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ORIGINAL ARTICLE

Computational Studies for Selected Medicinal Plants against Dolutegravir using Ligand Based Pharmacophore, Molecular Docking, ADMET Predictionsand Molecular Dynamics Simulation

ANDREW RABONTSI MOTSILANYANE[1], ZIMBILI MKHIZE[2], SPHELELE SOSIBO[3]
[1]*Department of Organic Chemistry and pharmaceutics, Faculty of Natural and Agricultural Sciences,North West University, South Africa*
[2]*Head of Department, Organic and Pharmaceutic Chemistry,Faculty of Natural and Agricultural Sciences, North West University, South Africa*
[3]*Lecture Department of Organic and Pharmaceutic Chemistry, Faculty of Natural and Agricultural Sciences, North West University, South Africa*
Corresponding author: Andrew Rabontsi Motsilanyane, Email: rabontsikya@gmail.com, Cell: +27828922208

ABSTRACT

Human immunodeficiency virus type 1 (HIV-1) is the causative agent for acquired immunodeficiency syndrome (AIDS). In 2020, South Africa recorded an estimated 8,2 million people living with HIV. This extensive figure is a red flag to the country, as it causes serious economic burden to its health care system. In the quest for finding a suitable inhibitor for HIV-1 protease, computer aided drug design (CADD) approachstands out to be one of the leading fields of study in pursuit of a new drug for HIV. The Lipinski rule of five was applied in screening the ninety-two plant extracts from Ocium santum, Carica papaya, Persea Americana, Azadirachta indica and Spondias mombin medicinal plants, and forty-six of the compounds complied with this rule. Afterwards, a ligand-based pharmacophore was constructed based on the active properties of the three (3) best binding compound obtained from the screened ZINC compounds (Zinc_001456687980, Zinc_001445792073 and Zinc_001461099137). Then the compounds with less than 0.5 RMSD were picked out. The best 10 compounds were docked and compared with a drug that is already in the market, dolutegravir. 3, 5-di-O-galloyl-4- O-digalloylquinic acid 3,5,4,4-Tetragqa (-8.6), epicatechin (-8) and quercitrin (-8) obtained the highest binding affinity.Even though Tetragqa had the highest binding affinity, it failing the test because of its large molecular weight. The safety evaluation and other chemical parameters that included the lipophilicity, physicochemical other properties of these compounds was performed through SwissADME/T web server. On the best top three binding compounds, only epicatechin (-8) had promising features of a drug candidate. However, the remaining compounds from the best 10 compounds were also analysed using the SwissADME/T tools, whereby two of them (juglanin and catechin) satisfied the ADMET prediction analysis. Catechin showed some promising features as well after it displayed good druglike properties, suitable for a novel compound. Lastly, molecular dynamics simulation was then performed on the three lead compounds namely; epicatechin, juglanin andcatechin against dolutegravir. The ligand protein interaction between catechin and the protein displayed minimal shift of the protein during the simulation that was performed over 100ns, signifying a strong complex association.

INTRODUCTION

The first case of human immunodeficiency virus was recorded in 1981 (Greene, 2007). Over the years to date, there has been serious scientific work done in attempting to eradicate this disease from humankind. In 2020, HIV claimed around 690 000 lives globally (UNAIDS, 2020). However, since the first case of HIV (AIDS), a lot of progress has been made in the pharmaceutics, with numerous computer aided drug design (CADD) approaches being applied in finding a cure for this disease (Stuart et al., 2018). Subsequently, there is a strong need to manufacture antiretroviral drugs (ARVs) that are affordable, with minimal side effects and are moreeffective treatment than the heavy burden pills that were used some decade ago. South Africa, with the largest HIV treatment program in the world (AIDSmap), introduced dolutegravir to its patients with an estimate of over 4.8 million people on HIV treatment programs (Global information and education on HIV and AIDS, 2020). Dolutegravir, also known as “the game changer” proved that it has the capacity to suppress the patients’ viral load quicker than other ARVs, and, was used as a control in this study against selected medicinal plants (A publication of the Southern African HIV Clinicians Society, 2021).

Protease being an important structure found in the human immunodeficiency virus (Kräusslich et al., 1989), helps in the processing of Gag-Pol and Pol polypeptide into mature functional proteins. It is also responsible for the maturation of virions that are released by the virus, and, it belongs to the class of aspartic acid(Oroszlan and Luftig, 1990). This class functions as a catalytic dimer. These virions only become non-infectious when the protease is blocked in order to maturate the virions(Konvalinka et al., 2015). This inhibits the replication of HIV-1 through the introduction of HIV-1 inhibitors that are competitive towards the binding site of the protease (Louis et al., 1994), (Kohl et al., 1988).

In this study, the application of CADD techniques were used in finding an inhibitor/s from five plant extracts namely: Ocium santum (Rajinikanth et al., 2013), Carica papaya (Yogiraj et al., 2014), Persea Americana (Owolabi et al., 2005), Azadirachta indica (Mahapatra et al., 2012) and Spondias mombin(de Lima et al., 2016). The screened phytochemicals were then compared with dolutegravir, which is an ARV that is currently been administered to HIV patients in South Africa(Hauser et al., 2020). The active biological activity of dolutegravir were compared with the lead compounds retrieved from PubChem database. The application of literature was an important tool in finding respective biological composition for each plant, which in total, a number of 92 phytochemicals were identified (Mulligan et al., 2018).

Computer Aided drug design (CADD) is a molecular modelling approach that can be used to search for new drugs thatcan cure diseases. This approach have yielded a lot of success over the years with some of the ARVs’ being discovered through CADD(Surabhi and Singh, 2018), (Veselovsky and Ivanov, 2003). With the administration of highly active antiretroviral therapy (HAART) there is a lot of progress that has been made in an attempt to curb this epidemic. However, some of these medications creates a lot of pill burden to patients who are placed on suchtherapeutic processes (Shafer and Vuitton, 1999). Other challenges that includes the antimicrobial resistance make it difficult to treat some patients who are failing extensive antiretroviral therapy(Rackal et al., 2011), hence a need for a permanent solution to this disease.

Docking studies between virtually screened ligands from the ZINC database (for pharmacophore modelling)and PubChem (for selected phytochemicals)playedan important role in finding potential drug compounds that can be used, by contributing to the fight against this HIV.ZINC and PubChem being the largest databases of small ligand compounds with approximately more than 1, 3 billion compounds (Ton et al., 2020) and111 million structures(Gaulton et al., 2013) respectively, marks a good start for the screening of suitable novel compounds (Sabe et al., 2021).

Auto Dock Vina is one of the tools used to dock such compounds with the protein. It has yielded great success in an attempt to understand the protein-ligand interactive properties and also in the quest of findingnovel compounds(Grinter and Zou,

2014), (Karplus and McCammon, 2002). One of the best tools of filtering these compounds is pharmacophore modelling, which is a process of mimicking already existing biologically active properties on known structures, either in complexed or uncompleted structures, in order to filter compounds in a class based on their similarity and likeness(Walters and Wang, 2020).

Using MD as an approach to gain more insightpertaining to prominent molecular interactions, it is also possible to analyzedynamic features that are being formed by such interactions. Simulation process entails a post-docked protein-ligands compound, used in order to analyze the different orientation that might have raised in the process. Only the best-docked compounds, which were predicted to satisfy the health and safety administration analysis using ADMET were simulated in time of nanosecond scale. These simulated results includes the statistical parameters such as the RMSD, RMSF and Hydrogen contacts (Borhani and Shaw, 2012), (Vora et al., 2019).

In this study, we followed these CADD processes of finding a possible dug candidate for HIV-1 protease.ADMET property analysis, wereperformed on the lead compounds to predict the bioavailability of those compounds. In drug discovery, determining the toxicity level of compound is one of the fundamental routines that is encouraged to be performed early in the search for a new drug. Therefore, SwissADME as a web server, is an approach that predicts the different parameters of compounds. It saves time and it limits risks of putting patient's life in danger (Daina et al., 2017), (Brenk et al., 2008). At a later stage, these multiple chemical parameters are very essential in determining the efficacy of a novel compound.(Baell and Holloway, 2010).

MATERIALS AND METHODS

The following flowchart was prescribed for the computer aided drug design and its methodology, as shown below:

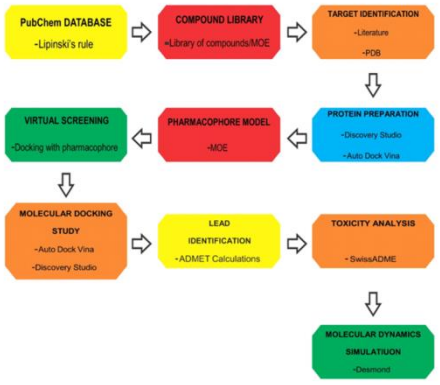


Figure 1: The Flowchart of adopted computer-aided drug design (CADD) methodology.

5.2.1 PubChem database

Phytochemicals were retrieved from PubChem database. This database contains unique chemical structure. Eighty-nine compounds that were used in this investigation were retrieved from except for three, which were drawn on MOE software.

5.2.2 Phytochemicals Library

A library in the MOE was created for all the retrieved phytochemical. In addition, the Lipinski's rule was used to screen all the ninety-two stored phytochemicals.

5.2.3 Target Identification

HIV-1 protein (1rv7) was also retrieved from the Protein data bank (O'Leary et al., 2016). This structure is one of the five wild type structures stored in the Protein Data Bank and it has a resolution from 2.7 Å (Sillanpää et al., 2008). 1rv7 is a protease with two chains (A and B) with a sequence length of 99. It was isolated from a patient who was failing antiretroviral therapy and subsequently deposited into the database (Liu et al., 2015).

5.2.4 Protein preparation

The retrieved protein was downloaded from the PDB (Liu et al., 2015). Water molecules and hetatoms were then deleted using Biovia discovery studios. Since protein was retrieved as a co-crystallized complex with the ligand, the present ligand was removed by the "Define and Edit binding site" then "Current selection" and delete ligand. Water molecules were then added by applying Chemistry, Hydrogen then add polar (Adeniji et al., 2020).

5.2.5 Pharmacophore Model

Using molecular operating environment (MOE 2015.08) software, a pharmacophore model was constructed using the structures of the best binding ZINC compounds (ZINC_001456687980, ZINC_001445792073 and ZINC_000015276354) (from the first stages of this investigation). Forty-Six compounds were energy minimized the MMFF94 forcefield, were the of0.01 RMSD was maintained. The main features of the three ligands were isolated in order to mimic the compound likeness so that the phytochemicals are further screened using this pharmacophore model. This method is helpful in categorizing structures, since there are many compounds with a range of structural diversity that has unique biochemical activities (Mannhold et al., 2006).

5.2.6 Virtual Screening

The phytochemicals were screened from the create MOE library using the constructed pharmacophore model, based on the developed pharmacophore query.

5.2.7 Docking Procedures

A blind docking analysis between the phytochemicals and the protein was performed using the AutoDock Vina v.1.2.0 using the following axis: center = 19.1732 center_y = 41.6246 center_z = 0.0403 size_x = 37.819451558 size_y = 37.9149091911 size_z = 58.311979351. The interactions between the ligand and the protein was observed on the Biovia discovery studio.

5.2.8 Lead Compound Identification

Compounds with the most active inhibition capability were discovered based on the best binding affinity and ligand-protein interactions (Kim and Skolnick, 2008). These compounds displayed high biochemical activity, since they derived from a pharmacophoric culture and were also compared with a control drug, Dolutegravir, a drug that is already in the market and already in use in South African health care sector (Plewczynski et al., 2011).

5.2.9 Toxicity Analysis

The drug like descriptions and toxicity characteristics were identified through SwissADME (Daina et al., 2017). This calculation includes (ADMET calculation) adsorption, distribution, metabolism, excretion and toxicity (Xu et al., 2012). The mutagenicity and the carcinogenicity were also determined for the lead compounds. The determination of these lead compounds was based on the pharmacophore and the docking score, the ligand-protein interactions. Other related studies include, mol mw, donorHB, accptHB, QPlogPo/w, QPlogHERG, QPPCaco, QPlogBB and number of rings determination etc.(Low et al., 2011), (Mulliner et al., 2016), (Alavijeh et al., 2005).

5.2.10 Molecular dynamic simulation

After performing molecular docking and analysis the interaction between the protein and the ligands. Molecular dynamics simulation was carried out using Desmond, a Package of Schrödinger LLC (Alavijeh et al., 2005). The simulation was performed at 200ns, in order to predict the ligand binding properties in the physiological environment. In this system that were prepared by the System Builder tool, the Solvent Model with an orthorhombic box was selected as Transferable Intermolecular Interaction Potential 3 Points (TIP3P) using the OPLS_2005 force field throughout the simulation (Al-Shabib et al., 2018), . The models were then relaxed before the simulation can resume and the counter ions were added in order to neutralize the model. The following parameters were used to mimic the physiological

environment: a) Isothermal-Isaboric: Moles (N), pressure (P), and temperature (T) were conserved at 300K temperature, (these are The NPT ensemble) b) a 0.15 M salt (NaCl).c) (Deganutti et al., 2020), and in this simulation, trajectories were saved after every 100 ps for analysis.

RESULTS

In Silico Analysis: Based virtual screening

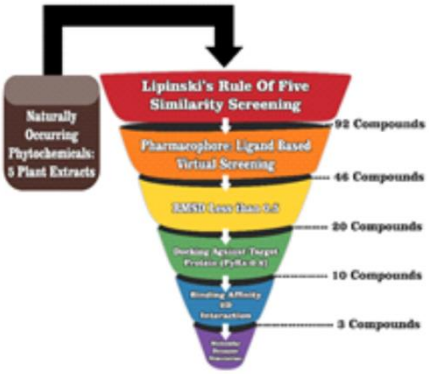


Figure 2: Flowchart of the results obtained from computer aided drug design (CADD)

5.3.1 Druglikeness Analysis: Molecular properties that includes the Lipinski rule, pharmacophore model, molecular weight, molecular docking and molecular dynamic simulation are some of the guided computational approaches that were applies in this study. The prediction using the Lipinski rule states that, a compound having either poor permeation or absorption is more likely to fail when it violates the Lipinski rule of 5 (Lipinski et al., 1997). Using a free web SwissADME server http://www.swissadme.ch/different chemical parameters were predicted. These includes, the pan assay interference compounds (PAINS), which predicts the structural alerts that has unstable, reactive and toxic elements in their biological components (Ferreira and Andricopulo, 2019).The essence of searching for a novel drug candidate relies on using the features of an existing drug that has been approved by the food and drug association (FDA) (Ekins et al., 2014). One such tool is the application of pharmacophore modelling, which is a tool that mimics the features of active biological components of a compound. This is done in order to have a library of druglikeness, which can be screened to find a suitable drug candidate (Ritchie et al., 2011).

5.3.2 Construction of A ligand based pharmacophore Model: Pharmacophore technique based on the active ZINC ligands mimicry;- Ligand based pharmacophore modelling**.**

Table 1: Interaction between the trio hot-spot residues of three lead ZINC ligands structure (from previous investigation): PDB ID: 1rv7.

ligands hot-spot residue	Type of interaction	Residue
F1 = Aro	Alky/Pi Alkyl	23, 28, 82, and 84,
F2 = Acc	Van der Waals	32 and 84
F3 = Don/Acc	Pi Sigma	32

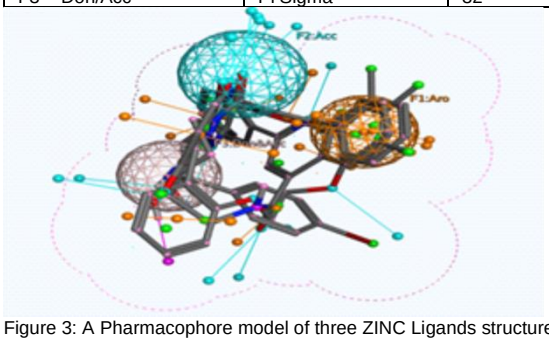


Figure 3: A Pharmacophore model of three ZINC Ligands structure.

The three best ZINC compounds which are zinc_1456687980, zinc_1445792073 and zinc_15276352 were used to construct a ligand-based pharmacophore on the molecular operating environment where a conformation database and the pharmacophore model was built. These compounds the most active compounds screened from the ZINC database. A pharmacophore query was also built. This query was searched to show the features that will determine the likeness from the phytochemicals library.

5.3.3 Virtual Screening of HIV-1 Protease Inhibitors Using PubChem Databank, AutoDock Vina and the Lipinski's Rule of Five

Virtual Screening of some phytochemical plant extracts: Below is a list of the phytochemical extracts that were screened.

a) Ocium santum: 1 α-Pinene 2 α-thujene 3 α-Camphene 4 β-Pinene 5 α-Myrcene 6 D-Limonene 7 Eucalyptol 8 cis-α-Terpineol 9 Sabinene 10 Borneol 11 Bornyl acetate 12 Camphor 13 Eugenol 14 Selinene 15 Caryophyllene oxide 16 Veridifloro 17Cubenol 18 Caryophyllene oxide 19 Selinene 20 β guaiene 21Phytol 22 Oleic acid 23 Aromadendrene oxide 24 β-gurjunene 25 Eicosane 26 Ethyl cyclohexenal ketone 27 n - butyl benzoate 28 3 – Furaldehyde 29 Benzaldehyde 30 Heptanol 31 1-Octen-3-ol

βguaiene21 Phytol22 Oleic acid

b) Carica papaya: 1. Decylene 2 Trans-Geranylacetone 3.Methyl tridecanoate 4.Palmitic acid 5.Myristic acid, methyl ester 6. Myristic acid 7.Palmitic acid, methyl ester 8.Hexadecanoic acid 9.Linolelaidic acid, methyl ester 10. Methyl cis-6-octadecenoate 11. Stearic acid, methyl ester 12. Oleic acid 13.Stearic acid 14 15-Tetracosenoic acid 15. Methyl heptacosanoate 16. Trans-13-Docosenoic acid 17. Methyl erucate 18. Methyl behenate 19. Heneicosanoic acid, methyl ester 20. Farnesyl cyanide 21.Quercetin 22. Chlorogenic acid 23. 5,7 dimethoxycoumarin 24. Caffeic acid 25. Kaempferol 26. P-Coumaric acid 27. Protocatehuic acid.

c) Persea Americana: 1. $C_{21}H_{20}O_{10}$ 2. Afzelin 3. Catechin 4.Juglanin 5. Quercitrin 6. Epicatechin 7. Astragaline 8. Trans-tiliroside 9. Senecin 10. Juglalin 11. Quercetin 12. (6R,9R)-3-oxo-α-ionol-9-O-β-D-glucopyranoside 13. Roseoside 14. Ficumegasoside 15 Icariside B_1 16. (+)-lyoniresinol 17. (+)-isolariciresinol 9-O-β-D-xylopyranoside 18 Flavonol glycoside 19. Megastigmane glycosides 20 Lignans.

d) Azadirachta indica (neem): 1. Azadirachtin 2. Nimbolinin A. 3. Nimbin 4. Quenrcetin 5 Sitosterol 6. Salannin 7. Gedunin

e) Spondias mombin: 1.) Geraniin 2.) 3, 5-di-O-galloyl-4- O-digalloylquinic acid 3.) 3-O-digalloyl-4,5- di-O-galloylquinic acid 4) 1,3,4,5-tetra-Ogalloylquinic acid 5) 2-O-Caffeoyl-(+)-allohydroxycitric acid. 6) 6-(8'Z,11'Z, 14'Zheptadecatrienyl)-salicylic acid 7) 6-(10'Zheptadecenyl)- salicylic acid.

g) Control drug = Dolutegravir (A recommended ARV in South African healthcare system)

The three phytochemicals that were not found in the ZINC Data Base: All the phytochemicals were found in the ZINC Database except for three, which are:Senecin, (6R,9R)-3-oxo-α-ionol-9-O-β-d-glucopyranoside and Megastigmane glycosides from the plant Persea Americana. There structures were constructed using the MOE.

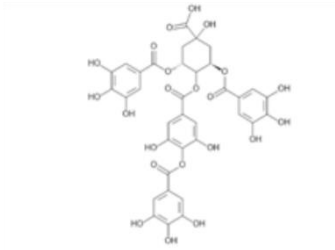
Phytochemical library: A library of all the ninety-two phytochemicals was created on the molecular operation environmental. A total of forty-six phytochemicals was identified after employing the Lipinski's rule of five. The retrieved extracts were compounds that met the following criterion: a) H-Bond Donor > 5, Molecular weight >500, Hydrogen Bond acceptors>10, LogP>5 (Lipinski et al., 1997). This method is often employed in finding a category of inhibitors that has the same pharmacological properties.

Phytochemicals-Pharmacophore properties based on the RMSD: The compounds that had the best pharmacophoric hit were identified and filtered using an RMSD score. Twenty of the forty-six

compounds had a score that is less than that of 0.5 RMSD score. These compounds were then chosen as candidate compounds for molecular docking studies.

5.3.4 Molecular Docking Studies: Compounds that were docked displayed different binding affinities and the one with the least binding affinity were picked and analyzed further using Autodock Vina and MGL tools. Their interaction was viewed on Biovia discovery studio. This observation tool assisted in visualizing the different poses and the residues interaction between the protein and the ligands. 2D were structured from this software. The chain structures of important active sites were also displayed. From the hierarchy window the amino acid sequence for the complexes was determined. The Amino acids that makes up the active site were identified and analyzed, using discovery studio.

Best 10 Compounds for Molecular docking Studies: Table 2: The table below shows structures of the best 10 compounds, after molecular docking.



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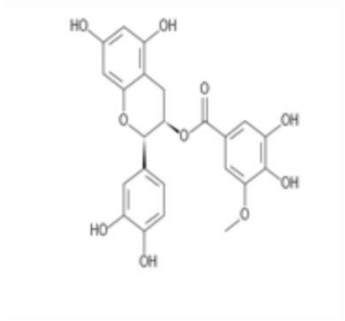

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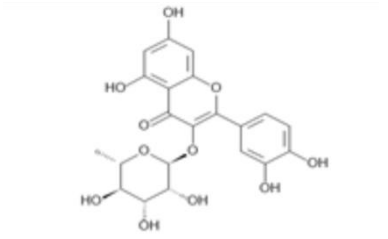

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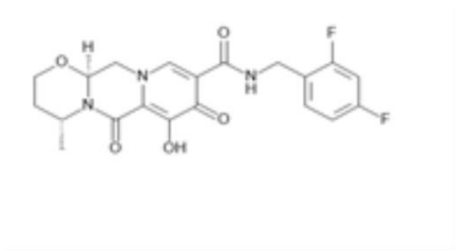

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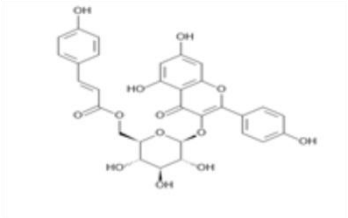

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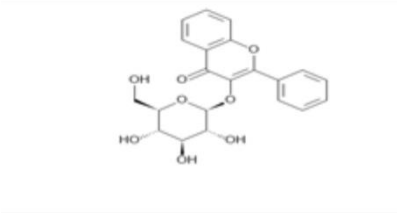
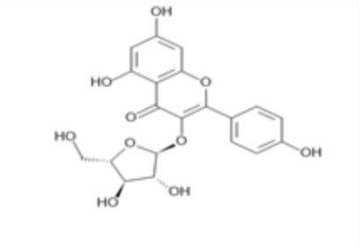
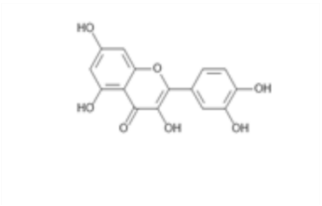


6.PubChemID_11953828



7.PubChemID_5318771



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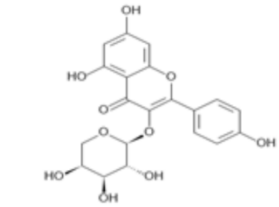

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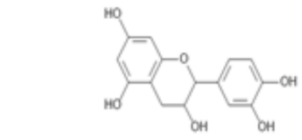


10.PubChemID_1203

5.3.5 SwissADME studies: The results of the ligand properties were obtained from SwissADME server as shown on table 3 and 5. SwissADME is a web server that can be used to predict the properties of the compounds. Using SwissADME web server,

lipophilicity was applied in predicting the physico-chemical properties for the best ten compounds. The five models of this parameter were determined as shown on table 3. These models are, iLOGP, XLOGP, MLOGP, WLOGP and SILICOS-IT. Based on these parameters, three compounds epicatechin, juglanin and catechin were identified as lead novel inhibitors, as highlighted in green and the control in red/ dolutegravir. The lead compounds were identified as epicatechin, juglanin and catechin.

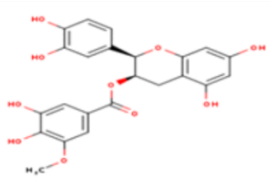
Table 3: Lipophilicity of the 10 best phytochemicals

PubChemID	M.W	Binding Affinity	RMSD Score	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	C/SUS LOG P $_{O/W}$
1. PubChemID_348294336/3, 5-di-O-galloyl-4- O-digalloylquinic acid 3,5,4,4-Tetragqa	800.59	-8.6	0.1377	1.15	1.83	1.25	-2.08	-1.17	0.20
*2.PubChemID_467296/epicatechin	456.40	-8	0.1800	2.35	1.85	2.51	0.53	1.59	1.77
3.PubChemID_5280459/quercitrin	448.28	-8	0.1819	1.60	0.86	0.49	-1.84	0.01	0.22
4.PubChemID_54726191/Dolutegrair	419.38	-8	control	2.10	2.44	1.66	1.05	1.85	1.82
5.PubChemID_5320686/transtilirosie	594.52	-7.7	0.1919	2.68	2.47	1.62	-1.04	1.56	1.46
6.PubChemID_11953828/flavonol g.	400.38	-7.6	0.2840	2.33	1.23	0.64	-0.60	1.30	0.98
*7. PubChemID_5318717/juglanin	418.35	-7.6	0.1820	1.76	1.33	0.39	-1.57	0.54	0.49
8. PubChemID_5280343/Quercetin	302.24	-7.2	0.2055	1.76	1.33	0.39	-1.57	0.53	0.49
9. PubChemID_5481882/juglalin	418.35	-7.1	0.1819	1.76	0.78	0.39	-157	0.38	0.38
10. PubChemID_1203/catechin	290.27	-6.9	0.2055	1.46	0,36	1.22	0.24	0.98	0.85

The lipophilic studies analyses if the drug is suitable for polar or non-polar activity. Uncharged and nonpolar drugs dissolve in oily substances and in contrast charged and polar drugs dissolves well in water, hence hydrophilic. In the body biomembranes are such fatty acids, which is a lipophilic barrier. When drugs are in an active state, the are usually lipophilic, hence the need to know the nature of the drug either it is lipophilic or hydrophilic(Olasupo et al., 2020), (Ejeh et al., 2021), (Vivek and Swapna, 2021). These drugs feature has a great effect on the pharmacokinetic properties that includes the adsorption, distribution, metabolism and its excression(Chowdhury et al., 2021), and therefore, there is a great need to analyze these properties in the quest of finding a drug with suitable properties.

SwissADME shows two compounds with similar lipophilic properties, juglanin and quercetin, one passed the test and the other failed, respectively. The reason to that lies on the fact that quercetin has no rotational bonds.

Table 4: Swiss ADME properties Ligand ID QPLogHERG QPPCaco 2D structures



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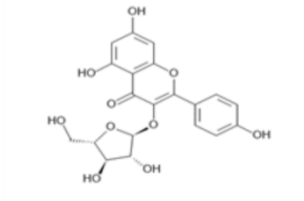
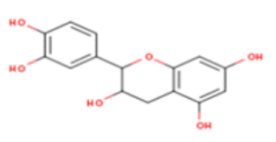
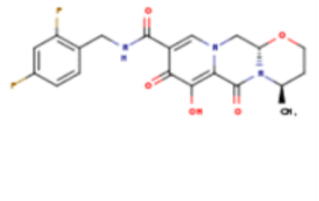


B. PubChemID_5318717-5.39169.995



C. PubChemID_1203 -5.223107.351



D. PubChemID_ 54726191 -0.9681341.852

Table 5: SwissADME/T properties for Lead Compounds Properties of lead compounds Epicatechin (l) Juglanin(l) Catechin(l)Dolutegravir (c)

Molecular weight	456.40	418.35290.27419.38
Toxicity	Catechol	Non-toxicCatecholNon-toxic
Rotatable bonds	5 4	14
Ring	4 4	34
RMSD Score	0.18000.18200.2055	Control
Carcinogenetic	Non-Carcinogen	N/C N/CN/C
Solubility	Soluble M/S	Soluble Moderately Soluble
Binding Energy	-8-7-6	-6-9-8
Molar refractivity	114.51 - 102-17	74.33 – 104.48
H-bond Acceptor	10 10	67
H- bond Donor	6 6	52
GI absorption	Low	High
BBB permeation	No	No
Leadlikeness	No: mw > 350	Yes No: 1 violation: mw > 350
Abbott BA	0.55	0.55
Skin Permeation	-7.77 -7.91 cm/s	-7.82 cm/s -7.13 cm/s
PAINS	1 alert: catechol0 alert	0 alert

MW: Molecular Weight; HBA: Num. H-Bond Acceptors; HBD: Num. H-Bond Donors; MR: Molar Refractivity; P-M: Poor-Moderate; P: Poor; GI: Gastrointestinal; BBB: Blood–Brain Barrier; Average of five prediction, 1 violation: MLOGP > 4.15, PAINS: Pan-assay Interference Compounds. PPB (Plasma Protein Binding); BBB (Blood–Brain Barrier).

All the properties of the drugs that are well known and are connected to the drug was retrieved from the sever. These properties are the adsorption, distribution, metabolism and excretion, and these results are mainly based on the following parameters: lipophilicity, physicochemical, water solubility, pharmacokinetics, druglikeness and medicinal chemistry. The lead compounds were analyzed, and their results matched against dolutegravir, a drug already in the market, and was used as a

control compound for this study. The canonical smiles for epicatechin, juglanin, catechin and dolutegravir was retrieved from PubChem in order to run each compound to obtain their properties.

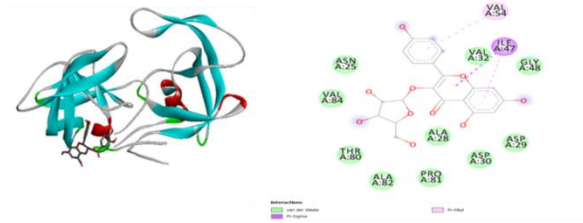
According to the SwissADME bioavailability colored radar, all the lead compounds were structure within the box, showed predictions of compounds that can used as suitable drugs candidate, hence a further analysis of results was carried out. Catechin with a molecular weight of 290.27 g/mol follows the Lipinski's rule with no violation as compared to epicatechin and juglanin which both compounds having 6 hydrogen donors and hence violating the Lipinski's rule. Epicatechin and catechin revealed the presence of a toxic substance called catechol, which when found in small amounts, has no dangerous effects, since it occurs naturally in fruits and vegetables(Harel and Mayer, 1971).

Catechin and dolutegravir demostrates a high gastrointestinal absorption. Having size as its advantage, the distribution of catechin through the blood vessels can be predicted a compound that can possess minimal resistance to its target, bearing in mind the intravascular blood pressure. Capillaries are tiny blood vessels, permitting passage of blood cells, hence the need to find a suitable drug that can pass through the blood vessels without blocking, damaging or breaking the cell membrane. Compared to dolutegravir, the lead compound in this study have no blood brain barrier (BBB), meaning their movement through the a highly selective semipermeable membrane of the brain is not restricted, whilst catechin shows low molar refractivity as compared to other compounds predicting how easy it be to infuse the dipole. Because these compounds show the ability to penetrate to form part of the digestive metabolites from the mouth to the gastrointestinal (GI) tract through the blood brain barrier, these are suitable for oral intake.

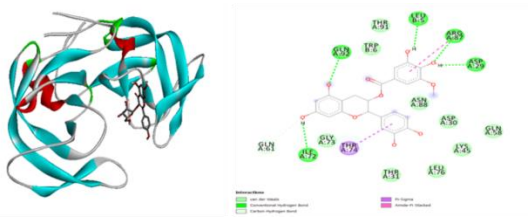
The druglikenessof these drugsshowed some similarities mainly for catechin and juglanin compared to certain components of dolutegravir. However, irrespective of epicatechin binding outside of the active site of the protein, it still possess important feature in some instances, which are similar to that of thecontrol. Epicatechin and dolutegravir have the same binding affinity of (-8), and they also have the same number of rings. In some instances epicatechin falls within the range of dolutegravir and the rest of the other compounds. Some of its properties might be of great importance in understanding the binding affinity against this disease.

Water soluble compounds plays a major role in determining the outcome of drug development and its activities. Since some of these drugs are administered orally, they their success rely mainly on the manner in which they dissolve when administered orally. Epicatechin and catechin predicted a soluble state when dissolved in water. The decimal logarithms of the molar solubility in water (log S), was predicted for all the four compounds, with juglanin and dolutegravir showing a moderate solubility when dissolved in water.

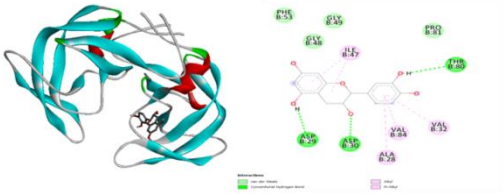
5.3.6 Docking analysis for lead compounds:



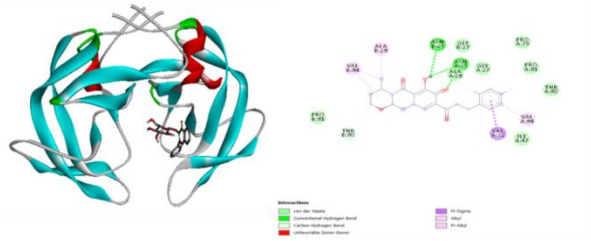
A) PubChemID_467296/Epicatechin



B) PubChemID_5318717/ Juglanin



C. PubChemID_1203/ Catechin



D) PubChemID_ 54726191/Dolutegravir

Figure 4: Binding interaction of epicatechin, juglanin and dolutegravir.

Table 6: The docked Van der Waals, Conventional Hydrogen Bonds, Pi-Sigma, Alkyl, Pi-Alkyl between 1rv7 protein and best three compounds

	Compounds	Van der Waals	Conventional H bonds	pi-sigma	Alkyl	pi-alkyl
A) Epicatechin	THR91, TRP6, GLN61	LEU5, GLN92, ILE72 THR74	GLY73, THR31,	LEU76ASP29, ARG87	LYS48, GLN58, ASN30	ASN88
B) Juglanin	ASN25, ALA82, VAL84	VAL54	PRO81, THR80, ALA28	GLY48 ASP30,	ASP29	VAL32
C. Catechin	PHE53, GLY48, GLY49THR80,	ASP30, ASP29ILEB47	PRO81	AlAB28	VALB84	VALB32
D) Dolutegravir	PRO79, GLY27, GLY27ASN25, ASN25VAL32	VALA84	VAL84	ALA28, PRO81,	ALA28	THR80, ILE47, THR80

A detailed interaction analysis between the inhibitors and the protein residue was made. Table 6, above shows the orientation and interaction of these lead phytochemicals compared todolutegravir. It can be observed in figure 4, that, juglanin and dolutegravir binds inside the protein at the same binding site together with dolutegravir.These drugs displays a good pose inside the catalytic pocket of the receptor. Juglanin displays the following hydrophobic interactive with the following residues:Asn25, Ala82, Val84, Pro81, Thr80, Ala28, Gly48 Asp30, Asp29, and Val32, whiles dolutergravir shows the following hydrophobic interaction Pro79, GlyB27, GlyA27, Ala28, Pro81, ThrB80, ThrA80, and Ile47.The interaction between juglanin and the protein shows no formation of hydrogen bonds, while dolutegravir forms two hydrogen bond with the proteinwith residue:Asn25, Asn25. The efficacy of the drug is evaluated based on the formed hydrogen bonds (Raj et al., 2020).The Van der Waals, which includes the hydrogen bonds, are one of the most important binding forces in protein-ligand interaction.

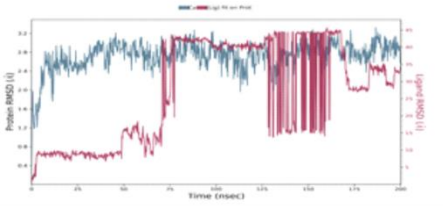
Catechin displays and the protein form three hydrogen bond on residue Thr80, Asp30, Asp29 with the following hydrophobic interaction Phe53, Gly48, Gly49, Val32.With Epicatechin binding outside of the binding pocked it has hydrophobic interactions with the following residues: Thr91, Trp6, Gln61, Gly73, Thr31, Leu76, Lys48, Gln58, Asn30, and Asn88. Interestingly, epicatechin forms five hydrogen bonds with the following residue: Leu5, Gln92, Ile72,Asp29, and Arg87, and has a single pi (Π) bond on residue Thr74, and Val54 for juglanin. In most instances, these pi bonds are not stronger than sigma (σ) bonds, they are usually weaker. In cooperate stability contribution, the stability added by pi bonds is lesser than that of sigma bond(Mhatre et al., 2021), (Iheagwam et al., 2019).Catechin and dolutegravir, with four pi bonds and residue Ile47, Ala28 Val84 Val32 and one pi bond on residue Val84, respectively has contributes independently to their association with the protein.

5.4Molecular Dynamics Simulation: A package of the Schrödinger, called Desmond LLC, was used for molecular dynamics simulation for the three lead phytochemical against the control Dolutegravir. Dolutegravir is a drug that is been administered to HIV patients in South African health care sector. The simulations for Epicatechin, Juglanin, Catechin and Dolutegravir were performed for 200 nanosecond to predict a ligand biding status along with their trajectories that were analyzed using the C-α atom. In molecular dynamics simulation, the RMSD was measures between the ligand and the protein. It was used to analyze the protein-ligand association and movements of all the simulated complexes in order to observe the structural stability during the simulation. For the complex to be regarded as functional its movements within the hydrated environment plays a vital role in the determination of the stability of the complex and catechin displayed such interactions as compared to other compounds.

Figure 5, Shows the root mean square deviation for epicatechin, juglanin, catechin and dolutegravir.Catechin at 25ns attained a value of 1.3 Å, while epicatechin displayed a value 0,7 Åfrom5- 50 ns. Looking into the RSMD pattern of dolutegravir, athree-phase pattern is observed with an increase of the RMSD value, which one trait the compounds exhibit. This pattern can be observed on the other the other compounds in study, as either a three-phase pattern or a four-phase pattern, usually in an incseasing RMSD value.

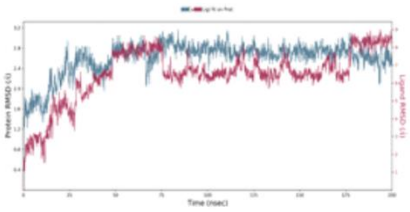
The protein RMSD maintains equilibrium at the ranges of 50ns, for epicatechin, juglanin and catechin.At time 50ns the protein RMSD for the interaction between juglanin and catechin reaches equilibrium until the end of the simulation, whiles equilibrium is reached at 115ns and 25ns for dolutegravir and epicatechin, with vast deviation between epicatechin and the protein between 0 – 75ns. Protein RMSD reached equilibrium at 2.8 Å at time 50ns for both epicatechin and juglanin.

Epicatechin and catechin shows the lowest RMSD of 3,5 and 3,6 Å respectively, at the end of the simulation, with two main observations picked from the molecular docking of these compounds, which are: epicatechin binding outside of the binding pocket and catechin binding at a location similar to that of delutegravir. Dolutegravir had an RMSD of 10,5 Å at the end of the simulation.

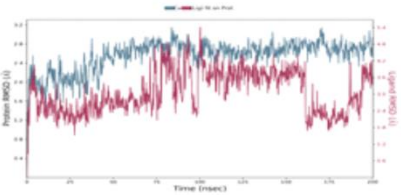


Epicatechin

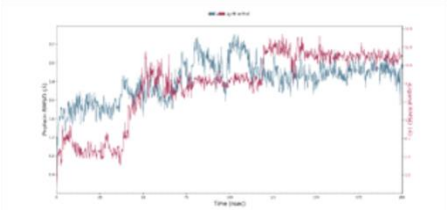
Figure 8. Shows the hydrogen bonds and the bond length that were formed by the compounds under study and the control. Catechin in one of the having the longest bond length of 1.6 at residue Asp30 and the second highest bond length that follows, is 0.9 at residue Asp29, while dolutegravir display its highest bond length of 0.2 at residue Asn25.



Juglanin

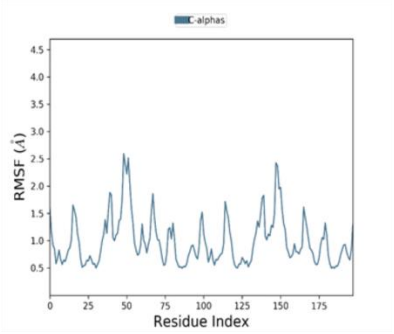


Catechin

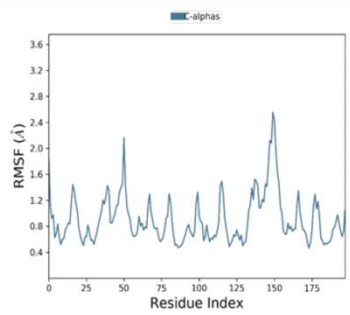


Dolutegravir

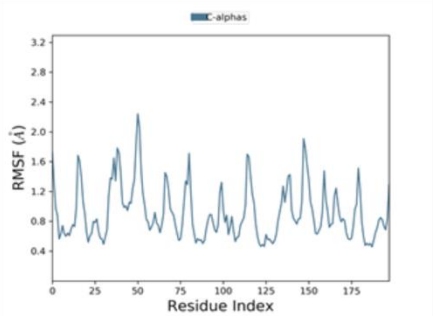
Figure 5: The diagram/s A, B and C: is obtained from Molecular dynamics Simulation and is of the root mean square deviation of the C-α atoms of the protein and the ligand with time in nano seconds (nsec). In this diagram the left γ- axis shows the variation of protein RMSD through time whereby, the right γ- axis shows the variation of the ligand RMSD through time.



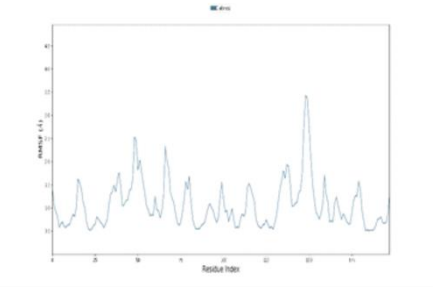
Epicatechin



Juglanin

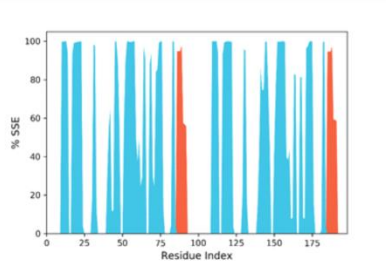


Catechin

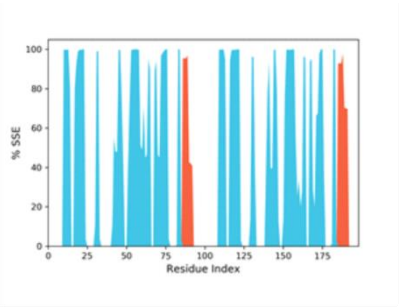


Dolutegravir

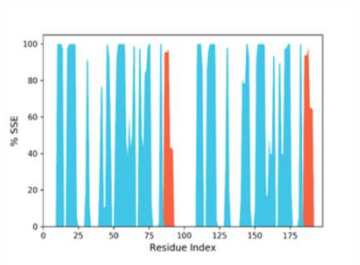
Figure 6: Residue wise Root Mean Square Fluctuation (RMSF)



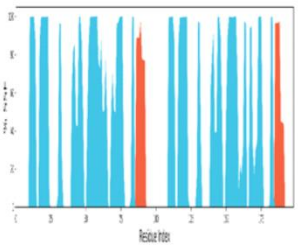
Epicatechin



Juglanin

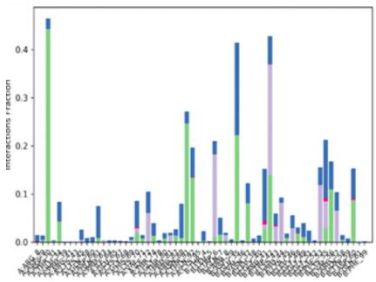


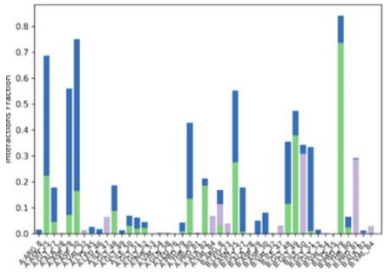
Catechin



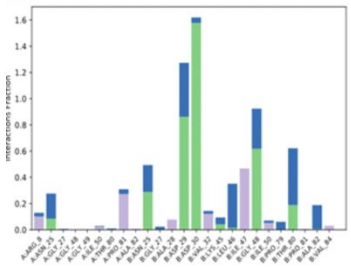
Dolutegravir

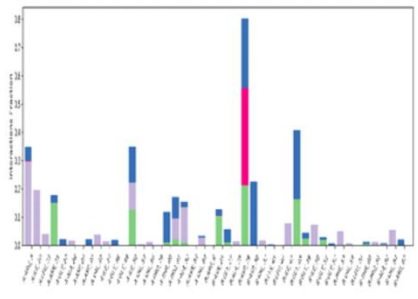
Figure 7: Protein Secondary Structures element distribution by residue index throughout the protein structure. Blue columns indicates beta-strands, red columns indicates alpha helices.





EpicatechinJuglanin





CatechinDolutegravir

Figure 8: Protein-ligand contact histogram

Interestingly, figure 6 shows similar trajectories between juglanin and dolutegravir when the trajectories are saved after every 10ps. This attest to the prediction that juglanin has some properties that resemble that of the control. However, the fluctuations between catechin are not as high as the one observed in the complex between dolutegarvir and 1rv7. Despite the similarity of trajectories between the novel compounds and dolutegravir, the fluctuations between the control and the protein remains a bit high when compared to the rest of the compounds in study.

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