RESEARCH ARTICLE

Mexicanolide, a bioactive compound from *Cedrela odorata:* In silico study of its pharmacokinetics, drug-likeness, potential drug targets, and cytotoxic activities against cancer cell lines

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ABSTRACT

Mexicanolide is a limonoids type of compound identified from *Cedrela odorata,* a forest plant with various medicinal properties. Several biological activities have been reported for Mexicanolide. In the present study, we used an in silico approach to evaluate the physicochemical, pharmacokinetics, drug-likeness, drug targets, and cytotoxic activities of mexicanolide from *Cedrela odorata*. The results revealed that mexicanolide has favorable physicochemical and pharmacokinetic properties of a good drug-like candidate. Notably, the compound has a high GI absorption rate but could not permeate the blood-brain barrier (BBB) and has poor synthetic accessibility. Several proteins targets including Kappa Opioid receptor, Mu opioid receptor, delta-opioid receptor, Cannabinoid receptor 2, Phosphodiesterase 10A (by homology), Platelet-derived growth factor receptor-beta, Stem cell growth factor receptor, Vascular endothelial growth factor receptor 2, Proteinase-activated receptor 1, and Epoxide hydratase were identified as target candidates for mexicanolide. Furthermore, mexicanolide demonstrated in silico activities against several types of cancer cell lines including the SK-MEL-2, HL-60, 8505C, SF-268, St-4, OVCAR-5, K562, SW-60, MKN-7, and Lu1. In conclusion, mexicanolide has favorable physicochemical and pharmacokinetic properties of a good drug-like candidate and could be considered a multi-target compound with potential anticancer activities

Keywords: Mexicanolide, *Cedrela odorata*; in silico study; pharmacokinetics; drug-likeness; drug targets; cytotoxity; cancer cell lines

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1.0 Introductions

Cedrela odorata is a commercially important species of tree in the chinaberry family, Meliaceae, commonly known as Spanish cedar or Cuban cedar or Cedro in Spanish [1]. *Cedrela odorata* L., embraces 28 other synonyms, including *C. mexicana* M. J. Roem. The taxon "*C. angustifolia*," a very vigorous type now in demand because of its apparent resistance to the shoot borer, was left in an indeterminate status due to insufficient herbarium material.

The tree is monoecious semi-deciduous ranging in height from 10 to 30 m (33 to 98 ft). The trunk has a thick grey-brown bark, with longitudinal irregular grain [1]. *Cedrela odorata* is in high demand in the American tropics because it is naturally termite- and rot-resistant. An attractive, moderately lightweight wood (specific gravity 0.4), its primary use is in household articles used to store clothing [2]. This plant is often used for honey production (beekeeping)

and humidor construction. It is occasionally used for tops or veneers on some kinds of electric guitars [3]. Several bioactive compounds including aliphatics acid and alcohol, flavonoids, tocopherol, monoterpenes, sesquiterpenes, triterpenes, cycloalkanes, steroids, and limonoids [1].

Limonoids, as the major secondary metabolites of the Meliaceae family, are well-known for their abundance, structural diversity, and a wide range of antifeedant, antimalarial, antimicrobial, cytotoxic, and growth-regulating activities [4,5]. The mexicanolide-type limonoids have been previously isolated and reported for various biological activities [6,7].

The experimental strategies for DTIs identification are challenging, expensive, and laborious [8]. Therefore, in silico analysis of drug-target interactions (DTIs) is crucial in the discovering of new drug targets or developing new drug candidates for known target proteins [9]. Pharmacological science is trying to establish the connection between target molecules, drugs/chemicals, and disease-related phenotypes. Proteomics and structural data have been generated, for the purpose of target-based discovery of new drugs [10].

The in silico approach of drug target identification is based on the principle of chemical similarity, which says similar drugs bind to similar [11]. Compound comparison is made through ligand-based chemical similarity search or through classifier-based machine learning approach [12]. The aim of the present study is to determine the in silico pharmacokinetic properties, drug targets, and in silico cytotoxicity of a mexicanolide.

2.0 Material and methods

2.1 Source of mexicanolide Structure

The chemical structure of mexicanolide is shown in figure 1.The three-dimensional (3D) structure of mexicanolide A (Compound CID: 267328) with the IUPAC namd methyl 2-[6-(furan-3-yl)-1,5,15,15-tetramethyl-8,14,17-trioxo-7-oxatetracyclo[11.3.1.$0^{2,11}$.$0^{5,10}$] was obtained from from PubChem (https://pubchem.ncbi.nlm.nih.gov).

2.2 In-silico Pharmacokinetics Analysis

The Pharmacokinetics, drug-likeness, and ADMET properties of the mexicanolide were evaluated using the SwissADME algorithm. The canonical smile of mexicanolide was used as a query ID on the SwissADME algorithm.

2.3 In-silico Drug-Target Analysis

The potential drug targets of mexicanolide were evaluated using the SwissTargetPrediction module of the SWISS algorithm. The canonical smile of mexicanolide was used as a query ID on the SwissADME algorithm.

2.4 In silico Cytotoxic studies against the Cancer Cell lines

We used the CLC-Pred (Cell Line Cytotoxicity Predictor) modules of the PASS server (Poroikov et al., 2019) created based on the training set of data on cytotoxicity retrieved from ChEMBLdb (version 23), to predict the cytotoxic activities of mexicanolide on cancer cell lines.

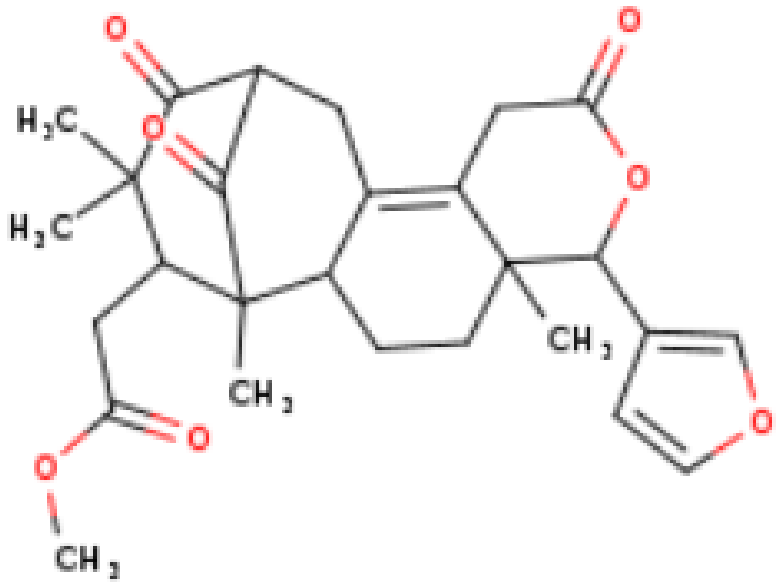

Figure 1: The chemical structure of mexicanolide

3.0 Results and Discussion

3.1 Physicochemical properties

Structural pharmacophore properties including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, and metabolic stability influence the behavior of a molecule in humans [13]. The physicochemical properties of the mexicanolide compound from *Cedrela odorata* are shown in table 1: The mexicanolide has a molecular formula and molecular weight of $C_{27}H_{32}O_7$ and 468.54 g/mol respectively. The number of heavy atoms, aromatic heavy atoms, rotatable bonds, H-bond acceptors, and H-bond donors was 34, 5, 4, 7, and 0 respectively.

The compound has Molar Refractivity and TPSA of 122.69 and 99.88 Å² respectively. The compound has lipophilicity of 2.54, 4.04, and 3.39 judging by the XLOGP3 and WLOGP with the Consensus Log $P_{o/w}$ value of 3.39.

The in silico topological model to predict water solubility and lipophilicity of small molecules in SwissADME is the implementation of the ESOL model with predicted values in the decimal logarithm of the molar solubility in water (log S) [14]. Interestingly, mexicanolide was found to be moderately soluble with the solubility value of -4.19 and -4.28 based on the Log *S* (ESOL) and Log *S* (Ali) threshold of the algorithm.

Table 1: Physicochemical properties of mexicanolide from *Cedrela odorata*

Physicochemical Properties	
Formula	$C_{27}H_{32}O_7$
Molecular weight	468.54 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	5
Fraction Csp3	0.63
Num. rotatable bonds	4
Num. H-bond acceptors	7
Num. H-bond donors	0
Molar Refractivity	122.69
TPSA	99.88 Å²
Lipophilicity	
Log $P_{o/w}$ (XLOGP3)	2.54
Log $P_{o/w}$ (WLOGP)	4.04
Consensus Log $P_{o/w}$	3.39
Water Solubility	
Log *S* (ESOL)	-4.19
Solubility	3.03e-02 mg/ml ; 6.46e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.28
Solubility	2.43e-02 mg/ml ; 5.19e-05 mol/l
Class	Moderately soluble

3.2 Pharmacokinetics and drug-likeness

Drug-likeness is molecular and structural based properties that determine whether an unknown molecule is like known drugs [15]. These molecular properties include molecule size, electronic distribution, hydrophobicity, and hydrogen bonding, and flexibility [16]. The pharmacokinetics and drug-likeness properties of the mexicanolide is shown in figure 2 and table 2: the compound has a high GI absorption rate but could not permeate the blood-brain barrier (BBB), suggesting that the drug would unlikely be useful in the treatments of glioblastoma and other diseases associated with the central nervous system.

It is a P-GP substrate and has a Log K_p (skin permeation) rate of -7.35 cm/s. However, the compound appears to be a non-inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. The compound satisfied the Lipinski, Ghose, Veber, Egan, and Muegge rules of drug-likeness. It has a good bioavailability score of 0.55.

Importantly, the Abbot bioavailability score [17] that predicts the probability of a small molecule drug to have F > 10% based on the pH charge of the biological system in the rat. This bioavailability module also helps to distinguish poorly permeable compounds from those that are permeable in Caco-2 cells.

Interestingly, the results of the present study revealed that mexicanolide good bioavailability score of 0.55 which is equivalent to 55%. However, the synthetic accessibility of the drug is poor having a value of 6.23 on a 1-10 scale

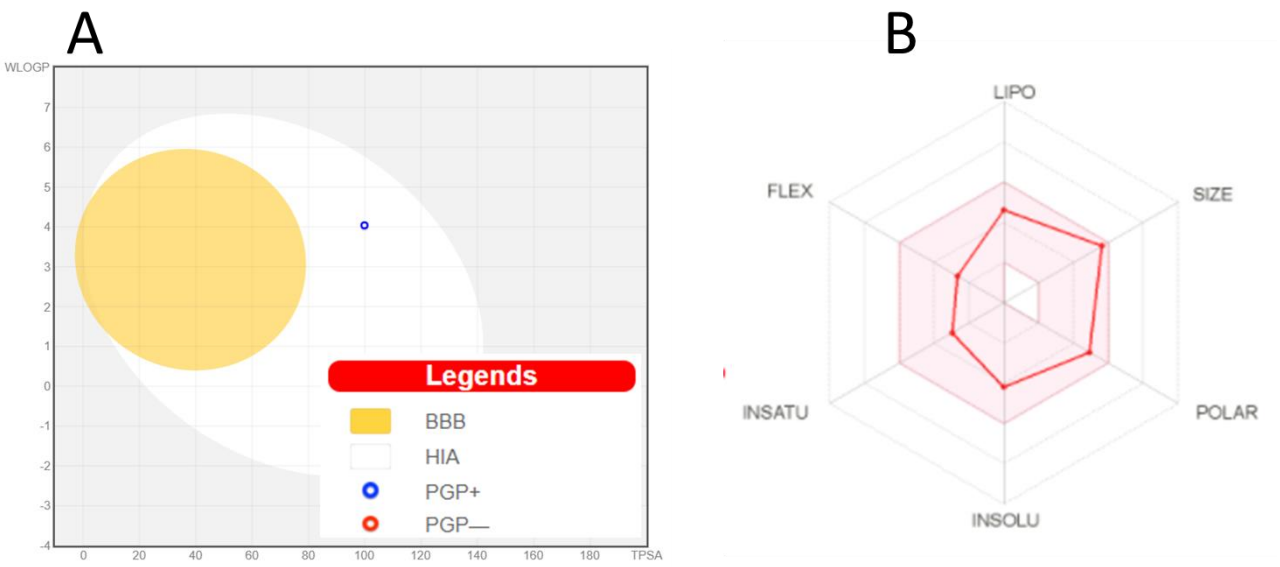

Figure 2: Pharmacokinetics modelling of the mexicanolide. (A) BOILED Egg model of GI absorption and blood-brain barrier (BBB) permeation of the mexicanolide (B) Bioavailability radar of mexicanolide

Table 2: Pharmacokinetics and drug-likeness of mexicanolide from *Cedrela odorata*

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.35 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Synthetic accessibility	6.23

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3.3 Potential drug target for mexicanolide from *Cedrela odorata*

One of the most important steps in drug discovery and development is target identification and validation. Target-based drug discovery has become the fundamental archetype used by biotechnology and pharmaceutical companies. These strategies are appealing because it holds the promise of identifying more efficacious compounds with fewer undesirable side effects [18].

The classification of the potential drug targets of mexicanolide from *Cedrela odorata* is shown in figure 3, while the identity of the individual targets is shown in table 3. Several targets were identified for mexicanolide from *Cedrela odorata*, however, the topmost identified targets with higher probability included Kappa Opioid receptor, Mu opioid receptor, delta opioid receptor, Cannabinoid receptor 2, Phosphodiesterase 10A (by homology), Platelet-derived growth factor receptor-beta, Stem cell growth factor receptor, Vascular endothelial growth factor receptor 2, Proteinase-activated receptor 1, and Epoxide hydratase. The list of other identified targets is shown in table 3. Altogether, the results of this study suggest that mexicanolide is a potential multitarget small molecule.

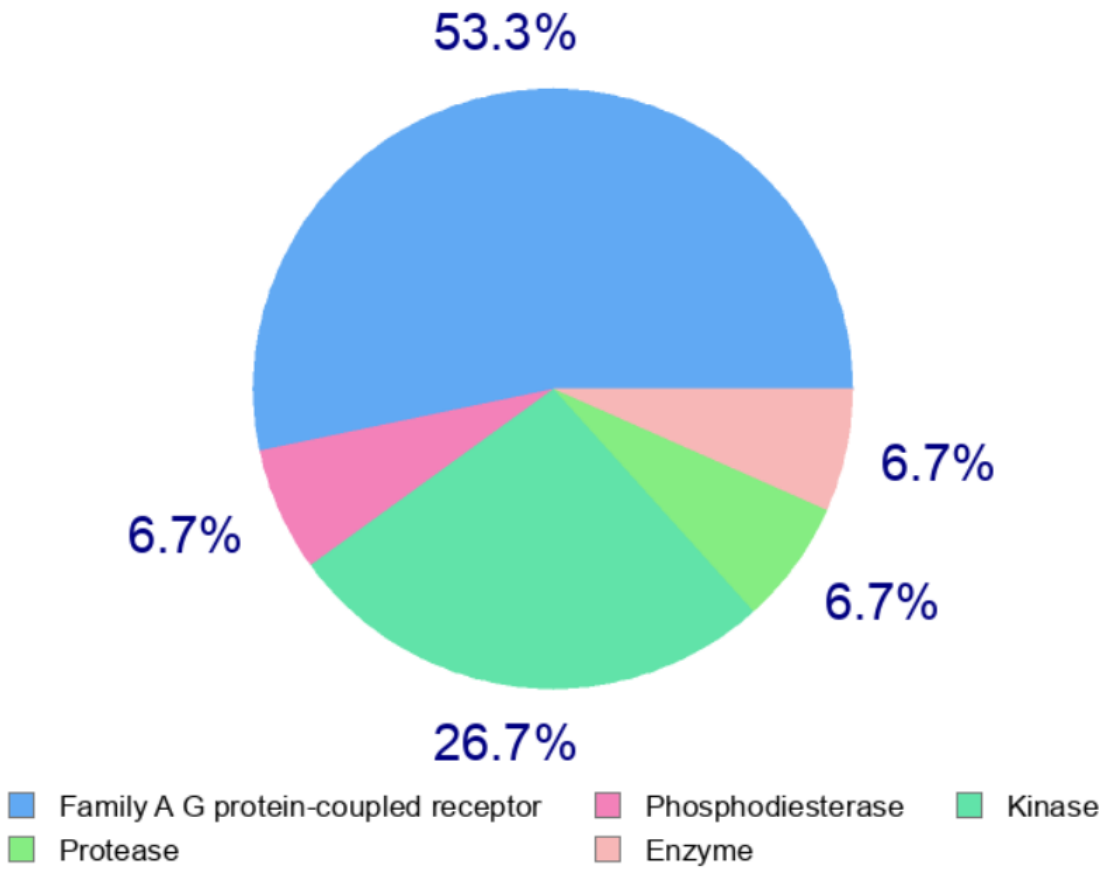

Figure 3: The classification of the potential drug targets of mexicanolide

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Table 3: Potential drug target for mexicanolide from *Cedrela odorata*

Target	Common name	Uniprot ID	ChEMBL ID	Target Class
Kappa Opioid receptor	OPRK1	P41145	CHEMBL237	AGCR
Mu opioid receptor	OPRM1	P35372	CHEMBL233	AGCR
Delta opioid receptor	OPRD1	P41143	CHEMBL236	AGCR
Cannabinoid receptor 2	CNR2	P34972	CHEMBL253	AGCR
Phosphodiesterase 10A (by homology)	PDE10A	Q9Y233	CHEMBL4409	Phosphodiesterase
Platelet-derived growth factor receptor beta	PDGFRB	P09619	CHEMBL1913	Kinase
Stem cell growth factor receptor	KIT	P10721	CHEMBL1936	Kinase
Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase
Proteinase-activated receptor 1	F2R	P25116	CHEMBL3974	AGCR
Epoxide hydratase	EPHX2	P34913	CHEMBL2409	Protease
C-X-C chemokine receptor type 3	CXCR3	P49682	CHEMBL4441	AGCR
Endothelin receptor ET-B	EDNRB	P24530	CHEMBL1785	AGCR
Endothelin receptor ET-A	EDNRA	P25101	CHEMBL252	AGCR
ALK tyrosine kinase receptor	ALK	Q9UM73	CHEMBL4247	Kinase
L-lactate dehydrogenase A chain	LDHA	P00338	CHEMBL4835	Enzyme
Thrombin and coagulation factor X	F10	P00742	CHEMBL244	Protease
Cathepsin S	CTSS	P25774	CHEMBL2954	Protease
Serine/threonine-protein kinase Aurora-B	AURKB	Q96GD4	CHEMBL2185	Kinase
Cyclin-dependent kinase 1	CDK1	P06493	CHEMBL308	Kinase
Serine/threonine-protein kinase Aurora-A	AURKA	O14965	CHEMBL4722	Kinase

AGCR: Family A G protein-coupled receptor

3.4 In silico cytotoxic activities of mexicanolide from *Cedrela odorata* against cancer cell lines

Cancer is a disease related to abnormal growth of cells, and several in silico approaches have been developed for evaluating the oncogenic role as well as therapeutic properties of small molecule drugs [19]. The in silico cytotoxic activities of mexicanolide from *Cedrela odorata* against cancer cell lines is shown in table 4. mexicanolide demonstrated in silico activities against several types of cancer cell lines including the SK-MEL-2, HL-60, 8505C, SF-268, St-4, OVCAR-5, K562, SW-60, MKN-7, and Lu1. These cell lines are representative of leukemia, melanoma, glioblastoma, carcinoma, and adenocarcinoma. Conclusively, the results obtained from this study suggested that mexicanolide from *Cedrela odorata* could be a valuable anti-cancer agent worthy of further experimental validation.

Table 4: In silico cytotoxic activities of mexicanolide from *Cedrela odorata* against cancer cell lines

pa	pi	Cell-lines	Cell-Line Full name	Tissue	Tumor Type
0.589	0.011	SK-MEL-2	Melanoma	Skin	Melanoma
0.370	0.055	HL-60	Promyeloblast leukemia	Haematopoietic/ lymphoid tissue	Leukemia
0.294	0.094	8505C	Thyroid gland undifferentiated (anaplastic) carcinoma	Thyroid	Carcinoma
0.274	0.099	SF-268	Glioblastoma	Brain	Glioblastoma
0.212	0.064	St-4	Stomach carcinoma	Stomach	Carcinoma
0.276	0.131	OVCAR-5	Ovarian adenocarcinoma	Ovarium	Adenocarcinoma
0.245	0.113	K562	Erythroleukemia	Haematopoietic/ lymphoid tissue	Leukemia
0.068	0.001	SW-60	Colorectal carcinoma	Colon	Carcinoma
0.222	0.170	MKN-7	Gastric carcinoma	Stomach	Carcinoma
0.088	0.063	Lu1	Lung carcinoma	Lung	Carcinoma

Pa=probability of active Pi=probability of inactive

4.0 Conclusion:

Based on the results obtained from the present in silico study, it is concluded that mexicanolide has favorable physicochemical and pharmacokinetic properties of a good drug-like candidate and could be considered a multi-target compound with potential anticancer activities.

Conflict of Interest: The author declared no conflict of interest exist

Ethical Approval: Not applicable

Authors contributions: The work was conducted in collaboration of all authors. All authors read and approved the final version of the manuscript.

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