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Research Article

IN SILICO DOCKING APPROACH FOR ANTIATHEROSCLEROTIC ACTIVITY OF PHYTOCONSTITUENTS OF *CORCHORUS AESTUANS* AND ADMET PREDICTION

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ABSTRACT

Objective: Atherosclerosis is a persistent inflammatory condition within the arterial wall characterized by alterations in lipid metabolism. Liver X alpha receptor is highly expressed in liver could regulate the cholesterol metabolism and suppress the inflammatory genes, so that its activation prevents atherosclerosis. The *Corchorus aestuans* possess anti-atherosclerotic property along with its anti-hyperglycemic activity. The objective of the present study is to investigate the anti-atherosclerotic activity of the *C. aestuans* leaves against Liver X alpha receptor by using GOLD study.

Methods: 3-Dimensional structure of Liver X alpha receptor (Protein Date Bank ID - 3IPQ) was retrieved using Protein Data Bank. Phytochemical molecules were retrieved from the pubchem database and the 2D chemical structures were generated from SMILES notation (Simplified Molecular Input Line Entry Specification) by using the Chemsketch Software. Screenings of different docked complex were performed by GOLD study. Absorption, distribution, metabolism, excretion and toxicity properties for all molecules is predicted by using ADMET structure-activity relationship database.

Results: Among the 14 phytochemicals, E-7-Tetradecenol was found to be the top compound with highest Gold score of 26.99.

Conclusion: Our study suggests that phytochemicals from *C. aestuans* leaves may act as better leads and in turn prevent atherosclerosis.

Keywords: Atherosclerosis, *Corchorus aestuans,* Liver X alpha receptor, GOLD, Absorption, Distribution, Metabolism, Excretion and Toxicity.

INTRODUCTION

Atherosclerosis is a sluggish and progressive building up of fatty substances, plaque, cholesterol, cellular waste products, fibrin and calcium in the inner lining of an artery, which may block the artery partially or fully. Liver X receptors (LXRs) could legalize cholesterol metabolism as well as stifle inflammatory genes expression and smooth muscle cell (SMC) proliferation, thus it is predicted that LXR activation can prevent the development of atherosclerosis [1,2]. The LXRα and LXRβ are ligand-dependent transcriptional factors, belonging to the nuclear hormone receptor super family [3]. LXRα and LXRβ share a lever of cDNA homology of about 63%, but differ in distribution. LXRα is highly expressed in liver, and at lower levels in the intestine, macrophages, kidney and other organs, while LXR β is expressed ubiquitously [4]. Drugs derived from natural sources play a major role in the prevention and treatment of human diseases. Many countries follow the traditional medicine as one of the prime health care systems [5]. Scientific interest in phytomedicine has grown due to increased efficacy of new plant-derived drugs, emerging interest in natural products and increasing concerns about the side effects of conventional medicine [6]. *Corchorus aestuans* (L.) (Syn. *Corchorus acutangulus* Lam), is a genus of about 40-100 species of flowering plants in the family Tiliaceae, native to tropical and subtropical regions throughout the world [7]. They are reported to exhibit various activities such as anti-inflammatory, plasma-cholesterol lowering activities, anticancer activity against epidermal carcinoma of nasopharynx in tissue culture [8-11]. Fourteen different bioactive constituents have been identified from the ethanol extract of leaves of *C. aestuans* by gas chromatography mass spectrography analysis [12]. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization [13]. The estimation of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties of lead compounds is a key challenge in the process of drug development [14]. This study, therefore, investigated the molecular interaction between the phytochemicals in the ethanol extract of *C. aestuans* leaves and the LXRα for preventing atherosclerosis through insilico docking by using GOLD [15]. Insilico screening ADMET profiles of phytochemicals by using ADMET structure-activity relationship database (admetSAR) [16].

METHODS

LXRα retrieval

3-Dimensional structure of LXRα (Protein Date Bank [PDB] ID – 3IPQ) was retrieved using Protein Data Bank which could act as target molecule for molecular docking. The structure was viewed using Swiss-PDB Viewer to form a better understanding of the molecule in order to use it as a drug target.

Building of herbal compounds

Fourteen phytochemicals identified from ethanol extract of *C. aestuans* leaves were screened against LXRα. List of phytochemicals identified are shown in Table 1. The phytochemical molecules were retrieved from the pubchem database and the 2-D chemical structures were generated from SMILES notation (Simplified Molecular Input Line Entry Specification) by using the Chemsketch Software. The structure were then converted to 3-D, their geometries were optimized and saved in "MDL mol file" format using Open Babel server [17].

Active site prediction

Active site of the target protein were predicted by using PDB sum which requires a PDB file as an input and this tool explains the total number of active sites along with information on their amino acid sequence, cavity points and the average volume of the cavity.

Screening of docked complex

The molecular docking of 14 compounds derived from *C. aestuans* with the LXRα was carried out. Screenings of different docked complex were performed by GOLD on the basis of energy as an important constraint of stability. GOLD is a program for calculating the docking modes of

small molecules in protein binding sites and is provided as part of the GOLD Suite, a package of programs for structure visualization and manipulation (Hermes), for protein-ligand docking (GOLD), for post-processing (GoldMine) and visualization of docking results. The ligand molecule which shows highest binding affinity with the receptor molecule was chosen as best drug.

ADMET analysis

AdmetSAR provides the latest and most comprehensive manually curate data for diverse chemicals associated with known ADMET profiles. This database is having 22 qualitative classification and 5 quantitative regression models with highly predictive accuracy, used to estimate mammalian ADMET properties for novel chemicals. The admetSAR server predicts the ADMET associated properties of the active compounds for different types of models, all of which shows the positive results [18]. The admetSAR tool was employed for the insilico screening of ADMET profiles for the active compounds derived from the ethanol extract of *C. aestuans* leaves.

RESULTS AND DISCUSSION

The molecular docking analysis of the 14 compounds derived from ethanol extract of *C. aestuans* leaves with the LXRα was carried out using the GOLD software. The GOLD software resulted in identifying the best compound that interacts with the receptor. The results were evaluated based on the binding compatibility i.e. Docked energy in kcal/mol (fitness) [19]. The final docked conformation obtained for different compounds were evaluated based on the number of hydrogen bonds formed and bond distance between atomic co-ordinates of the active site and inhibitor. The GOLD docking scores for the phytochemicals are given in Table 2. The results indicate that the compound E-7-Tetradecenol has the highest affinity to bind with LXRα with a GOLD score of 26.99. The compounds trans-2-Undecen-1-ol, Docosanoic acid, ethyl ester and n-Hexadecanoic acid show relatively good binding affinity with the GOLD score of 22.33, 21.75 and 21.03 respectively. The compounds 1-Eicosanol, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, Phytol, 3-Hexadecyloxycarbonyl-5-(2-hydroxyethyl)-4- methylimidazolium ion, Pentadecanoic acid, 2,6,10,14-tetramethyl-, methyl ester, 9,9-Dimethoxybicyclo[3.3.1] nona-2,4-dione, vitamin E shows comparatively less binding affinity with the GOLD scores of 17.65, 15.88, 15.88, 14.72, 14.04, 13.61 and 12.11. The compounds 9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-Heptadecanoic acid, heptadecyl ester and Squalene show the least affinity with the GOLD scores being 3.18, −4.31 and −4.58. The docking of E7 tetradecenol with LXRα is shown in Fig. 1. The different Docking schematic patterns for E7 tetradecenol with LXRα are given as Figs. 2 and 3. From the insilico docking results, it is quite evident that *C. aestuans* compounds have the great potential against atherosclerosis.

Table 1: Phytochemicals of *C. aestuans* leaves

Serial no	Name of the compound
1	3,7,11,15-Tetramethyl-2-hexadecen-1-ol
2	trans-2-Undecen-1-ol
3	E-7-Tetradecenol
4	n-Hexadecanoic acid
5	Phytol
6	9,12,15-Octadecatrienoic acid, methyl ester
7	Docosanoic acid, ethyl ester
8	1-Eicosanol
9	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione
10	Heptadecanoic acid, heptadecyl ester
11	Pentadecanoic acid, 2,6,10,14-tetramethyl-, methyl ester
12	3-Hexadecyloxycarbonyl-5-(2-hydroxyethyl)-4-methylimidazolium ion
13	Squalene
14	Vitamin E

C. aestuans: Corchorus aestuans

The presence of high-resistance tight junctions between endothelial cells of brain capillaries forms the barrier and prevents the brain uptake of most pharmaceuticals [20]. Absorption associated properties of the active compounds for different types of models such as BBB penetration, P-glycoprotein substrate, and renal organic cation transporter, human intestinal absorption and Caco2 permeability showed positive results which strongly support the ability of compounds to act as drug. Experimentally, blood brain barrier (BBB) is measured as the ratio of the compound concentration in the brain to that in the blood. The BBB permeability of a compound depends on several factors such as lipophilicity, hydrogen-bond desolvation potential, molecular size and pKa charge. Absorption properties for all compounds have been given in Table 3. All 13 compounds derived from ethanol extract of *C. aestuans* leaves showed positive results except 3-Hexadecyloxycarbonyl-5-(2-hydroxyethyl)-4-methylimidazolium ion which alone showed negative result.

Cytochrome P450 (CYP) is group of isozymes involves in the metabolism of drugs, fatty acids, steroids, bile acids and carcinogens. Human genome encodes nearly 57 CYP of which fifteen are involved in the metabolism of drugs and other xenobiotic chemicals [21]. Nearly 75% of

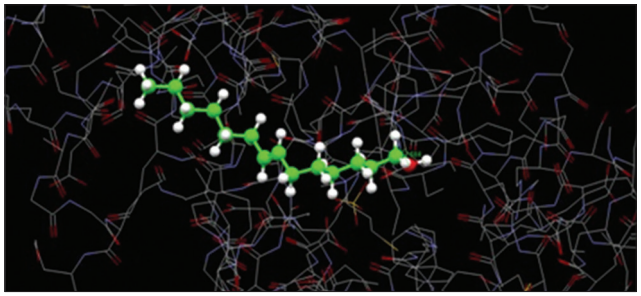

Fig. 1: Docking of E7 tetradecenol with Liver X alpha receptors; protein - chain branching, ligand - ball and stick

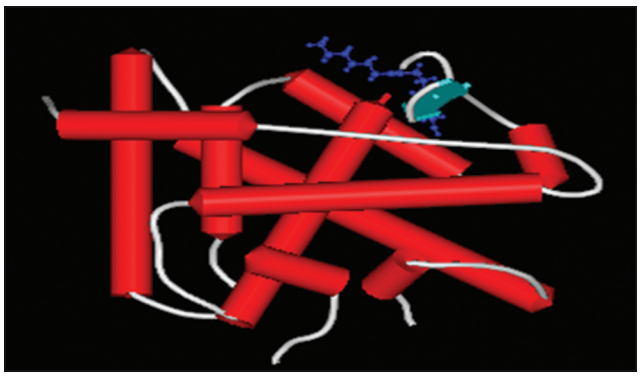

Fig. 2: Docking schematic pattern 2: protein - schematic, ligand - ball and stick

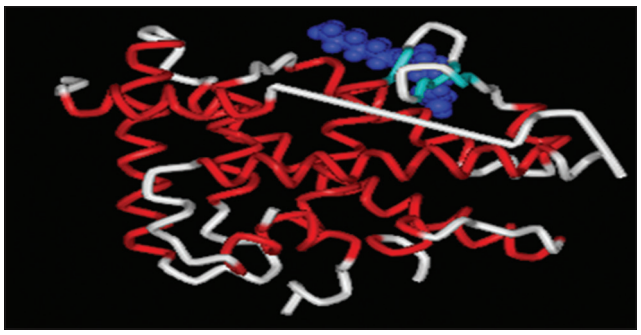

Fig. 3: Docking schematic pattern 3: protein - Tube, ligand - ball and stick

phase I drug metabolism depends on the involvement of CYP enzymes. Metabolism properties for all compounds derived from ethanol extract of *C. aestuans* leaves have been calculated with various CYP substrate and inhibitor models. The result shows that these active compounds are non-substrate and non-inhibitor of CYP enzymes (Table 4).

In terms of toxicity, all the toxicity models were calculated and the results are found to be non-toxic. Although some toxicity models show some negative results, the regression profiles indicates that they have very low probability values. Toxicity properties for all compounds have been given in Table 5.

CONCLUSION

These results suggest that phytochemicals from ethanol extract of leaves of *C. aestuans* may act as better leads and can be considered as a novel and effective drugs in the specific remedy of atherosclerosis.

Table 2: GOLD docking score of phytochemicals present in *C. aestuans* leaves

Serial no	Name of the compound	No. of H-Bonds	H-Bond distance	GOLD score
1	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	1	3.069	15.88
2	trans-2-Undecen-1-ol	-	-	22.33
3	E-7-Tetradecenol	1	2.584	26.99
4	n-Hexadecanoic acid	-	-	21.03
5	Phytol	-	-	15.88
6	9,12,15-Octadecatrienoic acid, methyl ester	-	-	3.18
7	Docosanoic acid, ethyl ester	1	3.030	21.75
8	1-Eicosanol	-	-	17.65
9	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	-	-	13.61
10	Heptadecanoic acid, heptadecyl ester	-	-	−4.31
11	Pentadecanoic acid, 2,6,10,14-tetramethyl-, methyl ester	-	-	14.04
12	3-Hexadecyloxycarbonyl-5-(2-hydroxyethyl)-4- methylimidazolium ion	-	-	14.72
13	Squalene	-	-	−4.58
14	Vitamin E	1	2.529	12.11

C. aestuans: Corchorus aestuans

Table 3: ADMET Predicted profile for active compounds from *C. aestuans* - Absorption

Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14
BBB	+	+	-	+	+	+	+	+	+	+	+	+	+	+
Human intestinal absorption	+	+	-	+	+	+	+	+	+	+	+	+	+	+
Caco-2 permeability	+	+	-	+	+	+	+	+	+	+	+	+	+	+
P-glycoprotein substrate	NS	NS	S	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S
P-glycoprotein inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Renal organic cation transporter	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

+: Positive, -: Negative, NS: Non-substrate, S: Substrate, NI: Non-inhibitor, BBB: Blood-brain barrier, *C. aestuans: Corchorus aestuans*, ADMIT: Absorption, Distribution, Metabolism, and Excretion and Toxicity

Table 4: ADMET predicted profile for active compounds from *C. aestuans*- Metabolism

Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14
CYP450 2C9 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 2D6 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 3A4 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S
CYP450 1A2 inhibitor	NI	NI	NI	NI	NI	NI	I	NI	I	NI	NI	N	NI	NI
CYP450 2C9 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 2D6 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 2C19 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 3A4 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

NS: Non-substrate; NI: Non-Inhibitor; I: Inhibitors; S: Substrate, CYP450: Cytochrome P450, *C. aestuans: Corchorus aestuans*, ADMIT: Absorption, Distribution, Metabolism, and Excretion and Toxicity

Table 5: ADMET Predicted profile for active compounds from *C. aestuans* - Toxicity

Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Human Ether-a-go-go-related gene inhibition	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI
AMES toxicity	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Carcinogens	NC	NC	NC	NC	C	C	NC	C	NC	C	NC	C	C	NC
Fish toxicity	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT
Tetrahymena pyriformis toxicity	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT
Honey bee toxicity	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT
Biodegradation	RB	RB	NRB	NRB	RB	RB	RB	RB	RB	RB	RB	RB	RB	NRB
Acute oral toxicity	III	III	III	III	III	III	III	III	IV	III	III	III	III	III

WI: Weak inhibition, NT: Non-Toxic, NC: Non carcinogen, C: Carcinogen, HT: High toxic, RB: Readily biodegradable, NRB: Not readily biodegradable, *C. aestuans: Corchorus aestuans*, ADMIT: Absorption, Distribution, Metabolism, and Excretion and Toxicity

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