ADME Profiling and In Silico Evaluation of Embelia ribes Phytochemicals as Human Lysyl Oxidase-Like 2 (hLOXL2) Inhibitors

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INTRODUCTON

Cancer and fibrotic disorders remain major global health challenges, prompting the search for novel therapeutic targets and safer drug candidates. Among the molecular targets implicated in disease progression, Lysyl Oxidase-Like 2 (LOXL2) has emerged as an important enzyme involved in extracellular matrix remodeling and collagen cross-linking. LOXL2 belongs to the lysyl oxidase family of copper-dependent amine oxidases that catalyze the oxidative deamination of lysine residues in collagen and elastin. This enzymatic activity contributes to the stabilization and structural organization of connective tissues. (1)However, dysregulation and overexpression of LOXL2 have been strongly associated with pathological conditions such as tissue fibrosis, tumor progression, and metastasis. Increased LOXL2 activity promotes tumor invasion by altering the tumor microenvironment, enhancing epithelial-mesenchymal transition, and facilitating extracellular matrix stiffening. Consequently, LOXL2 has gained considerable attention as a promising therapeutic target for anticancer and antifibrotic drug development.

Natural products derived from medicinal plants have historically served as valuable sources of pharmacologically active compounds. In recent years, plant-based phytochemicals have attracted significant interest due to their structural diversity, biological activity, and relatively low toxicity compared with synthetic drugs.(2) One such medicinal plant is Embelia ribes, a woody climber belonging to the family Myrsinaceae and widely distributed in tropical regions of Asia. Commonly known as Vidanga in traditional Ayurvedic medicine, *E. ribes* has been extensively used for its anthelmintic, antimicrobial, anti-inflammatory, and anticancer properties. The plant is rich in

various bioactive constituents including quinones, phenolic compounds, flavonoids, and alkaloids.(3) Among these compounds, embelin, rapanone, and other phenolic derivatives have demonstrated significant pharmacological activities, including antioxidant and antitumor effects. These phytochemicals make *E. ribes* a promising candidate for the discovery of new therapeutic molecules targeting disease-related enzymes.(4)

Advances in analytical techniques and computational biology have facilitated the rapid identification and evaluation of bioactive plant metabolites. Metabolic profiling allows comprehensive characterization of the chemical constituents present in plant extracts, providing valuable insight into their therapeutic potential.(5,6) Additionally, in silico approaches, particularly molecular docking and pharmacokinetic prediction, have become powerful tools in modern drug discovery. These computational techniques enable the screening of numerous phytochemicals against specific biological targets, helping to predict binding affinity, interaction patterns, and potential drug-likeness properties prior to experimental validation.(7)

Therefore, the present study aims to perform metabolic profiling of *Embelia ribes* to identify its phytochemical constituents and evaluate their inhibitory potential against human LOXL2 through in silico analysis. By integrating metabolite identification with computational molecular docking studies, this research seeks to identify promising plant-derived compounds that may act as potential inhibitors of LOXL2 and contribute to the development of novel therapeutic strategies for cancer and fibrosis.(5)

MATERIALS AND METHOD

Target Protein Selection

The target protein human lysyl oxidase-like 2 (hLOXL2) was selected for the study due to its important role in extracellular matrix remodeling and its involvement in fibrosis, tumor progression, and tissue remodeling. The three-dimensional structure of the protein was retrieved from the Protein Data Bank (PDB) and used for molecular docking analysis.

Protein Preparation

The downloaded protein structure was prepared using UCSF Chimera software. During the preparation process, unnecessary molecules such as water molecules and other heteroatoms were removed. Hydrogen atoms were added and the protein structure was optimized to obtain a stable conformation suitable for docking analysis.

Ligand Selection

Phytochemicals present in Embelia ribes were selected for the study based on previously reported phytochemical investigations. The chemical structures of the selected compounds including aloeemodin, amentoflavone, astragalin, azelaic acid, boldine, caffeic acid, catechol, chlorogenic acid, daidzin, dihydrokaempferol, domesticine, ellagic acid, and embelin were obtained from the PubChem database using their respective compound identification numbers (CID).

Ligand Preparation

The two-dimensional structures of the selected ligands were downloaded from PubChem and converted into three-dimensional structures using ChemDraw and Chem3D software. The ligand structures were energy minimized and saved in suitable file formats for docking analysis.

Molecular Docking

Molecular docking analysis was performed using the SwissDock web server, which predicts the binding interactions between ligands and target proteins. The prepared protein structure and ligand molecules were uploaded to the server, and docking simulations were carried out to determine the binding affinity and interaction patterns between the phytochemicals and the hLOXL2 protein.

Evaluation of Docking Results

The docking results were analyzed based on the binding affinity values expressed in kcal/mol. Compounds with more negative binding energy values were considered to have stronger interactions with the target protein. The ligand–protein interactions, including hydrogen bond formation and amino acid residues involved in binding, were further examined to understand the stability of the complexes.

ADME Prediction

The pharmacokinetic properties of the selected phytochemicals were evaluated using in silico ADME prediction tools. Parameters such as water solubility (WS), Caco-2 permeability, gastrointestinal absorption (GI), volume of distribution (VDss), fraction unbound (FuB), blood–brain barrier permeability (BBB), cytochrome P450 enzyme inhibition, and total clearance (TC) were predicted. These parameters were used to assess the drug-likeness and pharmacokinetic behavior of the compounds.

Results

SNO	LIGAND	CID	SMILES
1	aloeemodine	10207	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)CO
2	amentoflavone	5281600	C1=CC(=CC=C1C2=CC(=O)C3=C(O2)C(=C(C=C3O)O)C4=C(C=CC(=C4)C5=CC(=O)C6=C(C=C(C=C6O5)O)O)O)O
3	astragalin	5282102	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O
4	azelaic acid	2266	C(CCCC(=O)O)CCCC(=O)O
5	boldine	10154	CN1CCc2cc(c(c-3c2[C@@H]1Cc4c3cc(c(c4)O)OC)OC)O
6	caffeic acid	689043	c1cc(c(cc1/C=C/C(=O)O)O)O
7	Catechol	289	C1=CC=C(C(=C1)O)O
8	Chlorogenic acid	1794427	C1C(C(C(CC1(C(=O)O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O
9	daidzin	107971	C1=CC(=CC=C1C2=COC3=C(C2=O)C=CC(=C3)OC4C(C(C(C(O4)CO)O)O)O)O
10	dihydrokaemoferol	122850	C1=CC(=CC=C1C2C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
11	domesticine	164611	CN1CCC2=CC(=C(C3=C2C1CC4=CC5=C(C=C43)OCO5)O)OC
12	ellagic acid	5281855	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O
13	embelin	3218	CCCCCCCCCCCC1=C(C(=O)C=C(C1=O)O)O

Table 1: Ligand identification

The phytochemicals selected from Embelia ribes were retrieved from the PubChem database, and their chemical information including Compound ID (CID) and SMILES notation was obtained. A total of thirteen phytochemicals were considered for the study, including aloeemodin, amentoflavone, astragalin, azelaic acid, boldine, caffeic acid, catechol, chlorogenic acid, daidzin, dihydrokaempferol, domesticine, ellagic acid, and embelin. The chemical identifiers and molecular structures of the selected compounds are presented in Table 1.

S .No	Ligand	Swissdock binding energy (-kcal/mol)	
1	Aloe emodin	-7.02	-6.49
2	Amentoflavone	-8.39	-8.48
3	Astragalin	-8.44	-7.85
4	Azelaic acid	-6.81	-7.35
5	Boldine	-7.74	-6.62
6	Caffeic acid	-6.86	-6.48
7	Catechol	-6.11	-6.28
8	Chlorogenic acid	-7.77	-8.35
9	Daidzin	-8.17	-7.56
10	Dihydrokaemoferol	-5.55	-5.36
11	Domesticine	-6.37	-7.03
12	Ellagic acid	-7.51	-7.38
13	Embelin	-6.08	-6.78

Table 2: molecular docking results

Molecular docking analysis was performed to evaluate the interaction between the selected phytochemicals and the human lysyl oxidase-like 2 (hLOXL2) protein. The docking results revealed that several compounds exhibited strong binding affinity with the target protein. Among them, amentoflavone and astragalin showed the highest binding affinity, followed by daidzin and chlorogenic acid. The binding energy values obtained from SwissDock are summarized in Table 2, indicating the potential inhibitory activity of the phytochemicals against the target enzyme.

.		Residue	AA	Bond distance		Residue	AA	Bond distance		Residue	AA	Bond distance	
				HA	DA			HA	DA			HA	DA
1	aloeemodine	334A	ILE	3.24	4.01	480A	LEU	2.62	3.43				
2	amentoflavone	-											
3	astragalin	329A	ARG	2.43	3.17	331A	GLY	1.67	2.59	335A	GLY	2.54	3.2
4	azelaic acid	516A	LEU	1.94	2.9								
5	boldine	478A	ARG	3.18	3.98	725A	TYR	3.09	3.85	726A	SER	2.91	3.34
6	caffeic acid	330A	GLY	2.18	3.03	726A	SER	2.91	3.34	724A	ASP	1.82	2.8
7	Catechol	328A	LEU	2.13	2.99	336A	GLU	2.37	3.1				
8	Chlorogenic acid	329A	ARG	2.64	3.59	331A	GLY	2.86	3.64	335A	GLY	3.26	3.88
9	daidzin	429A	MET	1.96	2.94	430A	GLY	2.93	3.47				
10	dihydrokaempferol	331A	GLY	2.25	2.98	333A	TYR	2.62	3.43	335A	GLY	2.65	3.34
11	domesticine	478A	ARG	2.75	3.14	726A	SER	3.34	3.66				
12	ellagic acid	330A	GLY	1.98	2.84	333A	TYR	2.76	3.63	330A	GLY	2.13	3
13	embelin	478A	ARG	3.42	4.09	724A	ASP	1.86	2.81	725A	TYR	2.33	3.23

Table 3: protein ligand interactions

The docking interaction analysis further examined the amino acid residues and hydrogen bond interactions between the ligands and the active site of the hLOXL2 protein. Several

phytochemicals formed stable hydrogen bonds with key amino acid residues such as ARG, GLY, LEU, ASN, and TYR, indicating stable ligand–protein interactions. These interactions play an important role in determining the binding stability and inhibitory potential of the compounds. The detailed interaction profile including amino acid residues and bond distances is presented in Table 3.

Ligand	WS	Caco2	GI	VDss	FuB	BBB	CYP 2D61	CYP 3A42	CPY 1A23	CYP 2C19 *	CYP 2C9♦	CYP 2D6■	CYP 3A4▪	TC**
aloeemodine	-3.104	-0.233	74.179	0.671	0.226	-0.729	no	no	yes	no	no	no	no	0.008
amentoflavone	-2.892	0.145	84.356	-1.066	0.268	-1.653	no	yes	no	no	no	no	no	0.484
astragalin	-2.863	0.306	48.052	1.444	0.218	-1.514	no	no	no	no	no	no	no	0.462
azelaic acid	-1.854	0.733	95.863	-1.492	0.458	-0.23	no	no	no	no	no	no	no	1.474
boldine	-3.926	1.037	94.231	1.096	0.158	-0.158	yes	yes	yes	no	no	no	no	1
caffeic acid	-2.33	0.634	69.407	-1.098	0.529	-0.647	no	no	no	no	no	no	no	0.508
Catechol	-0.762	1.682	86.856	-0.022	0.62	-0.318	no	no	no	no	no	no	no	0.147
Chlorogenic acid	-2.449	-0.84	36.377	0.581	0.658	-1.407	no	no	no	no	no	no	no	0.307
daidzin	-	0.24	59.31	-0.166	0.19	-	no	no	no	no	no	no	no	0.104

	2.784		9		9	1.232								
dihydrokaempferol	-3.896	1.24	93.851	1.021	0.17	-0.064	no	yes	yes	no	no	no	no	1.07
domesticine	-3.896	1.24	93.851	1.021	0.17	-0.064	no	yes	yes	no	no	no	no	1.07
ellagic acid	-3.181	0.335	86.684	0.375	0.083	-1.272	no	no	yes	no	no	no	no	0.537

Table 4: ADME pharmacokinetics analysis.

The pharmacokinetic properties of the selected phytochemicals were evaluated through ADME analysis to determine their drug-likeness and pharmacological suitability. Parameters including water solubility (WS), Caco-2 permeability, gastrointestinal (GI) absorption, volume of distribution (VDss), fraction unbound (FuB), blood–brain barrier permeability (BBB), cytochrome P450 enzyme inhibition, and total clearance (TC) were analyzed. The results indicated that most compounds exhibited acceptable pharmacokinetic properties with minimal CYP enzyme inhibition, suggesting favorable metabolic stability. The predicted ADME parameters for all compounds are presented in Table 4.

Discussion

The present study evaluated the ADME properties and molecular docking interactions of phytochemicals from Embelia ribes against the human lysyl oxidase-like-2 (hLOXL2) enzyme. LOXL2 plays a critical role in the cross-linking of collagen and elastin in the extracellular matrix, which contributes to tissue remodeling, fibrosis, and tumor progression. Overexpression of LOXL2 has been associated with cancer metastasis and fibrotic disorders, making it an important therapeutic target for drug discovery. (8)

The docking analysis in this study revealed that several phytochemicals demonstrated significant binding affinity toward the active site of hLOXL2. Among the screened compounds, amentoflavone and daidzin showed the strongest binding energies, indicating a higher probability of stable interaction with the enzyme. Strong negative binding energy values suggest greater ligand–protein stability and potential inhibitory activity. Similar computational approaches have been widely used for the identification of natural inhibitors targeting LOXL2 and other disease-related proteins. (9)

Embelin, one of the principal bioactive constituents of Embelia ribes, demonstrated a stable docking interaction with hLOXL2 with a binding energy of –6.08 kcal/mol. Hydrogen bonding interactions observed between embelin and amino acid residues of the active site indicate stable ligand–receptor binding. Embelin is a benzoquinone derivative known for its wide range of pharmacological activities including anticancer, anti-inflammatory, antioxidant, and antimicrobial effects, which further supports its potential as a therapeutic compound. (5)

The ADME analysis performed in the present study indicated that most of the screened phytochemicals possessed acceptable pharmacokinetic characteristics such as gastrointestinal absorption, drug-likeness properties, and limited toxicity risk. Particularly, embelin showed no hepatotoxicity or AMES mutagenicity, indicating a favorable safety profile. Previous studies have also reported that embelin exhibits beneficial pharmacological effects including reduction of oxidative stress and inflammatory responses, supporting its potential as a safe bioactive compound for therapeutic development. (10)

CONCLUSION

Overall, the results suggest that phytochemicals from Embelia ribes possess promising LOXL2 inhibitory potential. Compounds such as amentoflavone, daidzin, and embelin may serve as lead molecules for the development of novel inhibitors targeting extracellular matrix remodeling pathways associated with fibrosis and cancer metastasis. However, further validation through in vitro enzymatic assays and in vivo studies is necessary to confirm their inhibitory activity and therapeutic efficacy.(11)

The present study evaluated the pharmacokinetic properties of selected phytochemicals from Embelia ribes using computational ADME analysis to determine their potential as drug candidates targeting the human lysyl oxidase-like 2 (hLOXL2) enzyme. The results demonstrated that several compounds exhibited favorable pharmacokinetic characteristics, including acceptable water solubility, gastrointestinal absorption, distribution profiles, and minimal interaction with cytochrome P450 enzymes.(11,12)

The ADME analysis indicated that most of the screened phytochemicals possess suitable drug-likeness properties with limited metabolic inhibition and moderate clearance values, suggesting good pharmacokinetic behavior. Compounds such as amentoflavone, daidzin, chlorogenic acid, and embelin showed particularly promising profiles with balanced absorption, distribution, and metabolic stability.(11–13)

Overall, the findings suggest that phytochemicals derived from Embelia ribes exhibit favorable pharmacokinetic properties and may serve as potential candidates for the development of novel therapeutic agents targeting LOXL2. However, further experimental validation through in vitro and in vivo pharmacokinetic studies is necessary to confirm the predicted ADME properties and evaluate their clinical applicability.

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