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PHARMACOLOGICAL PROPERTIES OF LINEAROLACTONE AGAINST THE AMOEBIASIS CAUSED BY *Entamoeba histolytica*: AN *IN-SILICO* STUDY

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INTRODUCTION

Entamoeba histolytica **is the causative agent of amoebiasis, a disease that produces dysentery for the perforation of the large intestine [1]. This parasite often invades other organs, primarily the liver, leading to an amoebic liver abscess (ALA), which can cause death [1]. Metronidazole is the drug of choice for the treatment of ALA; however, it produces toxic side effects in patients [2]. Therefore, there is a need to search for new, safer, and more effective antiamoebic drugs. One option is linearolactone (LL) isolated from *Salvia polystachya* that presents antiparasitic activity against *E. histolytica* and *G. lamblia* through ROS production, an apoptosis-like process, and alteration of the actin cytoskeleton [3]. However, the possible toxicological effects or molecular mechanisms of LL are still not understood.**

AIMS

The aim of this study was to determine the pharmacological and toxicological properties of LL by bioinformatic analyzes.

RESULTS

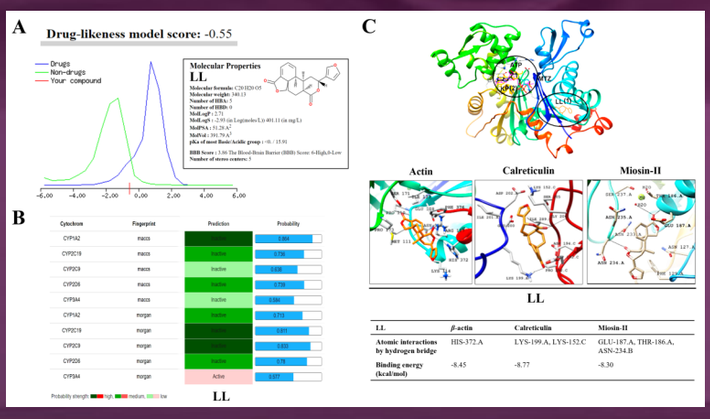

Figure 1. Pharmacological and toxicological properties of LL by *in silico* analysis. The prediction of drug-likeness and molecular properties of LL by Molsoft (**A**). The estimation of LL metabolism via the cytochrome P450-system by MACCS and MORGAN models in SuperCYPsPred (**B**). Molecular docking of LL between actin (right circle), representative bonds of LL with cytoskeleton proteins of *E. histolytica* as β-actin, calreticulin or miosin-II, as well as atomic interactions of LL with specific aminoacids of cytoskeleton proteins and binding energy respective (**C**). Representative results of 3 independent replicates (n = 3; triplicates).

Table 1. Molecular targets of LL in human.

Compound name	Gene key	Target protein	Organism	Description	*P*-Value	Max Tc*
LL ZINC 95912874 *CID: 145952768 CAS: 113973-98-1	OPRK1_HUMAN (SP: 41145)	GPCR-A (membrane receptor)	Eukaryote (Human)	Kappa-type opioid receptor	6.49×10^{-37}	0.49

*Affinity binding of compound vs protein ≤ 10 μM. *PubChem identifier. LL, linearolactone ($C_{20}H_{20}O_5$, MW: 340.4); SP, Swiss-Prot protein sequence database (UniProt); GPCR-A, G protein-coupled receptors type-A.

CONCLUSION

LL is a compound with possible moderate toxicity, sedative effects on CNS, and anti-inflammatory properties. In addition, LL probably inhibits amoebic liver abscess formation through interactions with myosin-II and calreticulin from *E. histolytica*, but in-depth studies are necessary to confirm these claims.

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METHODS

Molsoft Drug-Likeness model (Molsoft©, U.S.) (http://molsoft.com/mprop/), which uses the Lipinski criteria (structure-activity relationship) for classifies the activity as: null/toxic (-X > 0) and active/without toxicity (0 < +X).

ToxiM (IISER©, India) (http://metagenomics.iiserb.ac.in/ToxiM/index.html) was used for the toxicity prediction of small molecules soluble in water and determined possible permeability in CACO-2 cells by regression models.

Similarity ensemble approach (SEA)

Identification of target pharmacophores was made with the **Similarity Ensemble Approach-model (SEA)** (http://sea.bkslab.org/) to find proteins with binding sites for the active compounds through an inverse protein-ligand approach. The parameters used were as follows: pKi, P-Value, or Max TC, for selecting the possible target protein.

Molinspiration© (version 2018.10, Molinspiration Cheminformatics©, Slovak Republic) (www.molinspiration.com), to calculate molecular properties and bioactivity by comparation with standard drugs as MTZ.

SuperCYPsPred (version 2020, Structural Bioinformatics©) (http://insilico-cyp.charite.de/SuperCYPsPred/index.php?site=home) was used to predicted drug metabolism (via the cytochrome P450 system), possible toxicological interactions, reduced pharmacological effect, and adverse drug reactions by induction/inhibition of enzyme substrate thought ML models based on the RF algorithm

Molecular docking with key proteins for the pathogenic activity of Entamoeba histolytica trophozoites, such as β-actin, myosin-II, and calreticulin, was performed with AutoDock-Vina and UCSF-Chimera.

Table 2. Prediction of toxicological properties to LL by bioinformatic analysis.

Samples	LL	MTZ
Molinspiration©: Bioactivity score		
Lipinski violations	0	0
nrotb	1	3
GPCR ligand	0.65	-1.09
Ion channel modulator	0.16	-0.87
Kinase inhibitor	-0.13	-0.59
Nuclear receptor ligand	0.66	-1.74
Protease inhibitor	0.04	-1.68
Enzyme inhibitor	0.47	-0.32
ToxiM: Toxicity prediction		
Score	0.958	0.653
LogS	-4.027	-1.285
LogPapp	-4.355	-4.636

ToxiM values: Score, molecule with score greater than or equal 0.8 can be considered as toxic; LogS, logarithm of aqueous solubility; LogPapp, logarithm of CACO-2 permeability. GPCR, G protein-coupled receptors.

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