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Phytochemical Analysis and *In Silico* Anti-HIV Activity Studies of Compounds from *Jatropha curcas* Leaves Extracts

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Abstract

Human immunodeficiency virus infection is a global public health concern, despite breakthroughs in its treatment. In many countries, medicinal plants remain a viable treatment option for HIV/AIDS. To gain insight into *Jatropha curcas* anti-HIV potential, this study aimed to identify phytochemicals present in *J. curcas* leaf extract and investigate their interaction with HIV-1 enzymes. Gas chromatography- mass spectrometry was used to identify the phytochemicals in aqueous extract of *J. curcas* leaves, and molecular docking studies were performed with the identified phytochemicals and HIV-1 enzymes. Sixteen (16) phytochemicals were identified from *J. curcas* extract, with eicosanoic acid having the highest relative percentage area of 38.7%. Other phytochemicals found in large amounts include cis-11-eicosanoic and pentadecanoic acids. The molecular docking analysis predicted how the major compounds in *J. curcas* extracts interact with HIV target enzymes. Thymol had moderate docking scores (-4.34) and stronger binding affinity with HIV-1 integrase, but only moderate affinity with HIV-1 reverse transcriptase and protease. Eicosanoic acid only showed notable interaction with HIV-1 protease, with binding affinity of -4.2. Molecular docking studies indicated the potential of *J. curcas* phytochemicals to interact with HIV-1 enzymes, implying that eicosanoic acid and thymol present in *J. curcas* could poses anti-HIV activity.

Keywords: *Jatropha curcas*, HIV-1 reverse transcriptase, integrase, HIV-1 protease, molecular docking

INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that causes HIV/AIDS. It has infected over 84 million people globally and caused the death of about 40 million (Bekker *et al*., 2023). This virus is transmitted from person to person through body fluids such as blood, sexual fluids or sharing of sharp objects. They gain access to the host cells through the CD4 receptor and coreceptors (CCR5 or CXCR4) found on the host cell surface (Grande *et al*., 2019). The binding to this receptor on the host CD4 + T cell lymphocytes caused the destruction of this cell by replicating virus. As the disease progresses, if untreated, the reduced T lymphocyte effectiveness will lead to AIDS; the infected person becomes immuno-compromised and susceptible to opportunistic infections (Grande *et al*., 2019). The use of highly active antiretroviral therapy (HAART) currently dominates HIV/AIDS management; it involved the combination of two antiretroviral drugs (ARV) class with one other class of ARVs (Peng *et al.*, 2023). These regimens were able to suppress viral replication and transformed this fatal condition into a chronic

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manageable disease. The advancement in drug management of HIV infection has reduced mortality and makes it a chronic disease with attendants' challenges such as drug side effects (Xu *et al*., 2023). Thus, people living with HIV/AIDS (PLWHA) use medicinal plants to treat antiretroviral drug side effects and the disease (Feyissa *et al*., 2022).

There is need to intensify the exploration of medicinal plants that may lead to newer phytotherapies that is affordable and devoid of side effects associated with the existing antiretroviral drugs. *Jatropha curcas* ethnomedicine is associated with various uses and studies have already demonstrated its antiviral action (Utshudi *et al*., 2022; Liyongo *et al*., 2023; AA *et al.,* 2023). Also, the use of *J. curcas* leaves extract by the traditional healers to treat HIV/AIDS have been documented in Kwara state, Nigeria (Njan *et al*., 2019). It is called *Botuje* or *igi lapalapa* (Yoruba), *Kasha* (Nupe), *Bini da Zugu* (Hausa) and *odo- ala* (Igbo) (Ndakidemi *et al*., 2021). It belongs to the family called Euphorbiaceaae, usually found in the wild and semi-cultivated areas in Central and South America, Africa, India and Southeast Asia and cultivated in rural areas of Nigeria as a fence round buildings or farmland (Zengin *et al*., 2021). It also has eminent potential for biodiesel production (Keshamma *et al.,* 2024). This potential has led to tremendous cultivation of *J. curcas* that will harness its seed oil for biofuel production and could open a sustainable ecofriendly energy production (Alherbawi *et al*., 2021, *de* Barros *et al*., 2024). Various parts of this plant are used to treat many disease conditions. Latex extracted from this plant is used to treat some dental condition when mixed with salts and to heal wound (Babaei *et al*., 2024). Its dry leaf is also used to stop bleeding in Senegal, Congo, Nigeria, and East Africa. Traditionally, in Nigeria it is used to treat hypotension, diabetes, fever, ulcer and many more diseases (Babaei *et al*., 2024, Eleojo *et al.,* 2024). The leaf of *J. curcas* is pounded and applied on the skin to treat dermatological conditions like ringworm, eczema, carbuncles, mouth blisters and body itching (Zengin *et al*., 2021). Although most of these claims have not been scientifically verified, such use must be with caution.

In the present study, the aqueous extract of *J. curcas* leaf was investigated and phytochemical constituents were identified with the aid of gas chromatography-mass spectroscopy (GC-MS) method. Furthermore, an *in silico* anti-HIV study was conducted to explore the binding interactions of the identified phytochemicals with HIV-1 reverse transcriptase (1rev), HIV-1 integrase (1qs4), and HIV protease (1hvr), key enzymes targets implicated in the pathogenesis of HIV infection using reference ligands as a benchmark by employing molecular docking technique (Jadaun *et al.* 2023, Serna-Arbeláez *et al.,* 2023).

MATERIALS AND METHOD

Plant collection, identification and preparation

Fresh leaves of *J. curcas* were obtained at Malete, Kwara State. The leaf was identified and authenticated by Mr. Bolu Ajayi who is a plant Botanist/Curator of the plant herbarium of the Department of Plant Biology, University of Ilorin. The specimen was filed in the University herbarium where the specimen number (UILH001/1030/2024) was obtained.

The plant extraction was done to mimic traditional method of plant extraction. The leaves of *J. curcas* were collected, cleaned, and air-dried at room temperature. The dried leaf was weighed (1g), pulverized and extracted with water (up to 3L for 3 days) using mechanical agitation. The extract was filtered using Buckner funnel and muslin cloth and concentrated at 40°C using water bath. The resultant extract was freeze dried, labelled (AJC) and stored in desiccator at 2-4°C.

Gas chromatography - Mass spectrometry analysis

The crude extract of *J. curcas* was analyzed to identify its phytochemical constituents using gas chromatography and a mass spectrometer (Agilent 6890 gas chromatograph, CA, USA) equipped with an on-column automatic injector, flame ionization detector, HP 88 capillary column (100m x 0.25µm film thickness). The oven temperature was programmed from 180°C (held for 1 min) to 220°C at a heating rate of 15°C/min (held for 5 min), then raised from 220°C to 250°C at a heating rate of 15°C (Al-Zubairi *et al.,* 2022). Then 1 µl of the diluted extracts were injected into column A using proper injection techniques. The chemical composition was determined by comparing the mass spectra obtained with the mass spectra from the National Institute of Standard and

Technology Spectral library (NIST), 2011 database incorporated within the computer system of the instrument.

Molecular Docking Studies

The five (5) most abundant phytochemicals of *J. curcas* extract from GC-MS analysis were selected for molecular docking analysis. The target proteins are HIV-1 reverse transcriptase, HIV-1 integrase and HIV-1 protease (Ferrão *et al.*, 2023). The three-dimensional structure of enzymes HIV-1 reverse transcriptase (1rev), HIV-1 integrase (1qs4) and HIV-1 protease (1hvr) were downloaded in a PDB format from the protein data bank (https://www.ncbi.nlm.nih.gov/).The structures were prepared for docking using UCSF Chimera Version 1.14 (build 42094) and Protein preparation wizard of Maestro Schrödinger suite (Version 12.5). Using Schrodinger's Receptor Grid Generation tool, a grid box was constructed around the active site, with its geometric center positioned at coordinates X = 34 Å, Y = 34 Å, and Z = 38 Å for 1hvr receptor. Whereas coordinates X = 32 Å, Y = 32 Å, and Z = 32 Å was applied for 1rev receptor. These Cartesian coordinates define the search space for ligand docking, ensuring comprehensive sampling of the binding site. Assignment of bond orders and additions of hydrogen atoms to the heavy atoms were carried out; water molecules were also deleted and only essential ones in the binding pockets were allowed. Unwanted metal ions, ligands repeated in the domains were also removed from the structure. Structures were pre-processed, minimized, and optimized using default force field parameters with Optimized Potentials for Liquid Simulations (OPLS_2005) were employed.

Glide tool was used to generate the receptor grid in the enzyme receptor. The Van der Waals radius was set to a scaling factor of 1.0 and partial charge cut off with 0.25 C. The Grid box three (3) dimensions were set to 16 Å x 16 Å x 16 Å to accommodate the already present ligand and the receptor cavity. The remaining parameters were left at their default values. OPLS_2005 force was maintained for the grid generation. The 3D conformation of ligands was prepared using a Perkin Elmer ChemDraw and Chem3D software and the file was saved in mol format. The ligands were again prepared using the LigPrep tool accompanied with the Maestro Schrödinger suite. Empirical pKa (Epik 2.2) was used to determine the bioavailability profile and within a pH 7.0 +/- 2.0. The minimization parameter was again carried out using OPLS_2005 force field with maximum capacity to generate up to 32 stereoisomers depending on number of chiral centers in ligands included for optimization. Ligand output files were saved in a Maestro file format for compatibility. Whereas Glide extra precision (XP) ligand docking was selected for the docking parameters. The parameter allows determination of binding affinity with a higher accuracy (Yang and Kar, 2024). Prior to submission for docking analysis, the Van der Waals scaling factor and partial charge cut-off was set to 0.80 and 0.15 C, respectively.

RESULTS AND DISCUSSION

GC-MS analysis of the aqueous extract of *J. curcas* leaf

The result of the GC-MS analysis of aqueous leaves extracts of *J. curcas* revealed the presence of different phytochemicals. The total ion chromatogram of the extract presented in Table 1 showed the retention time and the corresponding phytochemicals present in the extract. A total of sixteen (16) phytochemicals were identified, and their molecular formula, molecular weight, and percentage area are presented in table 1. Eicosanoic acid with relative percentage area of 38.17% was indicated as the major phytochemical followed by cis 11-eicosanoic acid, pentadecanoic acid, cyclotetracosane, and thymol with relative percentage area 23.14, 10.95, 7.94, and 5.72 % respectively. Traces of threonine and methylpyrole-2-carboxylate were also found in *J. curcas* extracts (Table 1).

Table 1. Phytochemicals identified in aqueous extract of *J. curcas* leaf from GC-MS.

	RT	%Area	Name	Molecular formula	Molecular weight	KRI
1	4.20	0.06	2,6,10-Dodecatrienal	$C_{12}H_{18}O$	178.27	1293
2	5.39	0.67	Threonine	$C_4H_9NO_3$	119.12	481
3	7.22	0.14	2-Heptanone	$C_7H_{14}O$	114.19	1042
4	8.00	0.02	2-Nonadecanone	$C_{19}H_{38}O$	254.5	2006
5	8.38	0.29	D-Limonene	$C_{10}H_{16}$	136.23	1071
6	11.0	0.02	MethylPyrrole-2-carboxylate	$C_6H_7NO_2$	125.13	2058
7	12.69	0.01	Hexadecanoic acid	$C_{16}H_{32}O_2$	256.42	1950
8	14.20	2.70	Methylmalonic acid	$C_7H_{12}O_4$	160.17	1011
9	14.49	5.72	Thymol	$C_{10}H_{14}O$	150.22	1290
10	14.49	2.25	Cyclohexanal	$C_7H_{12}O$	112.17	958
11	15.62	23.14	Cis 11-Eicosenoic acid	$C_{22}H_{38}O_2$	310.5	2024
12	15.74	7.94	Cyclotetracosane	$C_{24}H_{48}$	336.6	2445
13	16.13	38.17	Eicosanoic acid	$C_{20}H_{40}O_2$	312.5	2305
14	16.96	2.91	Cyclopropaneoctanal	$C_{11}H_{20}O$	168.28	1940
15	18.22	10.95	Pentadecanoic acid	$C_{17}H_{34}O_2$	270.5	1843
16	18.88	1.22	Methyl-2-hydroxy-dodecanoate	$C_{13}H_{26}O_3$	230.34	1619

KRI- kovac retention inde

Molecular Docking of Five Topmost Phytochemicals with HIV-1 Target Enzymes

The results of phytochemical interaction with the corresponding residues in the target enzymes are outlined in Table 2-4. The binding energy with a higher negative value corresponds to a more stable interaction between the phytochemicals and target enzymes. The five (5) topmost selected phytochemicals of *J. curcas* (eicosaonic acid, cis-11-eicosanoic acid, 1-pentadecanoic acid, cyclotetracosane, and thymol) were docked with the HIV-1 target enzymes. Also, a reference ligand (nevirapine, dolutegravir, and lopinavir) for each of the target enzymes were selected and docked with HIV-1 reverse transcriptase, integrase, and HIV-1 protease respectively. To predict the binding modes of the phytochemicals with the target enzymes and identify the interacting amino acids residues, the 2D interactions of the phytochemicals alongside with the 3D interaction of the target enzymes were created, as shown in figure 1-6.

The docking study performed on HIV-1 target enzymes: HIV-1 reverse transcriptase (PDB: 1rev), integrase (PDB: 1qs4), and HIV-1 protease (PDB: 1HVR) were evaluated with various ligands' (i.e. phytochemicals identified by GC-MS analysis of aqueous extract of *J. curcas* leaf) interactions and binding affinities. The primary metric used was docking score, representing the strength of ligand binding. Also, key interactions with amino acids were detailed, including hydrogen bonding (H-bonding), π-π stacking, ionic interactions, and water-mediated interactions. Table 2- 4 showed the type of interactions, interacting amino acids residue and docking scores when HIV-1 target enzymes were docked with the major phytochemicals (ligand) present in *J. curcas* leaves extracts and the standard known inhibitors (nevirapine, dolutegravir, and lopinavir) of HIV-1 enzymes.

The molecular docking study performed on HIV-1 reverse transcriptase (PDB: 1rev) showed that nevirapine (Table 2), a known standard inhibitor of 1rev exhibited a docking score of -9.0 Kcal/mol, attributed to its efficient interaction with hydrophobic pockets, particularly through Val179 (π-π stacking) and Tyr188 (aromatic H-bonding), along with minimal solvent exposure (Deogratias *et al.,* 2022). The π-π stacking with aromatic residues such as Tyr188 and Trp229 helps to stabilize nevirapine within the binding site (Table 2), which is common for non-nucleoside reverse transcriptase inhibitors (NNRTIs) targeting HIV-1 reverse transcriptase (Owoloye *et al.,* 2022). Similarly, thymol demonstrated binding affinity with a score of -7.72 Kcal/mol. Figure 1 showed thymol interactions were predominantly due to the π-π stacking with the aromatic ring of Tyr188, that is a widely known contributor to protein-ligand interaction (Singh *et al.,* 2024). Cis-11-eicosanoic acid suffered from partial solvent exposure, reducing its effective binding stability. Compounds with N/A docking scores in Table 2, such as some of the bulkier or highly hydrophilic molecules (cis-11-eicosanoic acids), did not bind effectively within the active site of 1rev due to either steric hindrance or inability to establish significant interactions. Larger molecules like cyclotetracosane and eicosanoic acid (due to their bulk structures) likely remain partially solvent-exposed, hindering stable binding within the active site and resulting in unassigned docking scores. Water molecules (within 5.0 Å) played a crucial role in stabilizing ligand-protein complexes (Sun *et al.,* 2024). However, excessive reliance on solvent interactions often resulted in lower docking scores. Ligands with high solvent exposure demonstrated reduced hydrophobic interactions and less effective binding to active site residues. For instance, cyclotetracosane's partial solvent exposure significantly limited their binding potential. Structure-Activity Relationship (SAR) analysis revealed that small, planar molecules like nevirapine benefited from tight fits within the active site and strong π-π stacking and H-bonding interactions, while bulky molecules like cyclotetracosane faced steric hindrance and weaker binding due to high solvent exposure.

Ligands like thymol highlighted the importance of balancing hydrophobic and polar interactions to achieve moderate binding affinity. Therefore, nevirapine (reference standard), with the lowest docking score and strong interactions, is likely the most effective inhibitor among the tested compounds. This analysis highlights nevirapine's specific suitability for the 1rev active site, likely resulting in effective inhibition of the enzyme.

Table 3 showed interactions of respective ligands with the HIV-1 integrase (PDB ID: 1qs4), with a distinct docking score, binding affinities, and interaction profiles. Among the ligands, dolutegravir and thymol demonstrated the strongest binding affinity with a docking score of-7.06 and -4.34 kcal/mol respectively. In figure 2, dolutegravir formed aromatic hydrogen bonding and hydrogen bonds with various residues including Glu152, Asn155, Lys156 and Lys159 suggesting its potential as a lead compound. These multiple types of interactions with residues in the binding pocket are likely to contribute to Dolutegravir's effective inhibition of HIV-1 integrase, aligning with its known potency as an integrase strand transfer inhibitor (INSTI) (Li *et al.,* 2023). Also, thymol formed hydrogen bonds with Glu154, however, due to exposure to solvent, it rendered a lower docking score.

In contrast, 1-pentadecanoic acid exhibited a poor docking score of 1.21 kcal/mol, interacting weakly with Thr66, Asn166, and Lys156 through hydrogen bonding and s/alt-bridge. The low docking score also suggests that 1-pentadecanoic acid is highly energetic (unstable) in the binding pocket. Analysis of the ligands' structural features revealed that smaller, polar molecules with functional groups capable of hydrogen bonding, such as hydroxyl (-OH) or amino (-NH_2) groups (also present in dolutegravir), demonstrated stronger binding affinities. For instance, thymol effectively leveraged these interactions, leading to stronger binding. Conversely, bulkier ligands like 1-pentadecanoic acid in figure 2, faced steric hindrance and exposure to solvent and hence showed minimal interactions, resulting in weaker binding. The diversity in binding modes, including hydrogen bonding and salt-bridge formation, underscores the importance of both the ligand's electronic properties and spatial compatibility for effective binding. Cis-11-eicosenoic-acid did not show interaction with HIV-1 integrase receptor due to its bulky conformation and absence of interactive groups compared to the other ligands. Therefore, thymol is likely to be the most effective among

the tested compounds and dolutegravir (reference standard).

Table 4 represents the molecular docking series of ligands targeting the HIV protease enzyme (PDB ID: 1hvr), revealing varying binding affinities and interaction profiles. Among the ligands tested, lopinavir exhibited the strongest binding affinity with a docking score of -10.96 Kcal/mol. As shown in figure 3, lopinavir demonstrated robust interactions, including hydrogen bonds with Ash25, Asp25, and Asp29, and aromatic hydrogen bonding with Asp30. These interactions underscore the established clinical efficacy of lopinavir in inhibiting HIV protease (Kandeel *et al*., 2023). Moderate binding affinities were observed for ligands such as thymol and eicosanoic acid. Thymol, with a docking score of -6.64 Kcal/mol, primarily interacted through hydrogen bonding with Gly48. Eicosanoic acid also exhibited moderate binding (docking score: -4.12 Kcal/mol), mediated through hydrogen bonding and ionic interactions with Lys45. These ligands demonstrate potential for optimization, as their interaction profiles suggest the possibility of enhancing binding affinity through structural modifications.

In contrast, low-affinity ligands such as 1-pentadecanoic acid showed weaker interactions with the HIV protease. The weakest binder, 1-pentadecanoic acid, had a negligible docking score of -0.02 Kcal/mol, forming minimal interactions with Arg8. These results suggest limited binding efficacy for these compounds, making them less promising as potential inhibitors without significant modification. Two ligands, cyclotetracosane and cis-11-eicosenoic acid, showed no notable interactions with the HIV protease, as indicated by the absence of docking scores. This lack of binding underscores the importance of structural compatibility for effective ligand-receptor interaction. Overall, the docking results provide valuable insights into the binding behavior of various phytochemicals present in the aqueous extract of *J. curcas* leaf and thymol is the best performed phytochemical in *J. curcas* leaf when compared to all the reference standard. A pilot study conducted by Njan et al 2019, documented the use of this plant to treat HIV infection. Further study should be undertaken to isolate and determine anti-HIV effects of phytochemicals present in this plant.

Table 2. Molecular docking of standard drug and *J. curcas* phytochemicals with HIV-1 reverse transcriptase

S/N	Compounds	Docking score with 1rev	Interacting residue	Type of interaction
1	Nevirapine	-9.00	Val179 Tyr188 Trp229	Aromatic H-bond π- π stacking π- π stacking
2	Thymol	-7.72	Tyr188	π- π stacking
3	1-Pentadecanoic acid	-5.67	Lys101 Lys103	Salt bridge H-bond
4	Eicosanoic acid	N/D	N/D	N/D
5	Cyclotetracosane	N/D	N/D	N/D
6	Cis-11-eicosanoic acid	N/D	N/D	N/D

1rev- HIV-1 reverse transcriptase; N/D- no notable interaction

Table 3. Molecular docking of standard drug and *J. curcas* phytochemicals with HIV-1 integrase.

S/N	Compounds	Docking score with 1sq4	Interacting residue	Type of interaction
1	Dolutegravir	-7.06	Gln148(0) Asn155(0) Lys156 Lys156 Lys156 Lys159	Aromatic H-bond H-bond π-cation H-bond Ionic interaction H-bond
2	Thymol	-4.34	Glu154	H-bond
3	1-Pentadecanoic acid	1.21	Thr66 Asn166 Lys159	H-bond, salt bridge H-bond H-bond
4	Eicosanoic acid	N/D	N/D	N/D
5	Cyclotetracosane	N/D	N/D	N/D
6	Cis-11-eicosanoic acid	N/D	N/D	N/D

1sq4- HIV-1 integrase; N/D- no notable interaction

Table 4. Molecular docking of standard drug and *J. curcas* phytochemicals with HIV-1 protease.

S/N	Compounds	Docking score with 1hvr	Interacting residue	Type of interaction
1	Lopinavir	-10.96	Ash25 Asp25 Asp29 Asp30	H-bond H-bond H-bond Aromatic H-bond
2	Thymol	-6.64	Gly48	H-bond
3	1-Pentadecanoic acid	-0.02	Arg8	H-bond, salt bridge
4	Eicosanoic acid	-4.2	Lys45, lys45	H-bond, ionic interaction
5	Cyclotetracosane	N/D	N/D	N/D
6	Cis-11-eicosanoic acid	N/D	N/D	N/D

1hvr- HIV-protease, N/D- no notable interaction

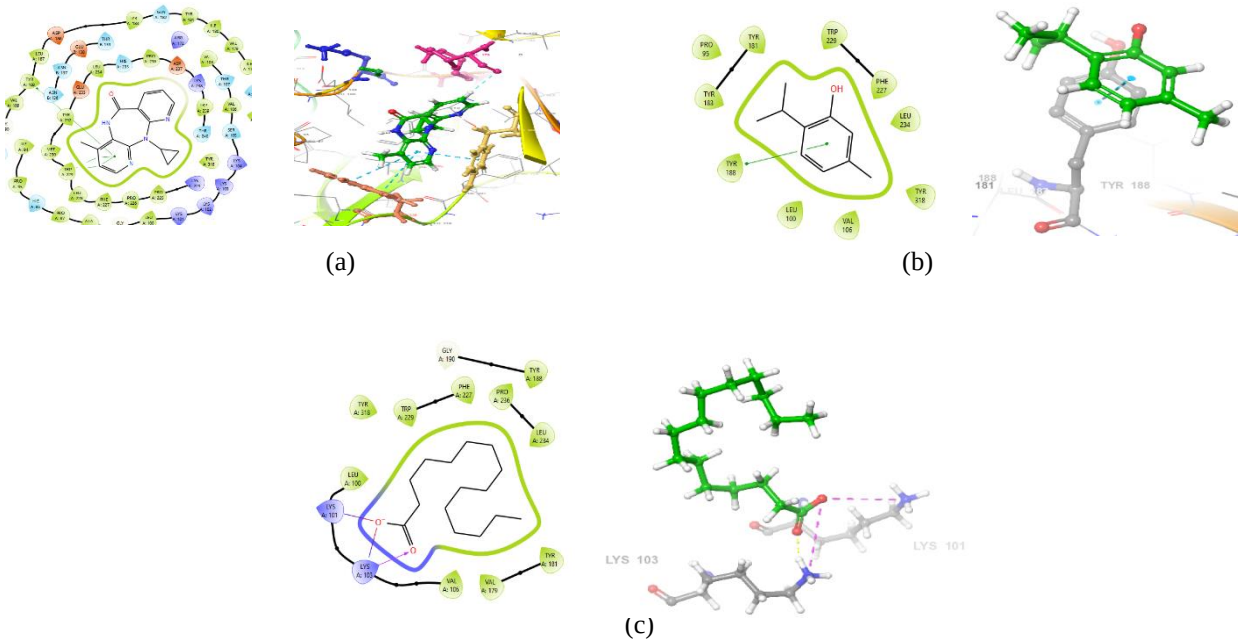
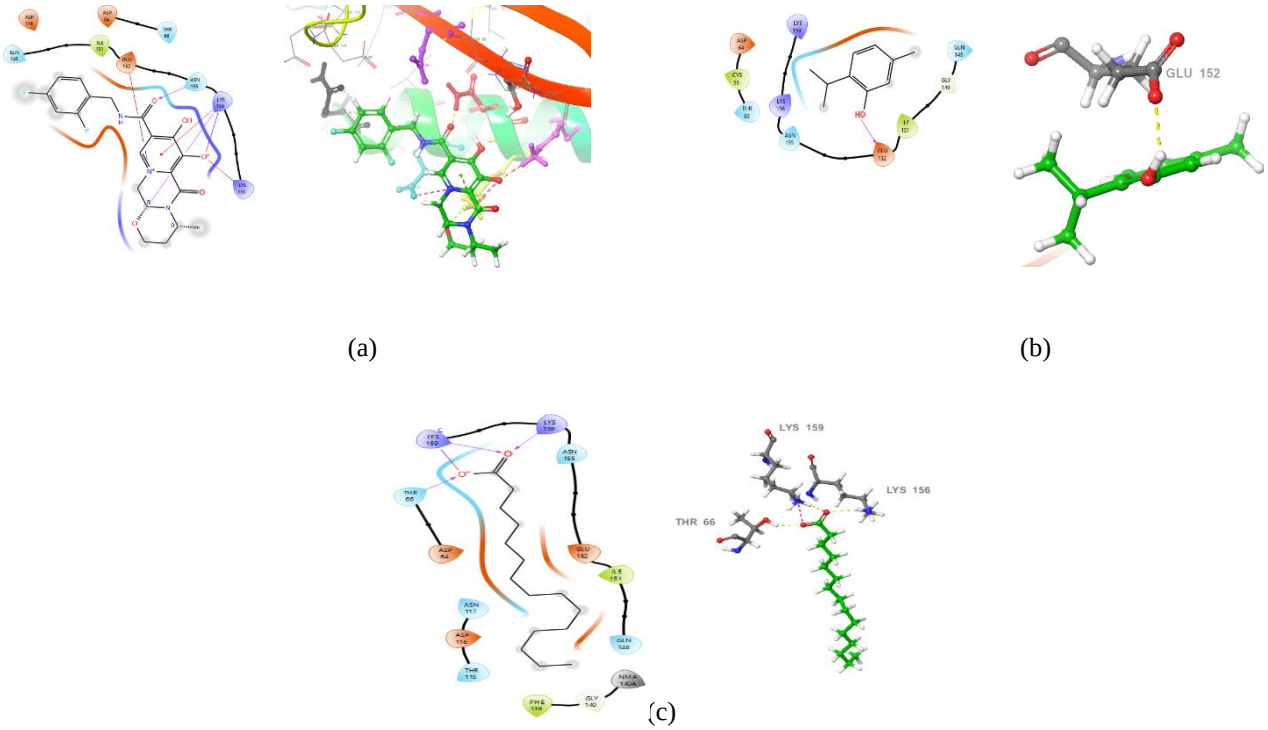
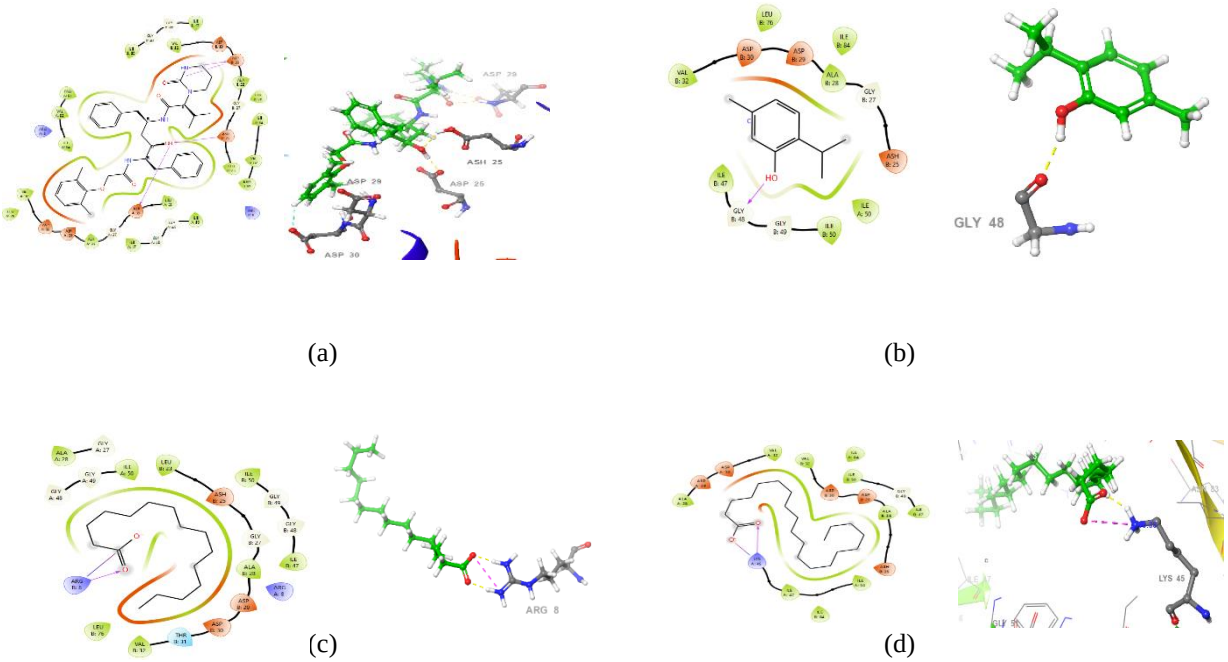


Figure 1. Molecular docking of results of (a) nevirapine; (b) thymol; (c) 1-pentadecanoic acid with and HIV-1 reverse transcriptase.



(a) (b) (c)

Figure 2. Molecular docking of results of (a) dolutegravir; (b) thymol; (c) 1-pentadecanoic acid with and HIV-1 integrase.



(a) (b) (c) (d)

Figure 3. Molecular docking of results of (a) lopinavir; (b) thymol; (c) 1-pentadecanoic acid, (d) eicosanoic acid with and HIV-1 integrase.

CONCLUSION

Out of the five (5) topmost phytochemicals identified from the GC-MS analysis of the aqueous extracts of *J. curcas* leaf, only cyclotetracosane and cis 11- eicosanoic acid did not display any significant interaction with the target enzymes (HIV-1 reverse transcriptase, integrase and HIV-1 protease). Thymol exhibits strong potent inhibition for HIV-1 integrase, moderate inhibition for HIV-1 reverse transcriptase and protease enzymes. It may require structural modifications to increase its interaction potential and effectiveness as an inhibitor of HIV-1 integrase strand enzyme. In conclusion, these five compounds contribute to the anti-HIV-1 properties of *J. curcas*. Therefore, further studies are necessary to validate the inhibitory properties of these compounds and possible development of new antiretroviral drug.

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