In-Silico Studies of Anti-Viral Activities of Phytochemicals in Berberis Vulgaris Against a Receptor of Chickenpox

Omolara Adeboye

Department of Chemistry, Emmanuel Alayande University of Education, Oyo, Oyo State, Nigeria

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ABSTRACT

The search for novel antiviral agents from natural sources has garnered significant attention due to the limitations and side effects (such as kidney failure, lowering red blood cells and platelets, seizure etc) of current antiviral therapies. Berberis vulgaris, commonly known as barberry, is rich in bioactive phytochemicals, particularly berberine, which have shown promise in inhibiting various pathogens. In this study, we investigate the in-silico antiviral activities of key phytochemicals from Berberis vulgaris against a receptor of the varicella-zoster virus (VZV), the causative agent of chickenpox. We performed molecular docking simulations to predict the binding affinity, interaction profiles, physicochemical and ADMET parameters of these phytochemicals with the VZV receptor protein, aiming to uncover potential inhibitors that could serve as lead compounds for the development of plant based antiviral drugs.The study focused on five selected phytochemicals, berberine, palmatine, quercetin, kaempferol, and caffeic acid, all known for their diverse pharmacological activities and two standard drugs, Acyclovir and valacyclovir. In this work, focus was on berberine. AutoDock Vina, Vina Wizard, and open Babel of PyRx virtual screening software were used for the docking studies. The docking output expressed in binding affinity/energy (kcal/mol) showed that the interaction energy between the protein and the Ligands/drug compounds, and the inhibition constant (Ki) in micromolar (µM) was evaluated to obtain the binding energies, hydrogen bonding interactions, and hydrophobic interactions between the selected compounds and the viral receptor for the phytochemicals and standard drugs. Result obtained revealed that berberine compared favorable well with the two standard drugs with binding affinity -7.4 $kalmol^{-1}$ for both berberine and acyclovir and 6.0 $kcalmol^{-1}$ for valacylovir. forming significant interactions with the receptor's active site, particularly through hydrogen bonds with key amino acid residues. Quercetin and kaempferol also demonstrated promising binding potentials, with high negative binding energies and stable interaction complexes. The analysis further revealed that these phytochemicals not only bind to the receptor but also interfere with key viral processes, such as the attachment and entry of the virus into host cells. Additionally, the compounds displayed favorable pharmacokinetic properties, including good drug-likeness and bioavailability, making them potential candidates for further in-vitro and in-vivo studies. These findings suggest that the phytochemicals from Berberis vulgaris could be developed as antiviral agents against chickenpox, with berberine being the most potent candidate for future drug development.

In conclusion, our in-silico study highlights the therapeutic potential of Berberis vulgaris phytochemicals, especially berberine, in inhibiting the varicella-zoster virus and the key findings suggest that berberine inhibits viral replication by interacting with viral glycoproteins, affecting viral entry into host cells. Moreover, in vitro studies have highlighted its role in modulating immune responses and preventing oxidative stress. [1] concluded that dietary supplementation of B. vulgaris root extract to quails reduces the detrimental effects of oxidative stress and lipid peroxidation resulting from HS via activating the host defense system at the cellular level. Further experimental validation is needed to confirm the antiviral efficacy of these compounds, which may pave the way for the development of novel, natural antiviral therapies for chickenpox and other viral infections.

Keywords: Berberis vulgaris, Chickenpox, molecular docking, in-silico

INTRODUCTION

Chickenpox is an illness caused by the varicella-zoster virus that primarily affects children and adults who have not been vaccinated. It brings on an itchy rash with small, fluid filled blisters. Chickenpox spreads very

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easily to people who have not had the disease or have not gotten the chickenpox vaccine. Chickenpox used to be a widespread problem, but today the vaccine protects children from it. The chickenpox vaccine is a safe way to prevent this illness and the other health problems that can happen during it.

In countries where chickenpox vaccination is not part of routine childhood immunizations, seasonal outbreaks remain a public health issue. This is particularly the case in the UK, Denmark, France, Portugal, and some Scandinavian nations, which have held off on making the chickenpox vaccine standard due to concerns about cost-effectiveness and potential increases in adult shingles cases. The reasoning is that exposure to chickenpox in children helps boost immunity in adults, reducing their risk of shingles. However, evidence from countries with vaccination programs indicates that these concerns may not outweigh the benefits of widespread chickenpox prevention.

These areas experience annual outbreaks, especially among children, since most people contract the virus naturally at a young age, but some cases still occur in adults, where the illness tends to be more severe.

The in-silico studies of the antiviral activities of phytochemicals in Berberis vulgaris (Figure 1) (commonly known as barberry) against receptors of chickenpox (caused by the varicella-zoster virus) is a promising research area that definitely deserves attention for several key reasons such as growing interest in natural antiviral especially due to the emergence of drug-resistant pathogens, natural products are an attractive source for drug discovery. Research [2] on the antiviral activities of phytochemicals in Berberis vulgaris (barberry) has grown steadily, primarily focusing on berberine, a key bioactive compound in the plant. Studies have demonstrated its broad antiviral potential, including against viruses like HIV, influenza, and possibly varicella-zoster (chickenpox). Despite these promising results, research gaps remain in understanding the full spectrum of Berberis vulgaris' antiviral potential, especially its efficacy against VZV using insilico method.

Figure 1: Berberis vulgaris

Despite these promising results, research gaps remain in understanding the full spectrum of Berberis vulgaris' antiviral potential, especially its efficacy against VZV and the synergistic effects of combining berberine with

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other phytochemicals in the plant, the purpose of this study is therefore to investigate the efficiency of the phytochemicals in Berberis vulgaris, its therapeutic efficacy against chickenpox, related viral infections using in-silico method and to contribute to the development of safer, affordable and accessible treatment for chickenpox.

The effects of crude aqueous extract of barberry on rat arterial blood pressure and the contractile responses of isolated rat aortic rings and mesenteric bed to phenylephrine were investigated [3]. The effect of the extract on potassium currents recorded from cells in parabrachial nucleus and cerebellum rejoins of rat brain was also examined.The data obtained support the hypothesis that the aqueous extract of barberry has beneficial effects on both cardiovascular and neural system suggesting a potential use for treatment of hypertension, tachycardia and some neuronal disorders, such as epilepsy and convulsion.

Phytochemical investigation of the fruits of Berberis vulgaris Linn [4] in the isolation and structure elucidation of four compounds showed that. The terpenoids lupeol (1) and oleanolic acid (2) and the steroids stigmasterol (3) and stigmasterol glucoside (4) are isolated for the first time from this plant and the structure and stereochemistry at various asymmetric centers were established by different spectroscopic techniques. [5] demonstrated that aqueous extract of B.vulgaris has higher antioxidant activities. [6] in their work, discovered that the phytochemicals have antioxidant activities and have potentials against hyperglycemia, hyperlipidemia anti-inflammatory effects 20%, [3,7,8] – antibacterial 16%,[9,10] – cholesterol regulation 12%,[11,12] – digestive disorders 12%, [13] – antidiabetic 9%,2 – cardiovascular disease 9%, [14] – anticancer 8%, [15,16] – mental disease 4%,17 – Alzheimer disease 4%,18 – osteoporosis 3%,18 – hypotensive properties 2%,19 – cerebral ischemia trauma 1%,[14]

The drugs are incorporated into the growing viral DNA chain by HSV DNA polymerase, it lacks a 3'hydroxyl (OH) group, which is necessary for the addition of further nucleotides. This results in chain termination, halting DNA synthesis and thus preventing viral replication.

Acyclovir (ACV) is an antiviral drug commonly used to treat infections caused by herpes simplex virus (HSV). Its inhibitory activity against HSV DNA synthesis is highly specific, largely due to its structural mimicry of guanosine, one of the nucleotides required for viral DNA synthesis. Here's a breakdown of the chemistry behind acyclovir’s inhibitory action:

Activation by Viral Thymidine Kinase, acyclovir, is initially inactive until it is selectively phosphorylated by HSV-specific thymidine kinase (TK), an enzyme that only HSV-infected cells produce at high levels.

This enzyme phosphorylates acyclovir into acyclovir monophosphate (ACV-MP). Cellular enzymes further phosphorylate ACV-MP into acyclovir diphosphate (ACV-DP) and eventually into acyclovir triphosphate (ACV-TP), the active form of the drug. Once acyclovir is incorporated into the growing viral DNA chain by HSV DNA polymerase, it lacks a 3'-hydroxyl (OH) group, which is necessary for the addition of further nucleotides Because the acyclovir has a higher affinity for HSV DNA polymerase than for human DNA polymerase, it specifically inhibits viral replication. The combined effects of selective activation, competitive inhibition, and DNA chain termination make acyclovir effective, and this could be applicable the phytochemicals in berberine.

METHODOLOGY

Ligand preparation

The study focused on five (5) selected phytochemicals, including berberine which has been reported as most applies species and the main natural compounds responsible for diverse medicinal properties palmatine, quercetin, kaempferol, and caffeic acid, all known for their diverse pharmacological activities [18]. Using AutoDock Vina and PyMOL for docking and visualization, we evaluated the binding energies, hydrogen bonding interactions, and hydrophobic interactions between the selected compounds and the viral receptor.

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ChemDraw professional software [19] was used to draw the chemical structures of ligands and the drug compounds (Figure 2). The structures are saved in MDL.Mol (V2000) file format.

Receptor preparation

The crystal structure of protein (PDB ID: 4PAE) (Figure 3) was retrieved from the RCSB Protein Data Bank [20] in PDB format with an atomic resolution of 2.76Å; a highly acceptable standard in pharmaceutical companies in designing therapeutic compounds. Heteroatoms and water molecules were removed from the crystal structures to avoid unwanted side molecular interactions and ensure no molecular interference with the potential binding site of the target protein during the docking simulation using Biovia [21] then saved in PDB format for further analysis. Alpha Beta–chain (D chain) was used for the docking study.

Determination of active sites of the receptor (4PAE) was determined using Computed Atlas for Surface Topography of Proteins (CASTp) [14] and Biovia Discovery Studio [21] were used in validating the binding pocket, ligand interactions, and all amino acids in the active site [22]

Molecular docking simulation AutoDock Vina, PyRx virtual screening software, Vina Wizard and open Babel [23] were used for docking studies. The docking output expressed in binding affinity/energy (kcal/mol) [24] shows the interaction energy between the protein and the ligands or drug compounds, and the inhibition constant (Ki) in micromolar (µM) was shown in Table 1. The energy of ligands was minimized to have a more stable configuration using molecular mechanic force field (MMFF) in spartan software. The pose/conformation with the lowest energy and the most stable cluster was considered for further analysis and visualization using Biovia Discovery Studio [21] and PyMol [25] to visualize the molecular interaction. Moreover, the protein was also docked with the first-line drugs commonly used against varicella-zoster virus. The interaction analyses of these drug compounds were used as a control for the study to compare the result of the interaction of protein and phytochemicals. To provide enough space for free movements of the ligands, blind docking was performed where the grid box was constructed to cover the entire receptor. The grid points for the selected phytochemicals in the grid center of (x, y, z) X = 85.84, Y= 16.36, Z= 65.74 with spacing of 1Å, grid points of - X=86, Y = 104, Z = 104 After the docking simulation was carried out, equations 1 and 2 were used to calculate the inhibition constants and inhibitory efficiencies of the docked ligands and drug compounds. The inhibition constant indicates how potent an inhibitor is; it is the concentration required to produce half maximum inhibition. Biovia discovery studio [21] and PyMol [25] were used to visualize and analyze the docking outputs. (1) Where R = Gas constant

(1.987 × 10–3 kcal mol 1K-1); T=298.15 K (absolute temperature); K_i=Inhibition constant; ΔG_{bind}= Binding energy. NOTE: AutoDock used binding energy to calculate inhibition constant. The binding energy is the free energy change for the protein inhibition interaction ΔG is used to calculate the constant inhibition ki, (Equation 1), which is the dissociation constant (k_d).

The canonical SMILES (simplified molecular input line entry system) strings of the five identified phythochemicals and two synthetic drugs, were procured from PubChem (https//pubchem.ncbi.nlm.nih.gov/compound). They were then incorporated into SwissADME tool and AdmetSARonlineserver (http://lmmd.ecust.edu.cn:8000/)[26] admetSAR 2.0 (http://lmmd.ecust.edu.cn/admetsar2/

The physicochemical characters of the compounds such as molecular weight (MV), number of hydrogen bond acceptors (nHBA), number of hydrogen bond donors (nHBD) and number of rotational bonds (nRB) were then predicted. The ADME parameters that include octanol-water partition coefficient lipophilicity (cLogP), solubility, gastrointestinal absorption (GIA), blood brain barrier (BBB), p-glycoprotein (P-gp) substrate, inhibition of isoforms of cytochrome P450 (CYP), and skin permeability (LogKp) were estimated by SwissADME.22. Lipinski's rule of five was applied to assess the drug-likeness of the compounds. The rule states that the drug-like compounds ought to have; MV ≤ 500 daltons, nHBA ≤ 10, nHBD ≤ 5 and clogP ≤ 5.

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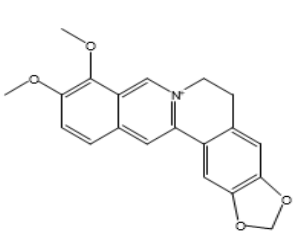
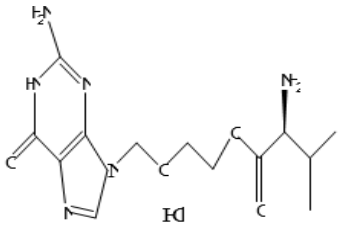
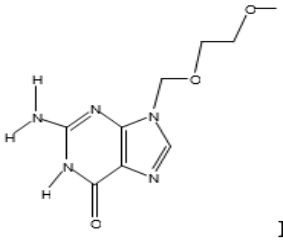
Results and Discussion Molecular Docking analysis







H Berberine Acyclovir Valacyclovir

Figure 2: Structure of the phytochemical and two standard drugs

The binding affinities and the inhibition constant of the docked 5 ligands and 2 standard drugs used against 4PAE are shown in Table 1. The results obtained showed that Berberine compares favorably well the standard drug with a binding affinity of -7.4 kcalmol^{-1} and inhibition constant of 3.78 μM for both berberine and acyclovir while with valacyclovir is -6.0 kcalmol^{-1} binding affinity with inhibition constant 40.15 μM with complementing values for the remaining

RESULTS

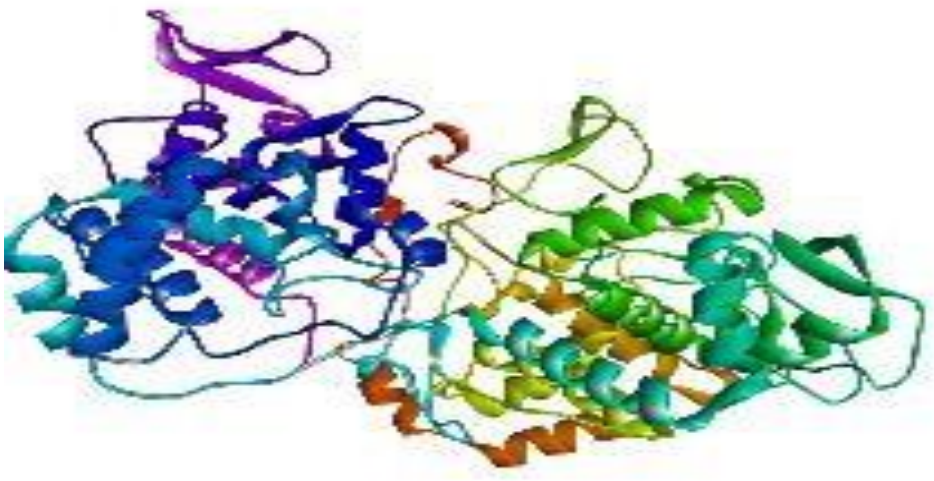


Figure 3: The crystal structure of the varicella-zoster virus (VZV), 4PAE

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Table 1: The ligands, two therapeutic drugs, their binding affinity and Inhibition Constant against 4PAE

S/N	Ligands	Pubchemcid	Binding affinity (kcalmol^{-1})	Inhibition Constant (μm)
1.	Berberine	2353	-7.4	3.78
2.	Caffeic Acid	68904	-7.1	6.28
3.	Kaemferol	5280863	-9.8	0.07
4.	Palmatine	19009	-7.2	5.30
5.	Quercetin	5280343	-9.9	0.06
6.	Acyclovir	135398513	-7.4	3.78
7.	Valacyclovir	135398742	-6.0	40.15

Table 1 reveals docking analysis of varicella-zoster virus (VZV), 4PAE (Figure 3) with some selected compounds with their binding free energy, inhibition constant. Some of the selected inhibitors considered in this investigation such as berberine, caffeic acid, kamferol, palmatine, quercetin showed binding energy of -7.4 kcalmol^{-1}, -7.1 kcalmol^{-1}, -9.8 kcalmol^{-1}, -7.2 kcalmol^{-1} and -9.9 kcalmol^{-1}, respectively compared favorably well with acyclovir (-7.4 kcalmol^{-1}) and valacyclovir (-6.0 kcalmol^{-1}) which was considered as standard drugs (Table I). The inhibition constant (K_i) of the interaction between berberine and acyclovir compares favorably well (Figure 4). The ligands formed extensive hydrogen bonds and hydrophobic/electrostatic interactions (Table 2) with the active site residues of 4PAE proteins. Quercetin formed hydrogen bonds with active residues such as GLY 107, SER 476, and ARG 174, creating a highly stable complex.

Kaemferol exhibited interactions with residues like ARG 91 and THR 259, reinforcing its strong binding. By contrast, the standard therapeutic drugs employed for this experiment, Acyclovir and Valacyclovir, interacted with fewer residues and displayed less robust bonding. For example, Acyclovir primarily engaged residues like THR 111 and ASP 183, while Valacyclovir showed minimal interaction with residues like ASN 475 and LYS 478. The ligands, particularly Quercetin and Kaemferol, demonstrated superior binding affinities indicative of strong inhibitory potential while their lower inhibition constants reflect higher efficacy at minimal concentrations compared to standard drugs which results to their extensive residue interaction which is suggesting enhanced stability of ligand-protein complexes. These properties and results highlight their potential as effective alternatives or supplements to existing chickenpox treatments, warranting further investigation.

Table 2: Showing Hydrogen bonding and electrostatic/Hydrophobic interaction between the ligands and the protein with their bond length **(Å)**

S/N	LIGANDS	4PAE Receptor amino acids forming H bond with ligands (H-Bond Distance, Å), Electrostatic/ Hydrophobic Interactions and inhibition constant of the Ligands and selected standard drugs
1.	Berberine	PRO 212 (4.61), ARG 474 (2.26), ILE 571(5.41), HIS 572 (5.10)
2.	Caffeic Acid	GLN 37 (2.28), HIS 38 (3.52), ARG 106 (5.22), GLY 107 (2.65,2.96), GLU 181 (3.79), ASP 183 (2.50), SER 476 (2.67), GLN 596 (2.98)
3.	Kaemferol	ARG 91 (4.11), TRP 94 (3.59, 3.99,4.10,4.70), THR 259 (3.99), GLY 262 (3.78), HIS 263 (2.84,5.16)
4.	Palmatine	PRO 212 (5.20), ASP 585 (5.50), ASP 593 (3.82)
5.	Quercetin	GLY 107 (1.76, 2.70), THR 111(3.59), ARG 174 (3.73, 5.31), ARG 419 (1.17),SER 476 (3.63), LYS 478 (4.75, 5.33)
6.	Acyclovir	GLN 37 (2.75), THR 111, GLU 181 (2.77), ASP 183 (3.32,2.10),ASN 475 (2.48, 2.63)
7.	Valacyclovir	ASP 183 (1.95), ASN 475(2.63) LYS 478 (2.26, 2.32)

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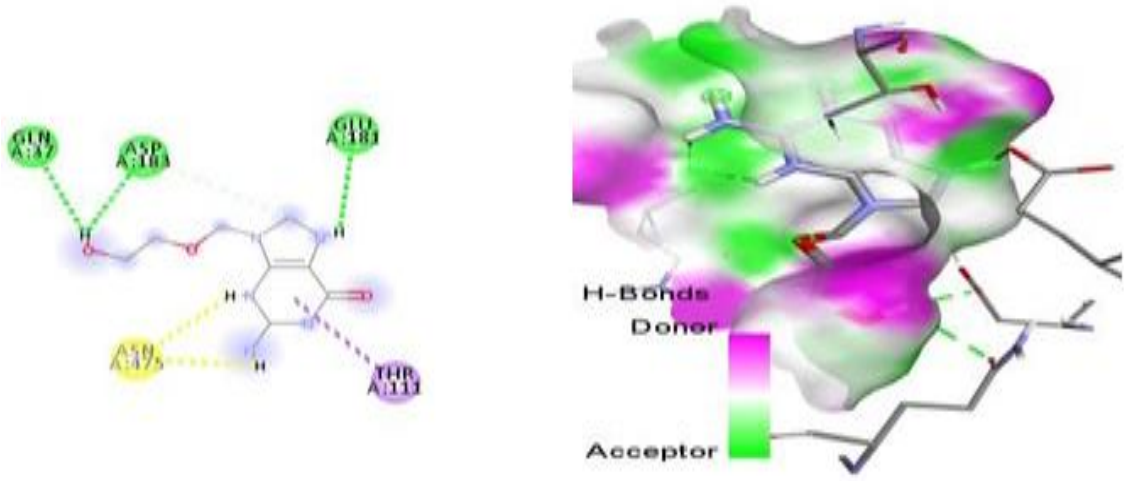
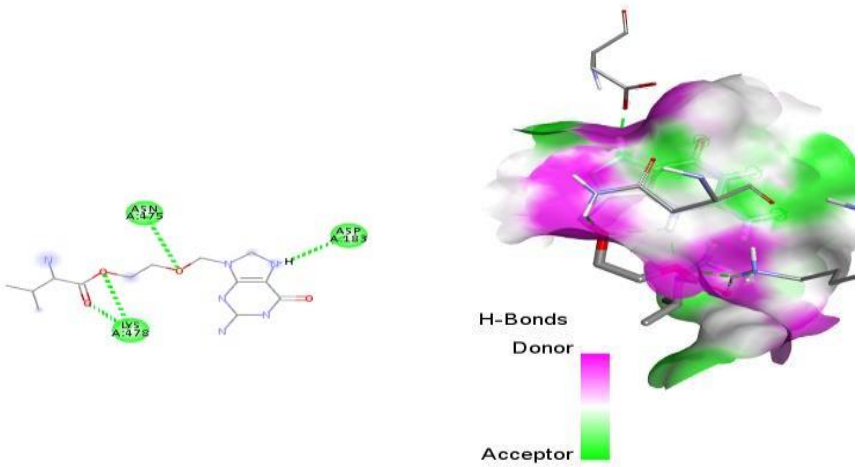
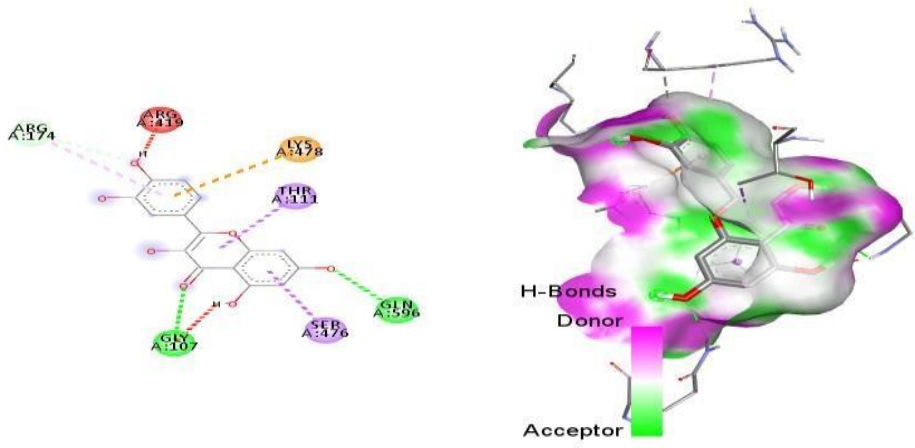
Acyclovir + 4PAE



Valacyclovir + 4PAE



3. Quercetin + 4PAE



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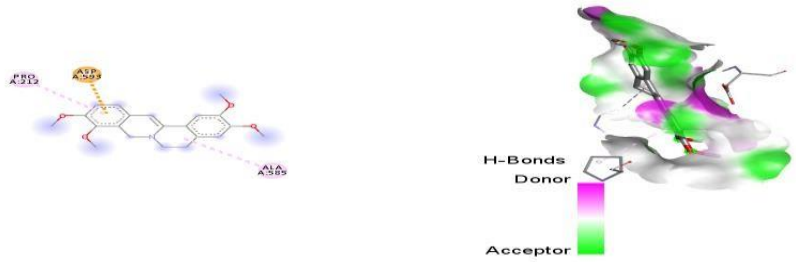
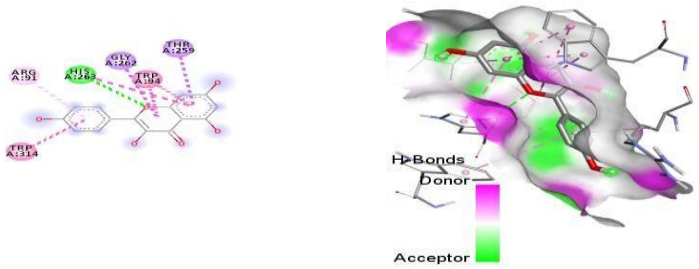
4. Palmatine + 4PAE

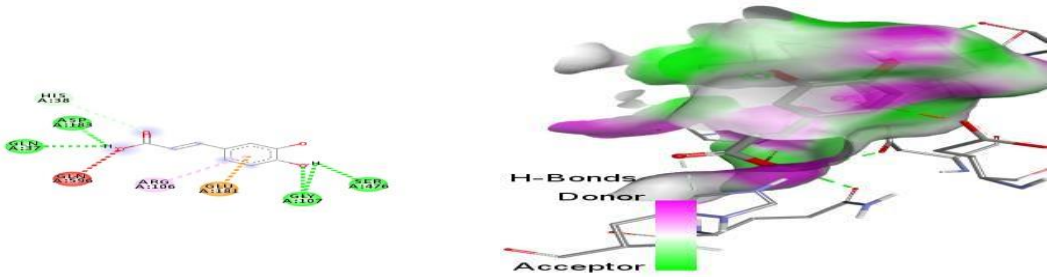


5. Kaemferol + 4PAE



6.

6. Caffeic acid + 4PAE



7. Berberin + 4PAE

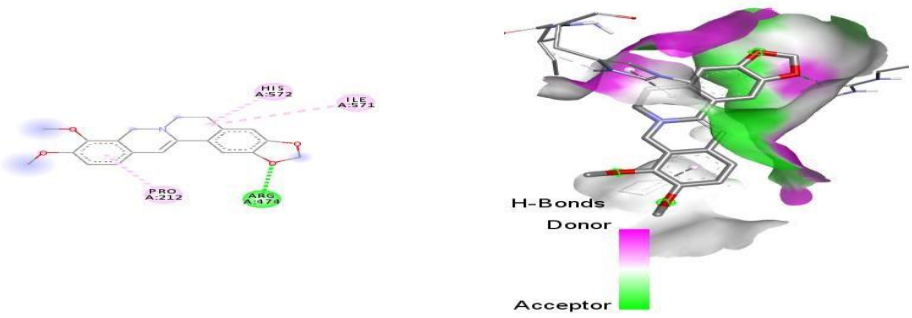


Figure 4: Interaction of Proteins with Ligands

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Table 3: Physicochemical Pararmeters7/15/2025

Parameters	Acyclovir		Valacyclovir		Berberine	
Molecular Weight	225.21	17.06%	324.34	29.67%	336.37	31.20%
nAtom	16	17.85%	23	30.35%	25	33.92%
nHet	8	38.88%	10	50%	5	22.22%
nRing	2	28.57%	2	28.57%	5	71.42%
nRot	4	19.04%	7	33.33%	2	9.52%
HBA	7	43.75%	9	56.25%	4	25%
HBD	3	33.33%	3	33.33%	0	0%
TPSA	119.05	43.54%	151.14	55.28%	40.8	14.92%
SlogP	-1.33	10.04%	-0.8	15.07%	3.1	51.70%
Application	Warning	50%	Warning	50%	Warning	50%

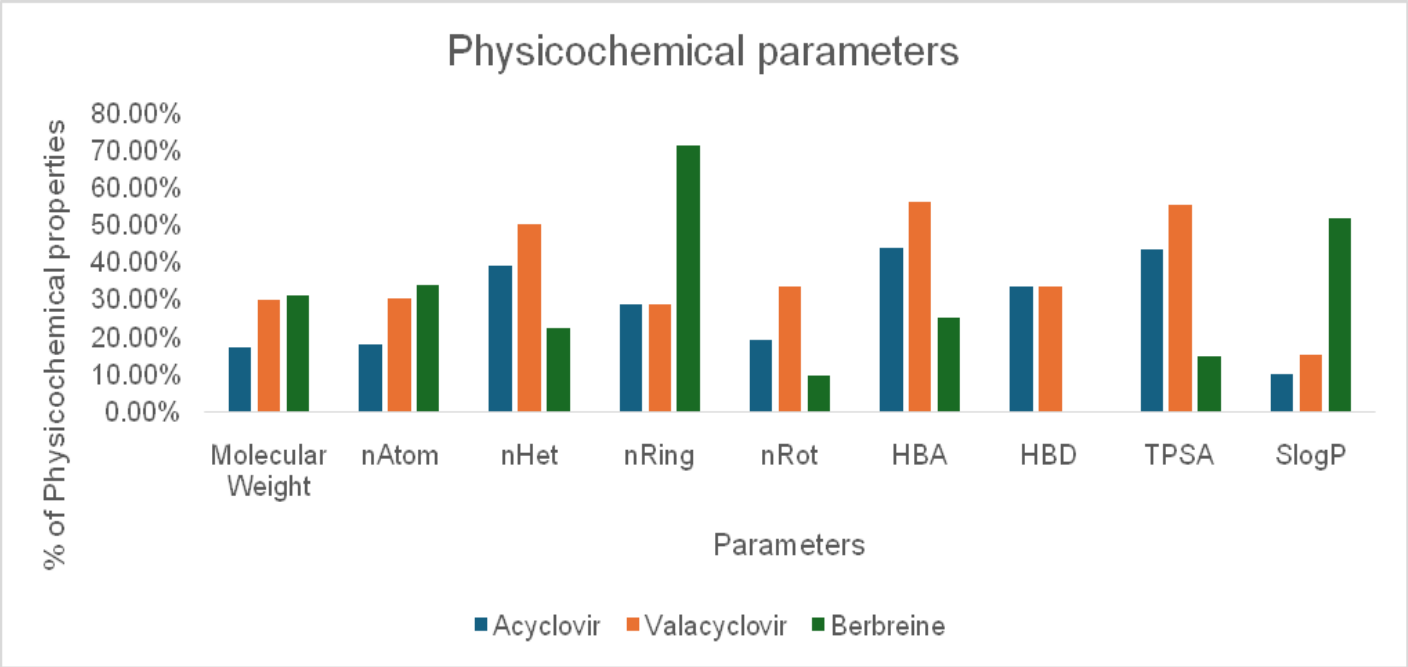

Figure 5: Chart showing Physicochemical parameters

Molecular weight (Table 3) indicates the mass as well as the size, volume, and density. The molecular weight of a drug depends on what kind of and how many elements are present in its structure; lower molecular weight is better for bioavailability. Molecular weight of berberine (31.20%) is higher compared with acyclovir (17.06%) and valacyclovir (29.67%). Although Berberine is higher it still falls within the range of standard molecular weight between 201 to 600 [27]. This implied that all the identified compounds with MW ≤ 500 have potential to be easily absorbed, diffused and transported in line with findings [28].

HBDs and HBAs present in drug structures are known to play an important role in water solubility, membrane transport, distribution, and biological targets or drug-receptor interactions [27, 28]. HBDs were counted by considering hydrogen atoms connected directly to oxygen and/or nitrogen atoms in their structures. As shown in Figure 5 hydrogen bond acceptor (25%) which is the measure drug-receptor interactions via hydrogen acceptors is lower in berberine compared with the two synthetic drugs acyclovir (43.57%) and valacyclovir (56.25%). and hydrogen bond donor is zero in berberine indicating that there is no hydrogen atoms connected directly to oxygen and nitrogen atoms in the molecule as evident in the structure.

Number of atoms are known to contribute to the polarity and dipole moment of the overall molecular structure [29]. zero to six nitrogen atoms [27] are necessary for the drugs to possess a satisfactory bioavailability and the optimum number of drug-receptor interactions via hydrogen acceptors and/ or donors, Figure 5 indicates that number of atoms in berberine, 25 (33.92%), is higher compare with acyclovir 16 (17.85% and valacyclovir 23 (30.35%). Aromatic rings play an important role in contributing to hydrophobicity by exhibiting Van der Waals

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forces of attractions or pi- stackings with target receptors [30]. Aromatic rings were counted manually. Cyclic and conjugated rings are considered aromatic if the pi- bond system follows the Huckel rule. The Huckel rule of aromaticity (4n + 2 = pi- electrons, where the value of n should be an integer) was followed as a criterion to identify the aromatic rings present in the structures. It should be noted that the number of rings (Figure 5) in berberine 5 (71.42%) is higher, an indication of higher hydrophobicity compares with 2 (28.57%) for acyclovir and valacyclovir but lower heteroatoms 5(22.22%), compared with acyclovir 8 (38.88%) and valacyclovir 10 (50%) respectively. According to [27], with many aromatic rings, the hydrophilicity is reduced, because of which the water solubility is decreased, leading to poor drug distribution in the body.

Topological polar surface area (TPSA) is related to membrane permeability and oral bioavailability. The TPSA indicates the surface area required to bind with most of the target receptors, and it was calculated by the methodology developed by [31] as the sum of fragment contributions. The TPSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, permeability, and blood-brain barrier penetration. Figure 5 indicates that beberine 40.8 (14.92%) has lower membrane permeability and oral bioavailability, blood-brain barrier penetration compares with synthetic drugs acyclovir 119.05 (43.54%) and valacyclovir 151.14 (55.28%).

Drug-receptor interactions are associated with the conformational distortions of both the drug and the receptor complementing one another. Conformational distortions in turn depend on the presence of rotatable bonds in drug structures. Rotatable bonds are defined as any single bond (not in a ring) bound to a nonterminal heavy (i.e., nonhydrogen) atom. Figure 5 and Table 3 shows that berberine 2 (9.52%) has the lowest rotatable bonds, evidence that interaction occurs between the drugs and the receptor which resulted into conformation disorder. However, Ro5 states that the drug-like compounds ought to have nHBA $\leq$ 10 and nHBD $\leq$ 5. The nHBA and nHBD for all tested compounds were found to be within Lipinski's limit. This implies that the compounds can be well absorbed or permeable from the gastrointestinal tract when they are administered [32].

Medicinal Chemistry

Table 4**:** Medicinal Chemistry

Parameter	**Acyclovir**		**Valacyclovir**		**Berberine**	
QED	0.55	57.61%	0.44	44.28%	0.67	71.9%
Lipinski Rule	Accept	100%	Accept	100%	Accept	100%
Pfizer Rule	Accept	100%	Accept	100%	Not Accept	0%
GSK Rule	Accept	100%	Accept	100%	Accept	100%

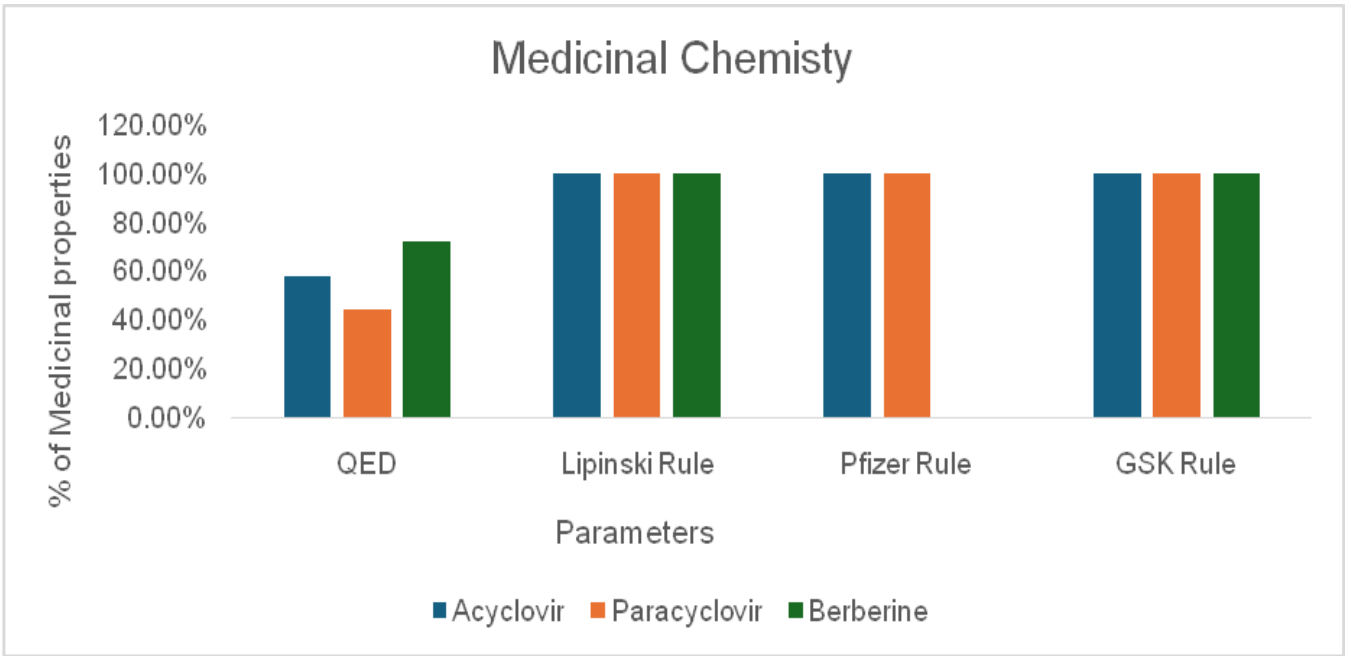

Figure 6: Chart of Medicinal Chemistry

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Considering the Quantitative Estimate of Drug-likeness (QED) (Table 4) score, the value ranges from 0 to 1 with higher values closer to 1 indicating better druglikness in medicinal chemistry. The parameter is a metric used to evaluate how "drug-like" a compound is. Developed to integrate multiple molecular properties, QED combines factors like molecular weight, lipophilicity (logP), number of hydrogen bond donors and acceptors, polar surface area, and rotatable bonds, among others, to give a single score, where a score closer to 1 indicates a higher likelihood that the compound has desirable drug-like properties. Figure 6 shows that beberine 0.67 (71.9%) has better druglikness compared with acyclovir 0.55(57.61%) and valacyclovir 0.44 (44.28%). QED is valuable in drug discovery for ranking and prioritizing compounds, especially in high-throughput screening processes, by providing a more nuanced, quantitative assessment of how a molecule aligns with known characteristics of successful drugs. Result showed that berberine compares favourably well with the two synthetic drugs as obeying Lipinski and GSK rule is on the same level. It is worth noting here that Berberine did not obey Pfizer rule as shown in Table 4 and Figure 6 as 'Not Accept' (0%).

Table 5: Absorption

Parameters	Acyclocir		Valacyclovir		Berberine	
logS	-1.15	77.30%	-2.31	65.24%	-3.53	52.63%
logP	-1.49	5.78%	-1.13	9.66%	2.04	43.73%
pKa	6.96	57.12%	7.17	58.60%	9.33	73.85%
Acidic pKa	9.65	67.14%	7.04	48.28%	9.32	64.81%
Basic pKa	4.71	49.27%	6.32	60.65%	1	67.23%
Caco-2	0	7.09%	0	7.40%	-3.96	89.50%
Caco-2	-5.87	47.55%	-5.7	52.59%	1	100%
HIA	1	76.80%	1	85.20%	1	96.60%
MDCK	1	55.90%	0	47.10%	0	60.80%
F50%	1	56.99%	1	72.20%	1	32.80%
F30%	1	69.90%	1	85.50%	1	60.20%
F20%	1	81.69%	1	91%	1	68.99%

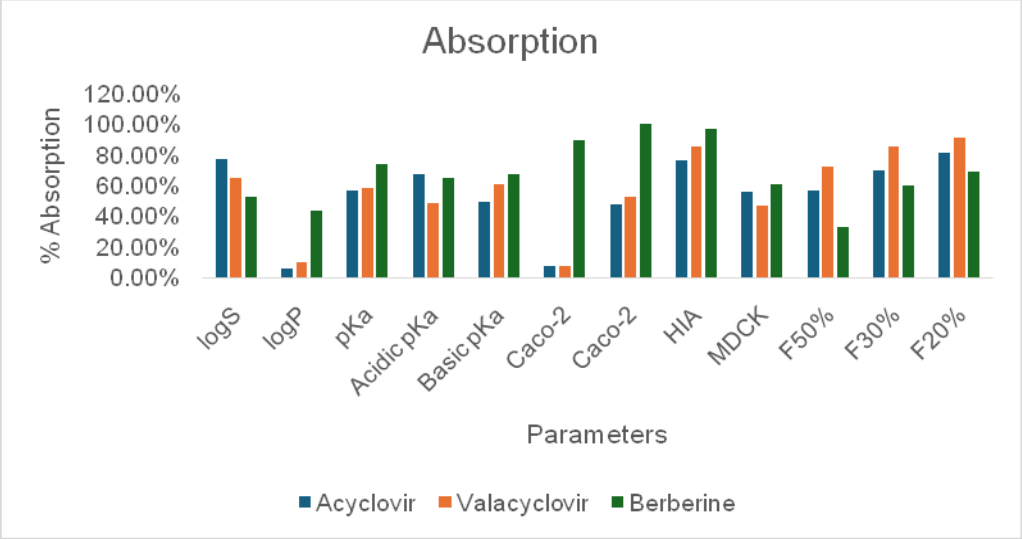

Figure 7: Chart showing Absorption

Lipophilicity (logP) (Table 5) is important for permeability and absorption. Most orally bioavailable drugs are absorbed via the intestine. Caco-2, Human colon carcinoma cells are cultured to measure active efflux ('Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals') of drugs that are pumped back into the lumen after being absorbed in the intestine [33]. An important transporter involved in this mechanism is P-gp [33], which is assayed by measuring active efflux of drugs like verapamil or cyclosporin. MDCK (Madine Darby Canine Kidney): This cell line is also used to measure drug efflux ('Testing of Carcinogenicity of Pharmaceuticals'). They are used in conjunction with Caco-2 because they can become confluent quickly ('Testing of Carcinogenicity of Pharmaceuticals'). This assay can be performed by either using wildtype

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MDCK cells or cells which have been transfected to express the MDR1 gene. The chart (Figure 7) shows that berberine compares favourably well with the two-line drugs acyclovir and valacyclovir.

Table 6: Distribution

Parameters	Acyclovir		Valacyclovir		Berberine	
BBB	1	80%	1	71.90%	1	95.90%
OATP1B1inhibitor	1	99.20%	1	98.20%	1	95.90%
OATP1B3 inhibitor	1	99.50%	1	99.30%	1	95.60%
OATP2B1 inhibitor	0	6.10%	0	6.90%	0	16.10%
OCT 1 inhibitor	0	5.80%	0	6.10%	1	63.20%
OCT 2 inhibitor	0	4.70%	0	8.50%	0	33.60%
BCRP inhibitor	0	2.50%	0	2.40%	1	66.40%
BSEP inhibitor	0	2.10%	0	3.90%	1	91.80%
MATE 1 inhibitor	0	3.70%	0	4%	0	25.80%
Pgp inhibitor	0	0.50%	0	1.60%	1	82.20%
Pgp substrate	0	12.90%	0	20.90%	1	63.70%
PPB	0	0%	0	23.10%	1	71.40%
VDss	-0.15	34.38%	-0.05	38.26%	-0.12	35.88%

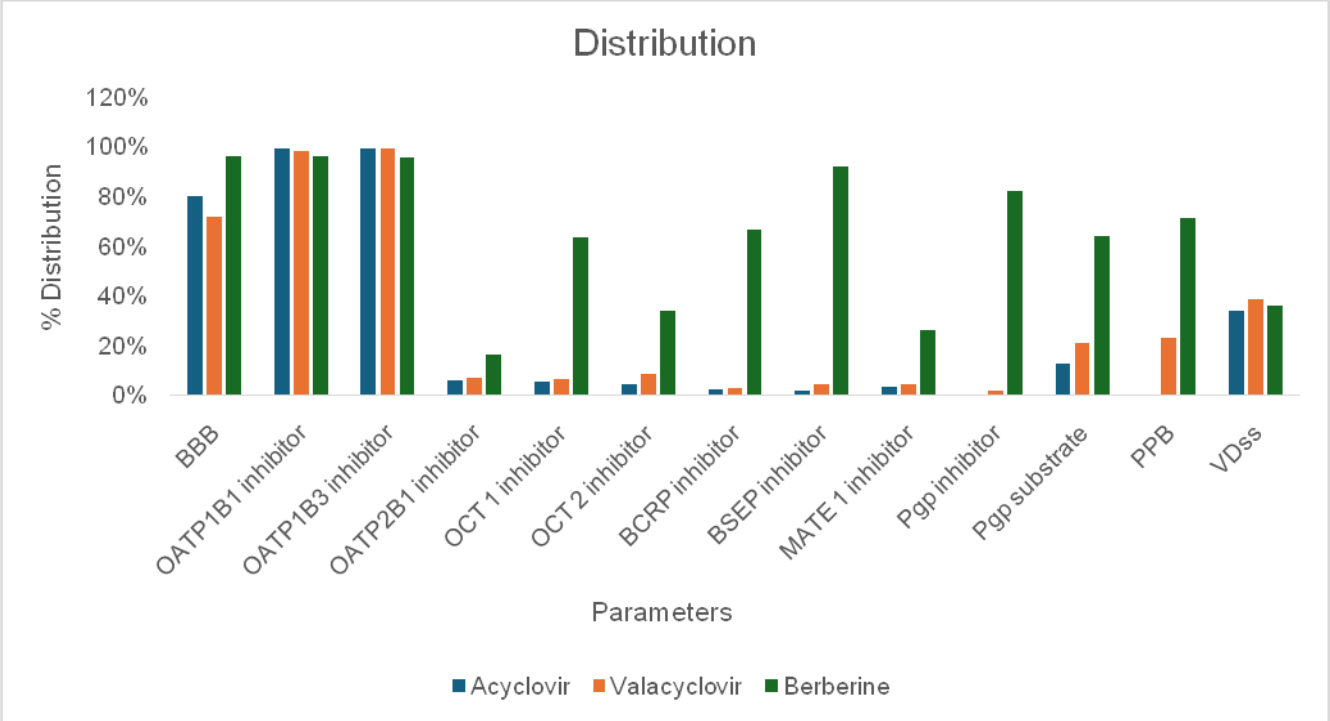

Figure 8: Chart showing Distribution

The ability of a compound to cross the blood-brain barrier, on the other hand, is determined by Blood-Brain Barrier (BBB) permeability index. Compounds with a BBB value greater than or equal to 0.3 can cross the BBB and potentially cause CNS toxicity [34]. From the results obtained, all the three compounds considered were able to cross the blood-brain barrier with berberine having the highest percentage 95% compare with acyclovir 80% and valacyclovir 71.90%. P-glycoprotein (Pgp) is an essential cell membrane protein that extracts many foreign substances from the cell. Cancer cells often overexpress Pgp, which increases the efflux of chemotherapeutic agents from the cell and prevents treatment by reducing effective intracellular concentrations of such agents - a phenomenon known as MDR. For this reason, identifying compounds that can either be transported out of the cell by Pgp (substrates) or impair Pgp function (inhibitors) is of great interest [35]. As observed in the result Table 6 and obvious in the plot showing distribution (Figure 8 Berberine has higher value (82.20%, 63.70%) as Pgp substrate and inhibitor compared to the standard drugs acyclovir (0.50%, 1.60%) and valacyclovir (12.90%, 20.90%) for Pgp inhibitor and substrate respectively.

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Table 7: Metabolism

Parameters	Acyclovir		Valacylovir		Berberine	
CYP1A2 inhibitor	0	5.09%	0	10%	1	58.80%
CYP3A4 inhibitor	0	2.10%	0	3.20%	0	22.40%
CYP2B6 inhibitor	0	3.80%	0	2.70%	0	49.40%
CYP2C9 inhibitor	0	1.40%	0	4%	0	27.50%
CYP2C19 inhibitor	0	1%	0	2.90%	1	55.80%
CYP2D6 inhibitor	0	0.20%	0	0.70%	0	28.70%
CYP1A2 substrate	0	2.70%	0	3.30%	1	90.10%
CYP3A4 substrate	0	1.60%	0	3.30%	1	93.70%
CYP2B6 substrate	0	4.40%	0	3.50%	1	62.70%
CYP2C9 substrate	0	1.40%	0	2.70%	1	71.80%
CYP2C19 substrate	0	2.10%	0	2.90%	1	85.50%
CYP2D6 substrate	0	1%	0	1.40%	1	81%
HLM	0	2.40%	0	2%	0	42.50%
RLM	0	3.80%	0	6%	0	44.20%
UGT substrate	1	84.40%	1	89%	0	22.90%

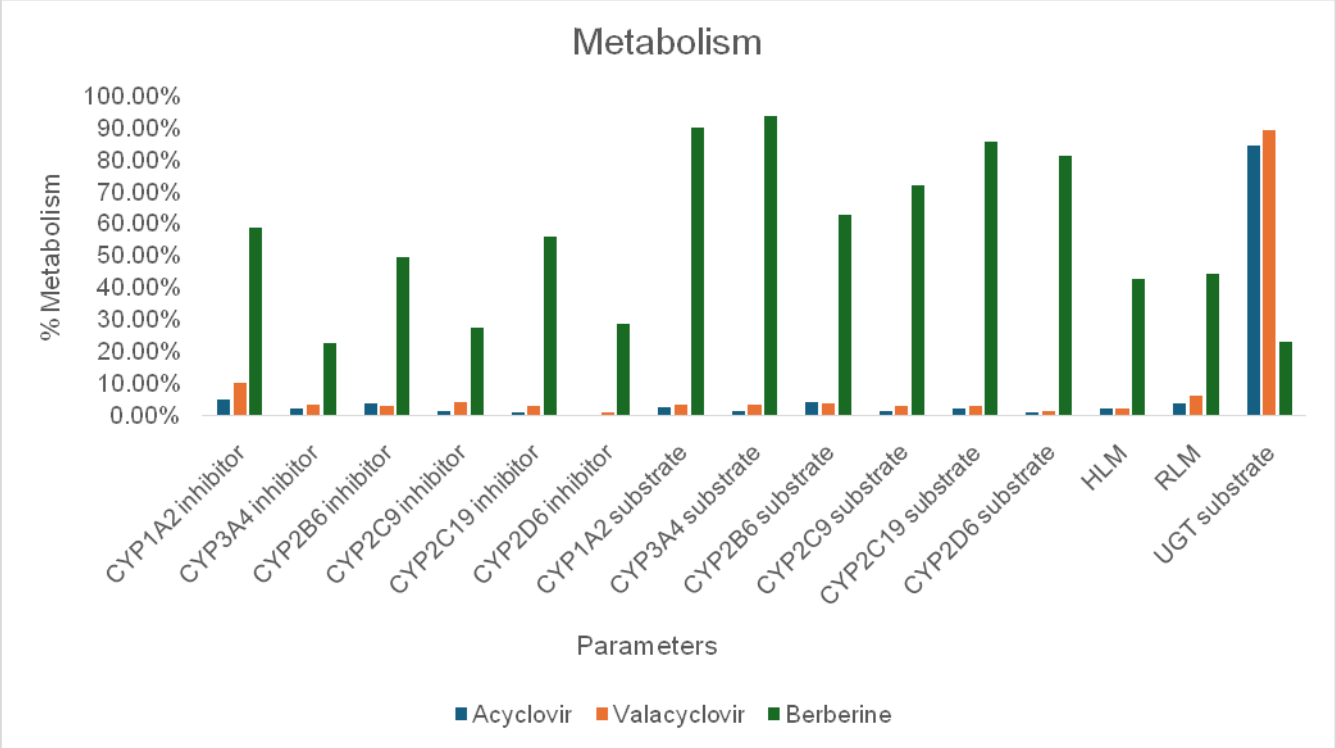

Figure 9: Chart showing metabolism

It is important to understand how the body will metabolize a drug, and how quickly those changes will occur. Metabolism prediction of lead compounds is one of the main priorities during drug discovery process. The metabolism predictions of the compounds were done (Table 7) against five isoforms of cytochrome P450 (CYP) monooxygenase family namely, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP2B6 and CYP3A4 and the results are displayed in Table 6. The three compounds showed not to inhibit CYP3A4, CYP2B6, CYP2C9 and CYP2D6 with barberine showing very high percentage (Figure 9) inhibition and showing inhibition against CYP2D6 (58.80%) and CYP2C19 (55.80%) of the cytochrome P450 (CYP). Cytochrome P450 monooxygenase plays a pivotal part in drug metabolization and elimination in biological systems. The non-inhibition action that is at zero of the identified compounds against these enzymes implies that the compounds have high probabilities of been transformed and consequently be bioavailable upon oral administration as also reported by [36]. Metabolites of a drug can be toxic, can have new efficacy properties, and/or can interact alter the metabolism of other coadministered drugs. The adverse effects of a drug may arise from its breakdown into

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toxic metabolites or can be associated to its interactions with other drugs already being administered to the patient. To assess its safety profile and pharmacokinetics, in vitro metabolism studies are required. Drug metabolism is facilitated by phase I oxidation by cytochrome P450 mono-oxygenases and phase II conjugation by UDP-dependent glucoronosyl transferase (UGT) and phenol sulfotransferase (PST) [33].

Table 8: Excretion

Parameters	Acyclovir		Valacyclovir		Berberine	
CLp	0	36.90%	0	40.89	1	80.60%
CLr	1	74.40%	1	71%	1	52.70%
T1/2	-0.42	59.67%	-0.34	62.30%	0.05	74.67%
MRT	-0.4	57.77%	-0.34	59.79%	0.07	71.75%

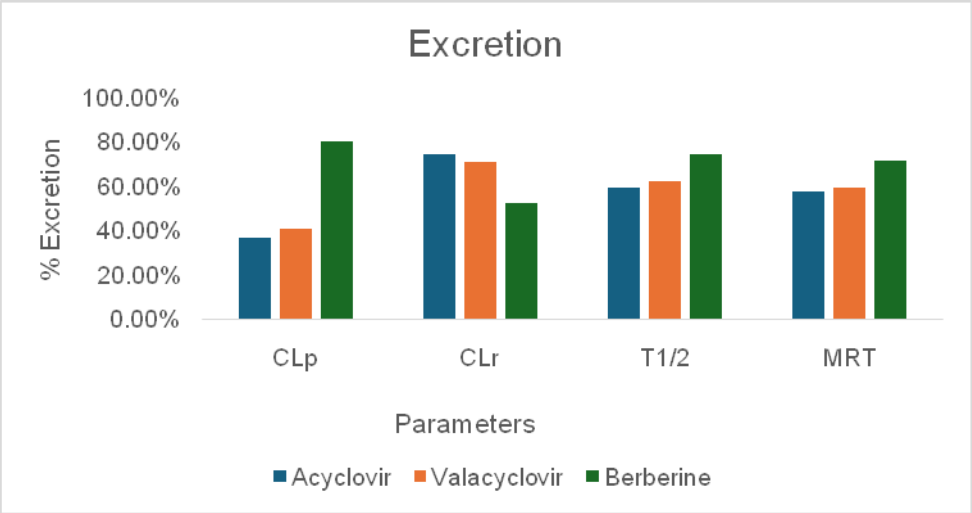

Figure 10: Chart showing Excretion

CLp which is plasma clearance that is a measure of the body's efficiency in eliminating a drug through all routes for Berberine is higher com pare with the other two drugs implicating that the volume of plasma from which the drug is completely remove per unit time is higher in berberine (80.60%) Table 8. On the other hand CLr (renal clearance) the volume of the drug cleared of the drug by the kidneys per unit time is lower compared to the two drugs (52.70%), this indicate that the amount of drugs excreted unchanged in urine is lower in berberine. The T1/2, the time taken by plasma concentration of drugs to decrease by half which is related to clearance of drugs and the volume is also higher in berberine (74.67%) and lastly the mean residence time that is the average time a drug stays in the body shows that berbeine stays a little longer (Figure 10) in the body than acyclovir and valacylovir.

Human Health Toxicity

Table 9: Organ Toxicity

Parameters	Acyclovir		Valacyclovir		Berberine	
Neurotoxicity	-2.8%	31.12%	-2.77%	32.29%	-2.07%	64.09%
DILI	1	55.10%	1	79%	1	60.10%
hERG 1uM	0	0.80%	0	0.40%	0	43.10%
hERG 10uM	0	9.40%	0	9.60%	1	95.10%
hERG 30uM	0	33.90%	0	41.90%	1	99%
hERG 1-10uM	0	0.80%	0	0.40%	1	82.10%
hERG 10-30uM	0	13.50%	0	16.10%	1	99.10%
Respiratory toxicity	1	52%	1	88.60%	1	59.60%
Nephrotoxicity	1	54%	1	52.70%	0	27.90%
Eye corrosion	0	4.10%	0	0.70%	0	1.10%

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Eye irritation	1	63.40%	0	14.90%	0	6.40%
Skin corrosion	0	1.60%	0	0.90%	0	3.20%
Skin irritation	0	17.10%	0	15.80%	0	15.00%
Skin Sensitization	0	4.7%	0	7.20%	0	5.70%
Acute dermal toxicity	1	61.20%	1	50.80%	1	67.70%
Neurotoxicity	-2.8	31.12%	-2.77	32.29%	-2.07	64.09%

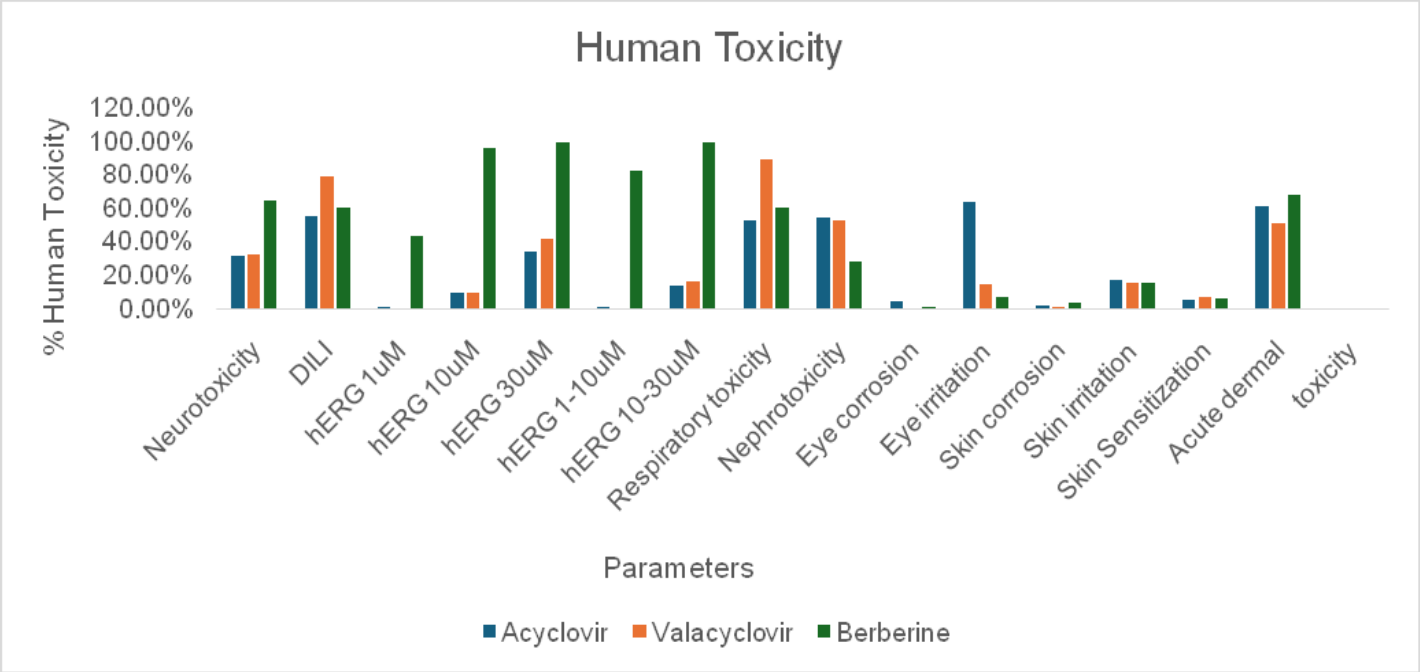

Figure 11: chart showing Human toxicity level

The human ether-à-go-go-related gene (hERG- cardiotoxicity) codes for a potassium ion channel involved in the normal cardiac repolarization activity of the heart. Drug induced blockade of hERG function can cause long QT syndrome, which may result in arrhythmia and death [35]. Of the three compounds considered, berberine (Table 9) has higher values for hERG at 1uM, 30uM and 10-30uM as shown in Figure 11.

Table 10: Toxicity Endpoint

Parameters	**Acyclovir**		**Valacyclovir**		**Berberine**	
Ames mutagenesis	0	36.30%	0	45,9%	1	67.90%
Mouse carcinogenicity	0	44.90%	1	62.30%	0	41.90%
Mouse carcinogenicity	-0.17	31.83%	1.02	53.52%	1.35	59.52%
Rat carcinogenicity	0	38.80%	1	52.60%	1	55.10%
Rat carcinogenicity	0.4	30.13%	1.15	41.24%	2.66	63.57%
Rodents carcinogenicity	1	50.80%	1	65.60%	1	51.70%
Micronucleus	1	77.50%	1	75.0%	1	82.20%
Reproductive toxicity	1	77%	1	83.80%	1	95.50%
Mitochondrial toxicity	0	33.20%	0	16.80%	0	32.20%
Hemolytic	0	28.59%	0	26.50%	0	7%
Repeated dose toxicity	0	36%	0	29.40%	1	84.20%
Acute oral toxicity	0	8.20%	0	3.60%	1	90.90%
Acute oral toxicity	-3.67	16.09%	-3.73	14.56%	-2.28	51.47%
FDAMDD	0	9.90%	0	8.10%	1	95.80%
FDAMDD	1.11	22.64%	0.88	18.44%	3.31	61.42%

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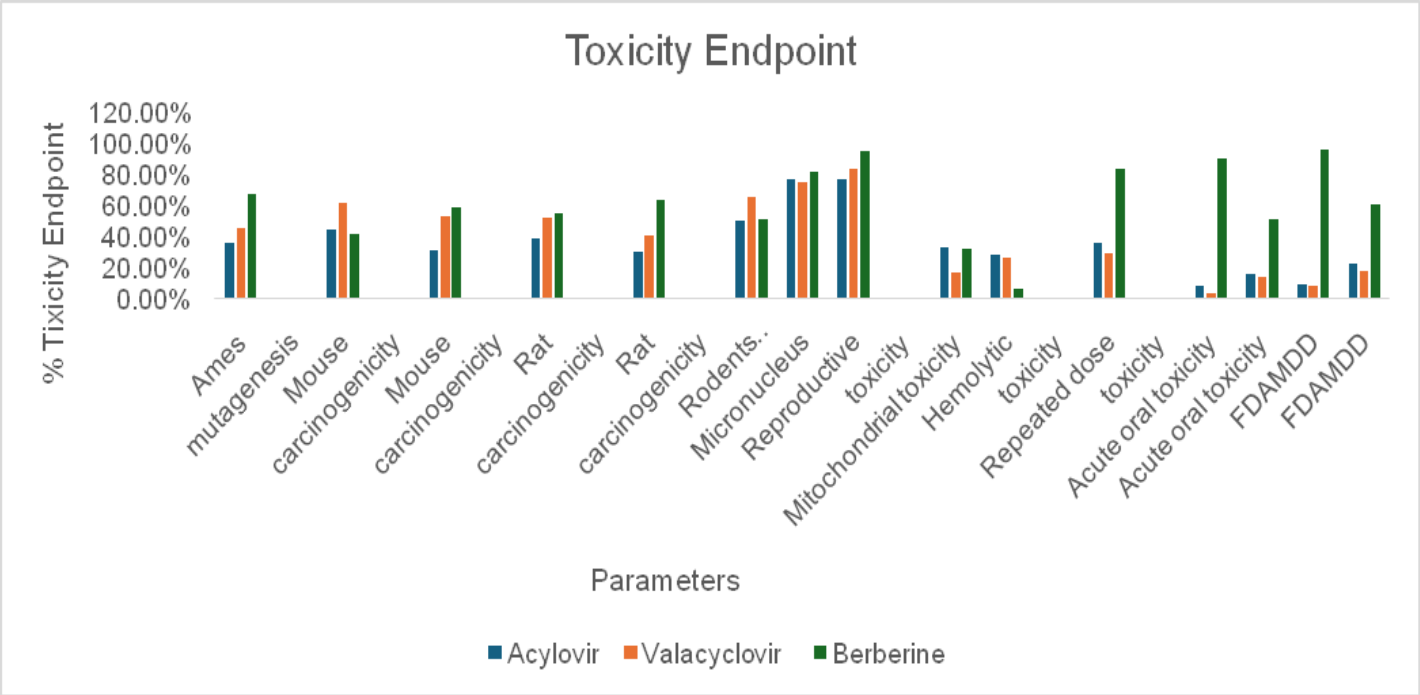

Figure 12: Chart showing Toxicity end point

Considering the toxicity endpoint, (Table 10) the Ames mutagenesis, mouse rodent and rat carcinogenicity, micronucleus, reproductive and mitochondrial toxicity, hemolytic repeated doe toxicity, acute toxicity and FDAMDD were calculated. The toxicological predictions including mutagenicity, carcinogenicity and inhibition of hERG by the compounds are shown in (Table 10) the result obtained showed that berberine exhibited high percentage endpoint toxicity (Figure 12). According to PreADMET, the negative prediction translates carcinogenic activity as shown in acute oral toxicity and in mouse carcinogenicity for only acyclovir, whereas positive means the compound does not have carcinogenic activity. Given the fundamental role of mitochondria in cellular energetics and oxidative stress, mitochondrial dysfunction has been implicated in cancer, diabetes, neurodegenerative disorders, and cardiovascular diseases. The results obtained show that the berberine and acyclovir show moderate toxicity while valacyclovir shows very low toxicity level. In Hemolytic toxicity, berberine shows extremely low toxicity (7%) compared with the two standard (acyclovir 28.59% and valacyclovir 26.50%) drugs considered. For repeated dose, acute oral and FDAMDD toxicity, berberine shows higher values 84.20%, 90.90% and 51.47% respectively.

Table 11: Endocrine Disruption

parameters	Acyclovir		Valacylovir		Berberine	
AR	0	1.0 %	0	1.20%	1	72.20%
ER	0	0.40%	0	0.30%	1	58.10%
AR-LBD	0	1.70%	0	1.60%	1	84.0%
ER-LBD	0	0.50%	0	0.40%	1	84.30%
Aromatase	0	3.30%	0	3.70%	1	76.10%
AhR	0	5.30%	0	3.30%	0	43.4%
ARE	0	2.60%	0	2.40%	1	72.90%
ATAD5	0	0.30%	0	0.20%	0	30.80%
HSE	0	0.60%	0	0.40%	0	15.80%
p53	0	1.20%	0	1.20%	0	43.90%
PPARγ	0	0.40%	0	0.50%	0	19.70%
MMP	0	2.0%	0	1.0%	0	46.50%
TR	0	1.0%	0	1.0%	1	58.60%
GR	0	2.40%	0	2.80%	1	70.10%

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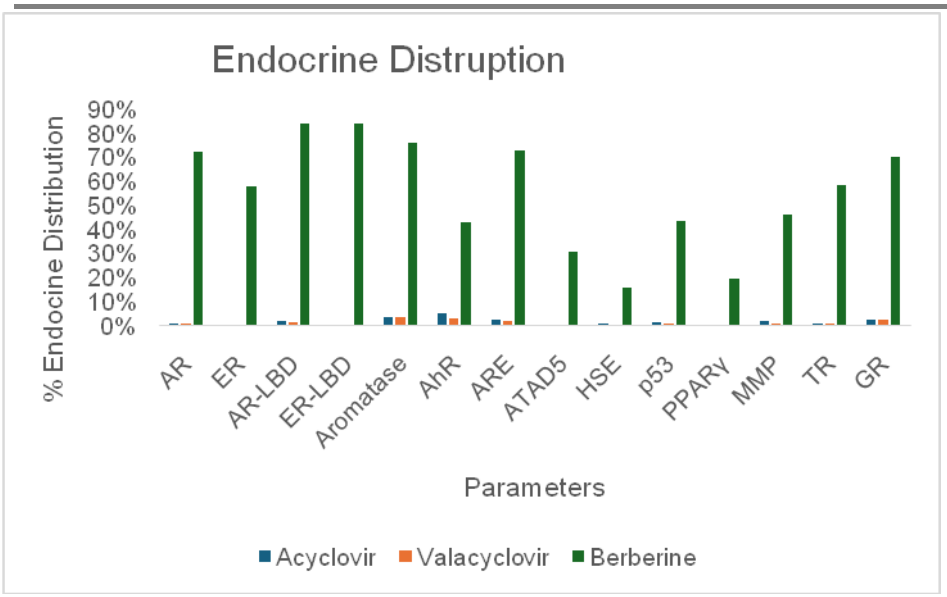

Figure 13: Chart showing Endocrine Disruption

A high percentage of endocrine distribution of drugs suggests that a significant portion of the drug is targeting or accumulating in endocrine tissues and organs, such as the thyroid, adrenal glands, pancreas, and reproductive organs. Drugs that concentrate in endocrine tissues may alter hormone synthesis, metabolism, or receptor interactions. This could lead to unintended pharmacological interactions or hormonal imbalances, impacting other bodily functions and potentially triggering a cascade of side effects. of all the parameter for endocrine disruption berberine Table 11 shows higher values implying that it could lead to unintended pharmacological interactions or hormonal imbalances, impacting other bodily functions and potentially triggering a cascade of side effects (Figure 13). However, there may be a need for serious considerations for Dosing and Monitoring. It may require adjusted dosing, more frequent monitoring of hormone levels, or specific pharmacokinetic adjustments to balance therapeutic benefits with the risk of side effects.

Ecological Risk

Table 12a: Toxicity to Terrestrial Orgamisms

Parameters	Acyclovir		Valacyclovir		Berberine	
Honey bee Toxicity	0	10.70%	0	5.90%	0	24.90%
Colinusvirginanus toxicity	0	7.09%	0	3.90%	0	18.1%
Anas platyrhynchos toxicity	0	7.30%	0	2.70%	0	10.60%

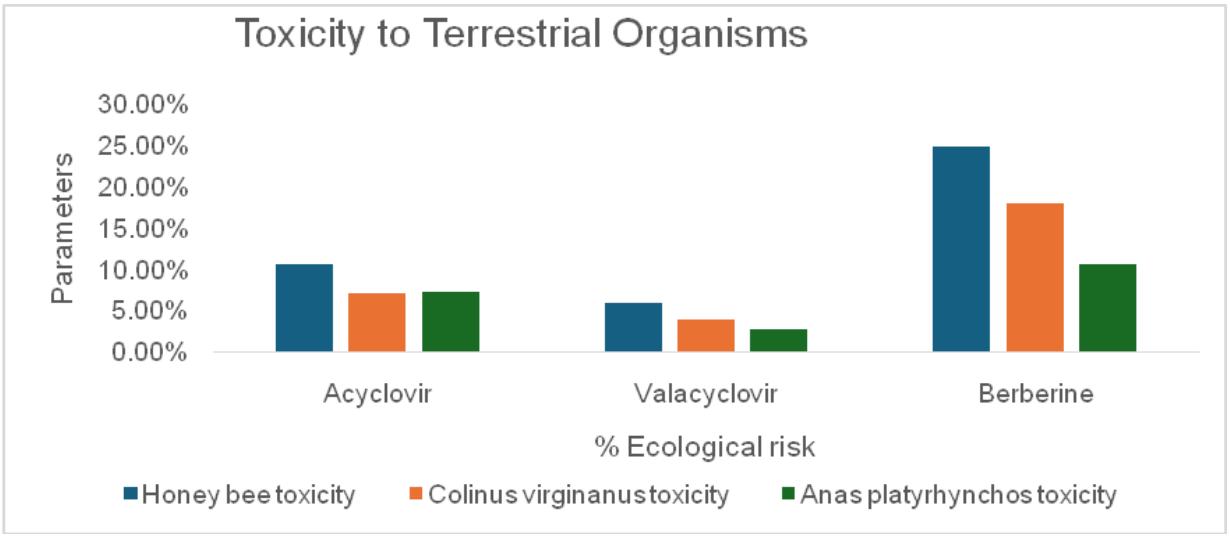

Figure 14: Chart showing Toxicity to Terrestrial Organisms

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Table 12b: Toxicity (others)

Parameters	Acyclovir	Valacyclovir	Berberine
BCF	0.50%	0.80%	2.80%
BCF	8.24%	1.84%	17.03%
Biodegradability	46.30%	32.20%	15.60%

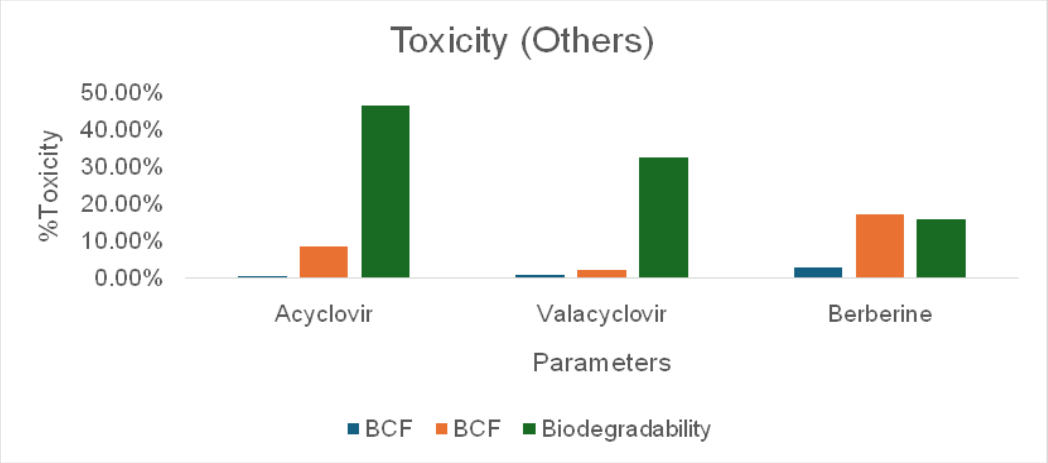

Figure 15: Chart showing Toxicity (Others)

Table 12c: Aquatic Organisms

Parameters	Acyclovir		Valacyclovir		Berberine	
P. subcapitata toxicity	0	14.90%	0	35.70%	1	56.10%
Crustaceans Toxicity	0	7.40%	0	8.30%	1	68.79%
D. magna toxicity	0	6.30%	0	7.09%	1	71.50%
Fish toxicity	0	8.10%	0	7.80%	1	84.40%
Fathead minnow Toxicity	0	4.90%	0	7.30%	1	60%
Bluegill sunfish toxicity	0	11.50%	0	6.80%	1	81.79%
Rainbow trout toxicity	0	11.90%	0	8.59%	1	80.90%
Sheepshead minnow toxicity	0	13.80%	0	11.70%	1	64.20%
T. pyriformis toxicity	0	6%	0	30.70%	1	89.70%
T. pyriformis toxicity	-1.26	15.51%	-0.1	39.62%	0.56	55.33%

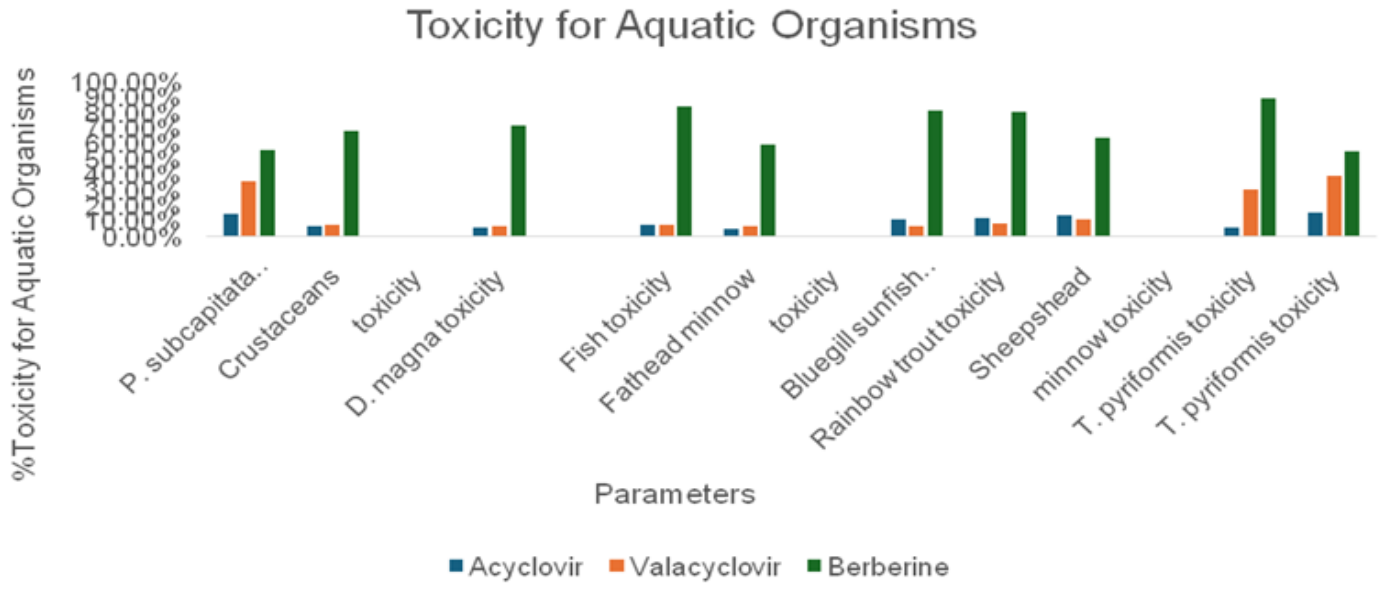

Figure 16: Chart showing Toxicity (Aquatic Organisms)

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Considering the ecological risk (Tables 12a, 12b and 12c) of the compounds in terms of terrestrial (Figure 14), other toxicity (Figure 15) and aquatic toxicity (Figure 16). The result showed that berberine has higher values of toxicity both in terms of aquatic and terrestrial organisms and to others such as bioconcentration (BCF) factor (Figure 15) which is the accumulation of chemicals dissolved in water in fish and aquatic organisms through the gills and body surface directly. The bioconcentration factor(BCF) is defined as the ratio of the concentration of a chemical in an aquatic organism to that in the aqueous phase under steadystate conditions. Berberine shows higher toxicity on terrestrial organisms with values at 25.00%, 15% and 10% for honeybee, Colinus virginianus and Anas platyrhynchos toxicity while valacyclovir shows very low value (5.9%, 3.9% and 2.7%). It is worth noting that the three compounds are biodegradable with acyclovir (46.30%)>valacyclovir (32.20%)> berberine (15.60%). Biodegradability or biodegradation is a commonly used term, which has no clear definition but is mainly used for describing the chemical breakdown of biomaterials that occur over days or years and causes changes in physical properties of the environmental tissues (https://www.sciencedirect.com/topics/immunology-and-microbiology/biodegradability).

Table 13: Cosmetic Risk Assessment

Parameters	Acyclovir		Valacyclovir		Berberine	
Eye corrosion	0	4.10%	0	0.70%	0	1.10%
Eye irritation	1	63.40%	0	14.90%	0	0.40%
Skin corrosion	0	1.60%	0	0.90%	0	3.20%
Skin irritation	0	17.10%	0	15.80%	0	15.60%
Skin sensitization	0	4.70%	0	7.20%	0	5.70%
Acute dermal toxicity	1	61.20%	1	50..8%	1	67.70%
Photoinduced toxicity	0	22.60%	0	49.70%	0	42.69
Phototoxicity	0	21.40%	0	42.40%	0	57.7

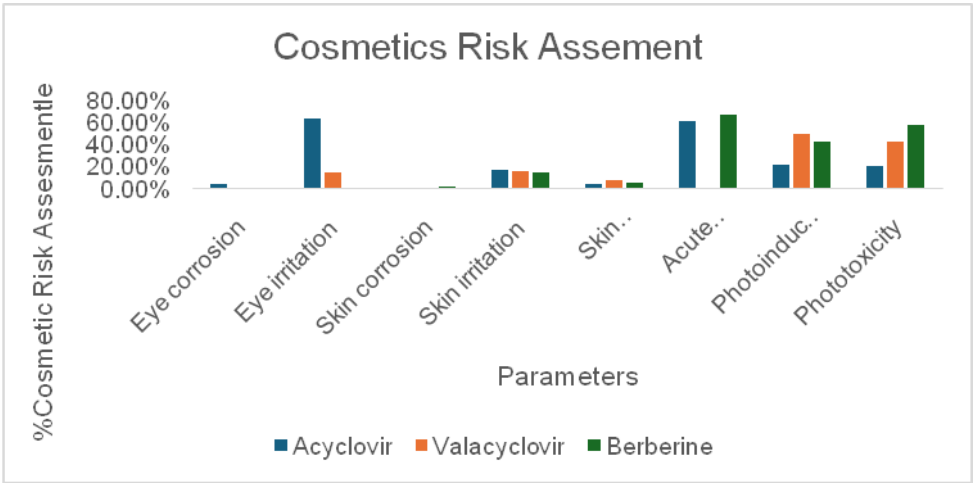

Figure 16: Chart Showing Cosmetics Risk Assessment

On cosmetic risk assessment, the three compounds showed (Table 13) moderate values for eye corrosion, skin corrosion, skin irritation except for acyclovir that shows very high-risk value for eye irritation (60.0%). For acute dermal toxicity, valacyclovir does not show any value indicating no acute dermal toxicity but photoinduced toxicity, valacyclovir has higher value than berberine (Figure 16) and acyclovir while in phototoxicity.

CONCLUSION

The key findings suggest that berberine inhibits viral replication of proteins by interacting with viral glycoproteins, affecting viral entry into host cells as shown in the value obtained for the binding affinities and the inhibition constant which compares favourably well with the standard drugs. in-silico antiviral activities of key phytochemicals from Berberis vulgaris against a receptor of the varicella-zoster virus (VZV), the causative agent of chickenpox it. Moreover, in vitro studies have highlighted its role in modulating immune responses

and preventing oxidative stress. [1] concluded that dietary supplementation of B. vulgaris root extract to quails reduces the detrimental effects of oxidative stress and lipid peroxidation resulting from HS via activating the host defense system at the cellular level. However,

B. vulgaris exhibited many anti-pharmacological effects. In silico studies of the antiviral activities of phytochemicals in Berberis vulgaris against chickenpox receptors are highly relevant in today's search for new antiviral therapies. By using computational methods, researchers can efficiently identify promising compounds that could contribute to the development of safer, more effective treatments for chickenpox and potentially other viral diseases. Given the potential of plant-derived compounds, this research area deserves significant attention.

Competing Interest: I declare that there is no potential conflicting interest arising from personal, financial or professional/academic relationships or dependencies upon the manuscript submission.

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