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Molecular Docking and Dynamic Simulation Studies for Antiretroviral Activity of phytochemicals isolated from *Croton dichogamus*

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Abstract:

The Human Immunodeficiency Virus (HIV) infection and the associated acquired immune deficiency syndrome (AIDS) remain global challenges even after decades of successful treatment, with eastern and southern Africa still bearing the highest burden of disease. To search for potential anti-HIV compound from natural products we subjected 28 phytochemicals previously isolated from *Croton dichogamus* to molecular docking and dynamic simulation studies against HIV-1 reverse transcriptase enzyme (PDB ID: 1REV). Molecular docking was performed using Autodock 4.2.6, while molecular dynamic simulations were performed for 100ns for compounds with top docking poses using the Desmond package, Schrodinger. Based on our finding, we report five potential inhibitors of HIV-1 RT, including aleuritolic acid, furocrotinsulolide A, crotoxide A, crotohaumanoxide and Crothalimene A, with respective free binding energies of -173.52, -40.53, -38.07, -35.78 and -32.73 kcal/mol. These compounds have shown high free binding energy as compared to standard FDA approved antiretroviral drugs. Our computational studies have also shown that these phytochemicals form hydrophobic interactions with ASN 265, GLU 378, GLY 352, HIS 96, ILE 382, SER 268, TRP 266, hydrogen bonding with ARG 355, ARG 356, ARG 358, GLN 269, ILE 94, LEU 92, LYS 350, LYS 353, LYS 374, TYR 232 amino acids in the active site of the enzyme. Thus, we report these top 5 phytochemicals as potentially potent, selective, orally bioavailable, and nontoxic leads based on the ADMET screening and effective binding analysis in the active site of the reverse transcriptase (PDB ID: 1REV) for further consideration.

Keywords: *Croton dichogamus*, HIV, Molecular Docking, Molecular dynamic simulation

Global data

Since the HIV Pandemic

75.7 million

Infected with HIV

>33 million

Died from AIDS related illness

UNAIDS, 2020

Introduction …

out of which 54% (20.7 million) live in southern and East African region.

> 25% (5 million) people donot have access to the treatment (UNAIDS, 2020)

Croton dichogamus

- 2-5 meters tall
- Local names
  - “l-akirding'ai”- Samburu
  - “Oloibor benek” – Loitoktok
  - “Mwalula,” – Kituti

Ethno medicinal uses of *Croton dichogamus*

chest complaints, malaria and stomach

arthritis and gonorrhea

respiratory diseases such as asthma, pneumonia, and cough

infusion of the stem bark and leaves

impotence and infertility→ root decoction

Tuberculosis→ roots milled then mixed with porridge

relief from fever →smoke of the burnt leaves

gonorrhea,

Pharmacological activities of the *C. dichogamus*

- Antimycobacterial
- Antimalarial
- Antibacterial
- Antioxidant
- Antitumor activity

- Insecticidal
- Hypocholesteremic
- Antiinflammatory
- Antihypertensive

- 10-epi- **Maninsigin** D, diterpenoid (Aldhaher et al., 2016; 2017a).

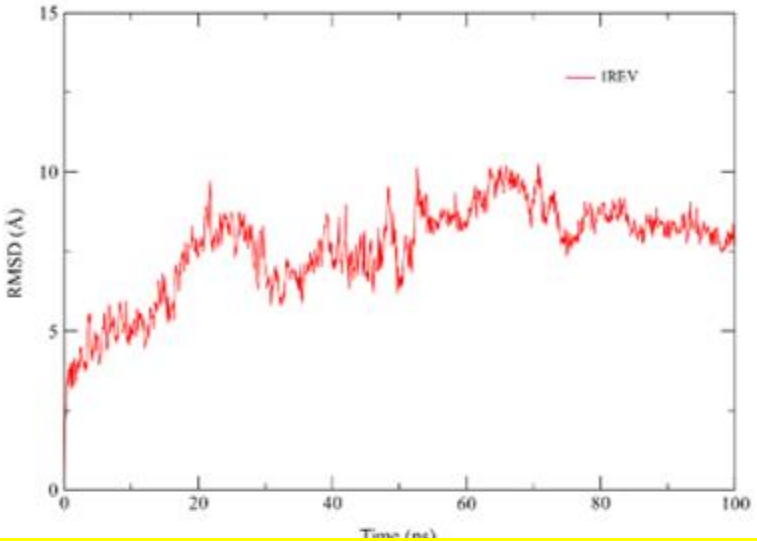
Results and discussion

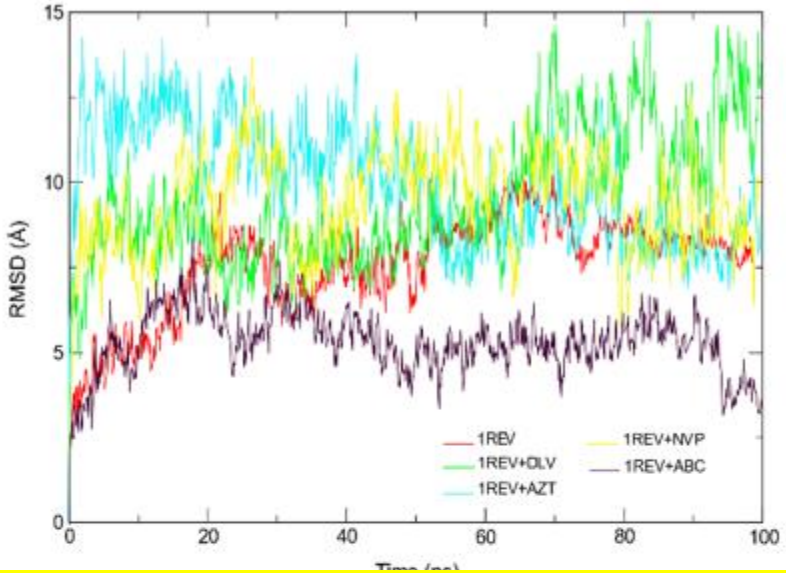
Table 1. Molecular docking analysis of phytochemicals isolated from *Croton dichogamus against HIV-1 reverse transcriptase (PDB: 1REV)*

Ser. No.	Code	Name of Phytochemicals	Binding energy (Kcal/mol)	Inhibition constant, Ki in uM
FDA approved drugs				
1.	DLV	Delaviridine	-6.85	9.54
1.	NVP	Nevirapine	-5.65	72.21
1.	AZT	Zidovudine	-5.68	68.71
1.	ABC	Abacavir	-5.63	74.74
Phytochemicals isolated from C. dichogamus				
1.	L12	Aleuritolic acid	-8.48	0.61
1.	L135	Crotoxide A	-7.73	2.12
1.	L292	Crothalimene A	-7.48	3.3
1.	L216	Crotodichogamoin B	-7.42	3.62
1.	L104	Crotonolide E	-7.31	4.42

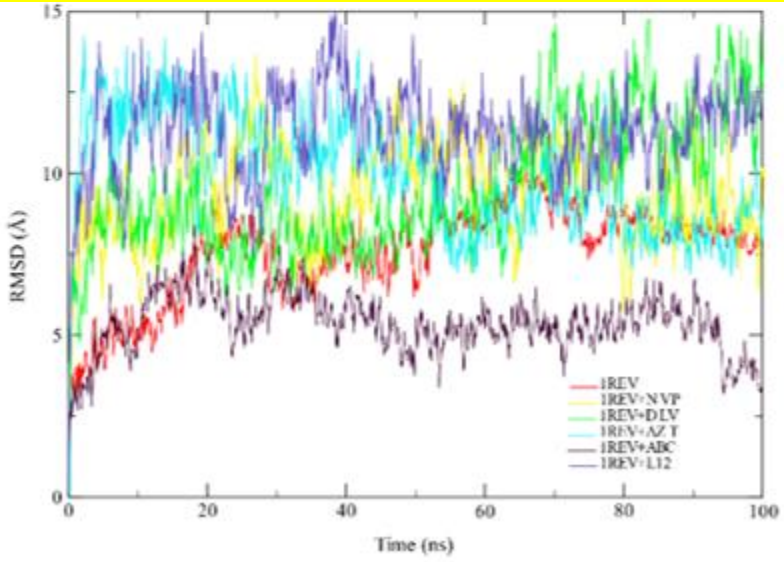
Table 2 Binding free energy for phytochemical compounds from *C. dichogamus* and FDA approved drugs to HIV-RT 1REV using MMGBSA

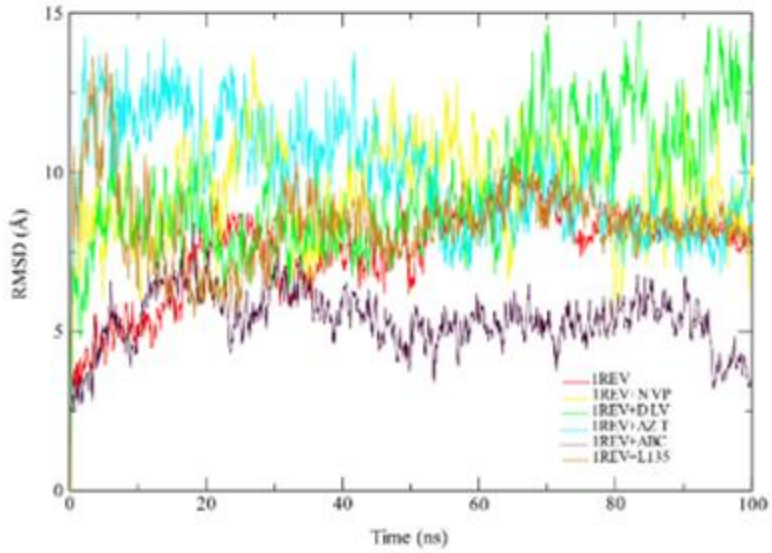
Code	Name of Complex	Energy component (kcal/mol)				
		ΔGbind	ΔGbind Coulomb	ΔGbind Covalent	ΔGbind SolvGB	ΔGbind vdW
FDA approved drugs						
DLV	Delaviridine	-50.85 ± 0.25	-19.24 ± 0.21	-0.11 ± 0.06	-52.49 ± 0.26	-32.09 ± 0.11
ABC	Abacavir	-29.01 ± 0.22	-3.38 ± 0.09	-0.22 ± 0.04	-43.09 ± 0.26	-20.58 ± 0.08
NVP	Nevirapine	-28.06 ± 0.17	-6.37 ± 0.11	-0.11 ± 0.09	-28.19 ± 0.19	-21.08 ± 0.09
AZT	Zidovudine	-27.39 ± 0.24	-3.58 ± 0.10	-0.59 ± 0.03	-40.57 ± 0.28	-23.04 ± 0.11
Phytochemical compounds						
L12	**Aleuritolic acid**	**-173.52 ± 1.28**	-35.35 ± 0.64	-0.41 ± 0.06	-114.78 ± 1.17	-27.79 ± 0.15
L105	**Furocrotinsulolide A**	**-40.53 ± 0.22**	-6.38 ± 0.13	-0.41 ± 0.08	-30.58 ± 0.23	-31.14 ± 0.18
L135	**Crotoxide A**	**-38.07 ± 0.16**	-8.9 ± 0.09	-0.67 ± 0.04	-25.47 ± 0.16	-28.4 ± 0.10
L140	**Crotohaumanoxide**	**-35.78 ± 0.19**	-8.76 ± 0.09	-0.99 ± 0.07	-37.55 ± 0.21	-24.93 ± 0.13
L292	**Crothalimene A**	**-32.73 ± 0.17**	-5.22 ± 0.07	-0.11 ± 0.07	-31.65 ± 0.18	-24.99 ± 0.11
L216	Crotodichogamoin B	-31.98 ± 0.21	-7.75 ± 0.11	-1.58 ± 0.09	-29.76 ± 0.18	-24.18 ± 0.13
L104	Crotonolide E	-30.95 ± 0.21	-5.73 ± 0.13	-0.11 ± 0.06	-26.85 ± 0.19	-29.04 ± 0.15

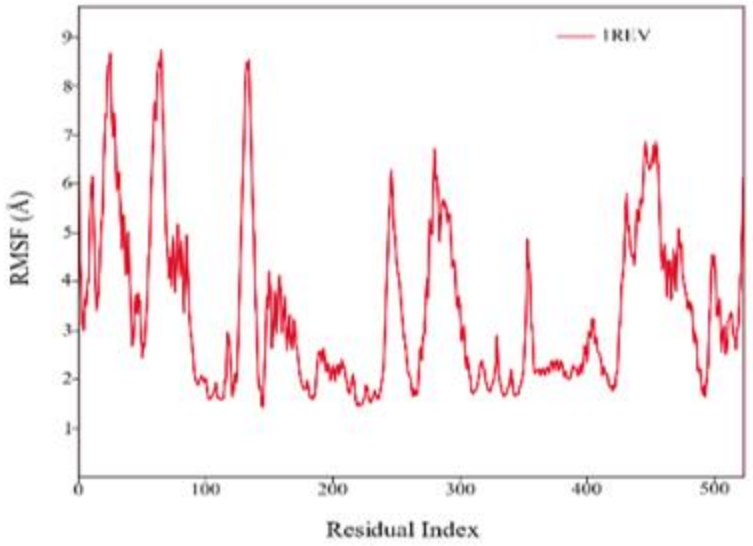


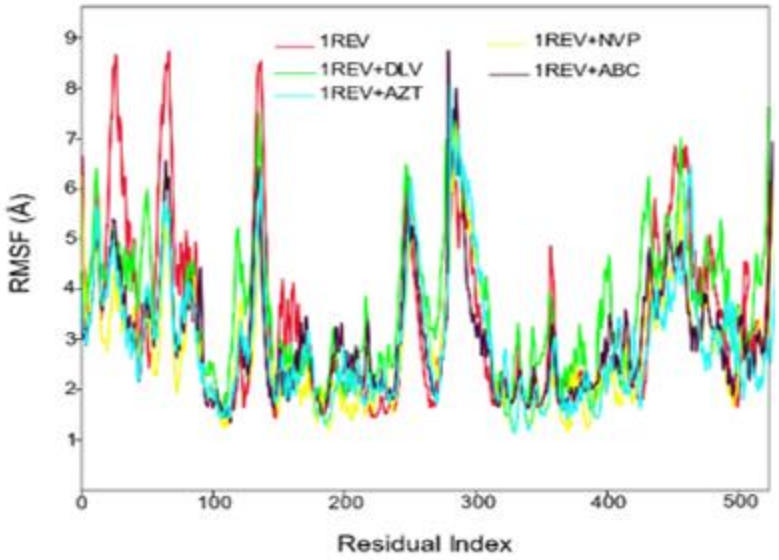


The calculated RMSD between the phytochemical compounds aleuritolic acid (L12), crotoxide A (L135), crothalimene (L292), crotohaumanoxide (L140) and crotodichogamoin B (L216) is within 0.1nm (1Å) as compared with the protein HIV-RT (1REV), and the control drugs nevirapine, etravirine and delaviridine indicating only a very small change in the ligands position during the simulation period

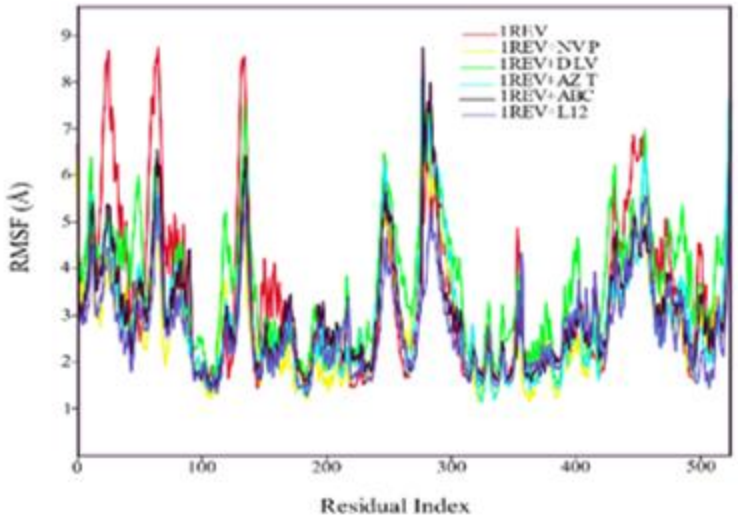








1REV+L135 showed that the amino acid residues have same trend in fluctuations as the control ABC, while 1REV+L292 and 1REV+L216 complexes showed related RMSF plot to NVP.



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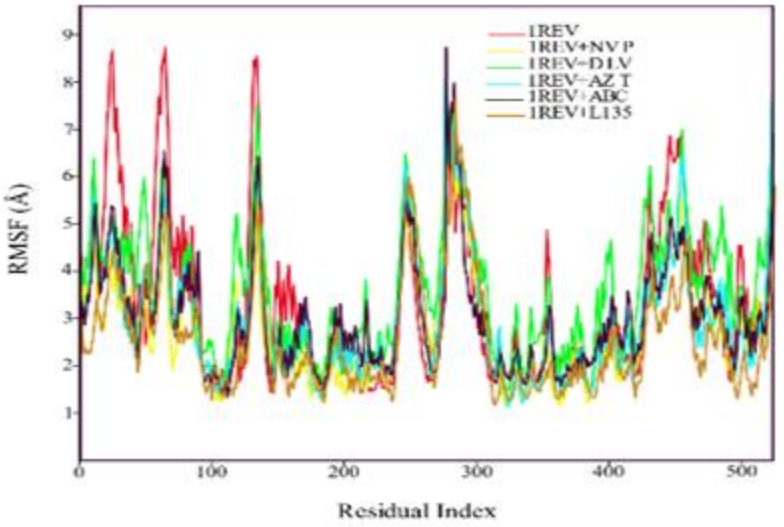

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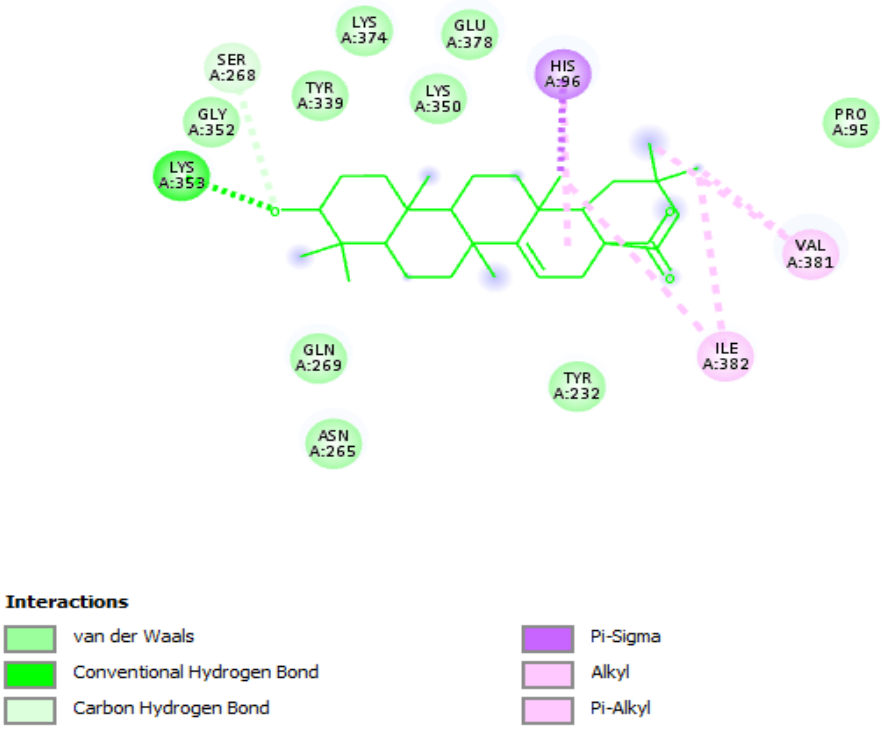

Figure 3. Docked poses of Aleuritolic acid (L12)

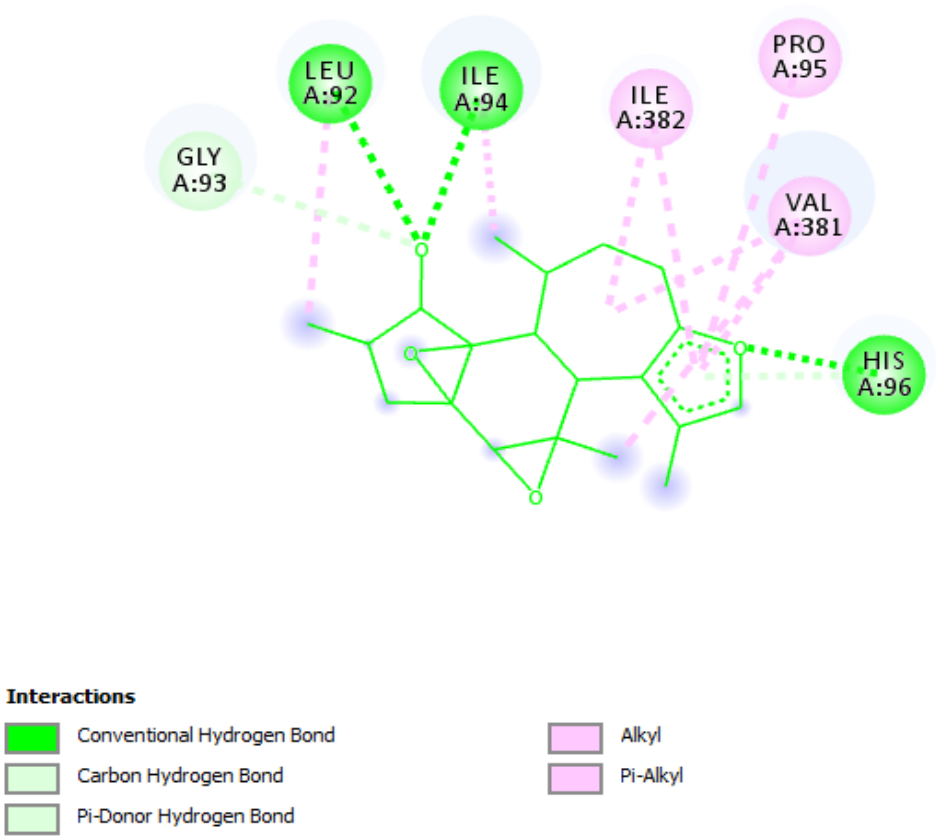

Figure 4 Docked poses of Crotoxide A (L135)

Conclusions

- We report five phytochemical compoiunds as potential inhibitors of HIV-1 RT including **aleuritolic acid, furocrotinsulolide A, crotoxide A, crotohaumanoxide and Crothalimene A**, with respective free binding energy of -173.52, -40.53, -38.07, -35.78 and -32.73 kcal/mol.
- These compounds have shown high binding energy as compared to standard FDA approved antiretreoviral drugs.
- Our computational studies have also shown that these phytochemicals form hydrophobic interactions with ASN 265, GLU 378, GLY 352, HIS 96, ILE 382, SER 268, TRP 266, hydrogen bonding with ARG 355, ARG 356, ARG 358, GLN 269, ILE 94, LEU 92, LYS 350, LYS 353, LYS 374, TYR 232 amino acids in the active site of the enzyme.

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