| Central Nervous System permeability | −3.301 | −1.945                 | −3.044   | −3.196         | −3.602       |
| Metabolism                 |              |                        |          |                |              |
| Cytochrome P2 D6 substrate | No           | No                     | No       | No             | No           |
| Cytochrome P3 A4 substrate | No           | Yes                    | Yes      | No             | No           |
| Cytochrome P1 A2 inhibitor | No           | Yes                    | No       | No             | Yes          |
| Cytochrome P2 C19 inhibitor| No           | Yes                    | Yes      | No             | No           |
| Cytochrome P2 C9 inhibitor | No           | Yes                    | Yes      | No             | No           |
| Cytochrome P2 D6 inhibitor | No           | No                     | No       | No             | No           |
| Cytochrome P3 A4 inhibitor | No           | Yes                    | Yes      | No             | No           |
| Excretion                  |              |                        |          |                |              |
| Total Clearance            | 0.305        | 0.019                  | 0.014    | 0.1            | 0.637        |
| Renal OCT2 substrate       | No           | No                     | No       | No             | No           |
| Toxicity                   |              |                        |          |                |              |
| AMES toxicity              | No           | No                     | No       | No             | No           |
| Max. tolerated dose (human)| 0.67         | 0.373                  | 0.508    | 0.501          | 0.937        |
| hERG I inhibitor           | No           | No                     | No       | No             | No           |
| hERG II inhibitor          | No           | Yes                    | No       | No             | No           |
| Oral Rat Acute Toxicity (LD50) | 1.786     | 2.178                  | 2.066    | 2.424          | 2.454        |
| Oral Rat Chronic Toxicity (LOAEL) | 2.867   | 1.091                  | 1.3      | 2.533          | 2.702        |
| Hepatotoxicity             | No           | No                     | No       | No             | No           |
| Skin Sensitisation         | No           | No                     | No       | No             | No           |
| T. Pyriformis toxicity     | 0.378        | 0.471                  | 0.599    | 0.335          | 0.285        |
| Minnow toxicity            | 1.69         | 0.606                  | 0.819    | 2.922          | 2.241        |
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Consent for Publication On behalf of the authors, I hereby assign the right of this entire article content to this journal.

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