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Virtual Screening of Alternative Antiretroviral through Integrase Inhibitor from Curcuma longa L. and Tamarindus indica Compounds Against HIV-1 Infection

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ABSTRACT
The development of new drugs with improved efficacy and reduced side effects is of utmost importance to combat the global HIV/AIDS pandemic. In this study, we aimed to explore the potential of natural compounds derived from *Curcuma longa* L. (turmeric) and *Tamarindus indica* (tamarind) as alternative antiretroviral agents through the virtual screening of integrase inhibitors. *Curcuma longa* L. and *Tamarindus indica* are widely recognized for their medicinal properties and have been traditionally used in various systems of medicine. These plants contain a rich repertoire of bioactive compounds that exhibit a wide range of pharmacological activities, including antiviral effects. By identifying potential integrase inhibitors from natural compounds, we aim to contribute to the discovery of novel antiretroviral agents that could be developed into effective treatments against HIV-1 infection through compoutational simulation. The computational method used in this study is sample preparation in the database and molecular docking to identify the activity of Tamarindus indica and Curcuma longa L. compounds on HIV-1. *Tamarindus indica* and *Curcuma longa* L. can be effective HIV-1 antretroviral agents because they have compounds with the most negative binding affinity consisting of Campesterol and Curcumin. Both compounds are predicted to inhibit the HIV-1 integrase enzyme to disrupt the integration of the viral genome in host cells.

Keywords: Antiretroviral, *Curcuma longa*, *In silico*, *Tamarindus indica*

INTRODUCTION

Effective antiretroviral therapies against HIV-1 infection remains a crucial area of research in the field of medicine[1,2]. The development of new drugs with improved efficacy and reduced side effects is of utmost importance to combat the global HIV/AIDS pandemic[3,4]. In this study, we aimed to explore the potential of natural compounds derived from *Curcuma longa* L. (turmeric) and *Tamarindus indica* (tamarind) as alternative antiretroviral agents through the virtual screening of integrase inhibitors[5,6]. Integrase, a key

† Footnotes relating to the title and/or authors should appear here.
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enzyme involved in the replication of the HIV-1 virus, has been identified as an attractive target for antiretroviral therapy. Inhibitors of integrase have shown promising results in blocking viral replication and preventing the progression of HIV-1 infection[7,8,9]. Natural compounds derived from medicinal plants have gained significant attention due to their diverse chemical structures and potential therapeutic properties[10].

Curcuma longa L. and *Tamarindus indica* are widely recognized for their medicinal properties and have been traditionally used in various systems of medicine[11]. These plants contain a rich repertoire of bioactive compounds that exhibit a wide range of pharmacological activities, including antiviral effects[12,13]. Therefore, we hypothesized that the compounds derived from *Curcuma longa* L. and *Tamarindus indica* might possess inhibitory effects against HIV-1 integrase and could serve as potential candidates for the development of alternative antiretroviral therapies.

In this study, we employed virtual screening techniques to identify and evaluate the binding affinity and potential inhibitory activity of compounds from *Curcuma longa* L. and *Tamarindus indica* against HIV-1 integrase[14,15]. The virtual screening approach allows for the efficient screening of a large number of compounds, reducing the time and cost associated with experimental screening[16,17]. By identifying potential integrase inhibitors from natural compounds, we aim to contribute to the discovery of novel antiretroviral agents that could be developed into effective treatments against HIV-1 infection through compoutational simulation. The findings of this study may provide valuable insights into the therapeutic potential of natural compounds and pave the way for further experimental and clinical investigations in the field of HIV/AIDS research.

METHOD

Sample Retrieval and Preparation

Chemical compounds from *Tamarindus indica* and *Curcuma longa* L. were used in this study as ligands. The compounds of the two medicinal plants are γ-Sitosterol, Campesterol, α-Amyrin, Curcumin, Ellagic acid, Quercetin. 2D structures, structure data format (*sdf*) files, compound names, molecular weight (g/mol) were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Energy minimization and structure conversion into protein databank format (pdb) through OpenBabel v2.3.1 software for ligand flexibility improvement and molecular docking preparation[18,19].

Integrase in HIV-1 plays a role for the integration of viral cDNA into the cell genome and then initiates the transcription of viral genes by host transcription enzymes for pathogenicity regulation such as immune response evasion, infection severity, and new virus formation or replication. The 3D structure of integrase in this study was obtained from RCSB PDB database (https://www.rcsb.org/) with *pdb* file. Removal of water molecules and native ligands was done through PyMol v2.5 software for target optimization in docking simulations[20,21,22].

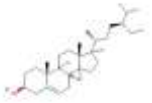
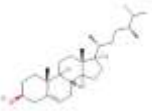
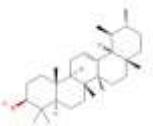
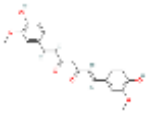
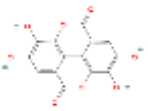
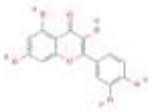
Molecular Docking Simulation

Identification and simulation of ligand binding activity to the target domain aimed at assessment for the determination of drug candidates is molecular docking. Docking in this study aims to identify the activity of chemical compounds from *Tamarindus indica* and *Curcuma longa* L. inhibiting integrase enzyme in HIV-1. The blind docking method with AutoGrid was set to cover the entire target for side screening and effective ligand binding pattern to affect the inhibitory activity. PyRx v1.0.0 software through VinaWizard plugin with gird setting (maximize) was used in this study. The binding affinity value of each compound was obtained to determine the most effective activity to affect the target[23,24,25].

RESULTS AND DISCUSSION

Information on compound names, CIDs, formula, 2D structures on γ-Sitosterol, Campesterol, and α-Amyrin from *Tamarindus indica* and curcumin, ellagic acid, and quercetin from *Curcuma longa* L. (Table 1). *Curcuma longa* L. is identified as an effective antiviral agent because it has curcuminoid compounds that act to inhibit viral activity, besides that curcuminoid class compounds can also inhibit bacterial replication and prevent fungi from adapting to the environment[26,27,28]. Extracts from *Tamarindus indica* can inhibit and reduce viral load in HSV-1 infection[29,30]. However, the molecular mechanism as antiviral in compounds from *Tamarindus indica* and *Curcuma longa* L. is not yet known.

Table 1. *Tamarindus indica* and *Curcuma longa* L. compounds from database

Natural Source	Compound	PubChem CID	Formula	2D Structure
Tamarindus indica	γ-Sitosterol	457801	$C_{29}H_{50}O$	
	Campesterol	173183	$C_{28}H_{48}O$	
	α-Amyrin	73170	$C_{30}H_{50}O$	
Curcuma longa L.	Curcumin	969516	$C_{21}H_{20}O_6$	
	Ellagic acid	5281855	$C_{14}H_6O_8$	
	Quercetin	5280343	$C_{15}H_{10}O_7$	

Prediction of the binding mechanism of compounds from Sambucus nigra on the three HIV-1 proteins was carried out through molecular simulation. The simulation aims to determine the level of binding ability of a ligand to a protein domain based on the binding affinity value in a stable ligand-protein complex and produces negative energy. Binding affinity is formed when there is interaction between protein and ligand, this energy is formed through reversible reactions at constant temperature and pressure in accordance with the laws of thermodynamics. The grid in the docking simulation plays a role to direct the ligand binding to the target protein. The simulation performed with refer to a docking grid consisting of Center (Å) X: -40.950 Y: 5.228 Z: -5.372 Dimensions (Å) X: 25.641 Y: 23.612 Z: 20.492 on HIV-1 INT. The docking results showed Campesterol from Tamarindus indica and Curcumin from *Curcuma longa* L. had the most negative binding affinity value (Table 2). This indicates that Campesterol and Curcumin are predicted to have high inhibitory activity on the HIV-1 integrase enzyme which may interfere with the regulation of viral genome integration with the host.

Table 2. The results of molecular docking simulation

Natural Source	Compound	PubChem CID	Target	Binding Affinity (kcal/mol)
Tamarindus indica	γ-Sitosterol	457801	INT (PDB ID: 6NCJ)	-7.0
	Campesterol	173183	INT (PDB ID: 6NCJ)	**-7.1**
	α-Amyrin	73170	INT (PDB ID: 6NCJ)	-7.0
Curcuma longa L.	Curcumin	969516	INT (PDB ID: 6NCJ)	**-6.6**
	Ellagic acid	5281855	INT (PDB ID: 6NCJ)	-6.2
	Quercetin	5280343	INT (PDB ID: 6NCJ)	-6.3

CONCLUSION

Tamarindus indica and *Curcuma longa* L. can be effective HIV-1 antretroviral agents because they have compounds with the most negative binding affinity consisting of Campesterol and Curcumin. Both compounds are predicted to inhibit the HIV-1 integrase enzyme to disrupt the integration of the viral genome in host cells. However, the results of this study must be proven through further tests such as wetlab for additional scientific evidence.

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