IJPSR (2018), Volume 9, Issue 9 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 22 January, 2018; received in revised form, 26 March, 2018; accepted, 26 June, 2018; published 01 September, 2018

# *IN-SILICO* MOLECULAR DOCKING STUDIES ON THE PHYTOCONSTITUENTS OF *CORCHORUS TRILOCULARIS* (LINN.) FOR ITS ANTIATHEROSCLEROTIC ACTIVITY AND ADMET PREDICTION

R. Dhanalakshmi [*1], P. Manimekalai [2] and R. Manavalan [3]

Edayathangudy G. S. Pillay College of Pharmacy [1], Nagapattinam - 611002, Tamil Nadu, India.
School of Pharmaceutical Sciences [2], VELS University, Pallavaram, Chennai - 600117, Tamil Nadu, India.
RVS College of Pharmaceutical Sciences [3], Sulur, Coimbatore - 641402, Tamil Nadu, India.

**Keywords:**

Anti-atherosclerotic, GOLD, *Corchorus trilocularis*, LXRα, SMILES, ADMET

**Correspondence to Author:**
**R. Dhanalakshmi**

Professor,
Department of Pharmacology,
Edayathangudy. G. S. Pillay College of Pharmacy, Nagapattinam - 611002, Tamil Nadu, India.

**E-mail:** sridhanadhi@gmail.com

**ABSTRACT:** Atherosclerosis is a condition where the arteries become narrowed and hardened due to an excessive build up of plaque around the artery wall. The disease disrupts the flow of blood around the body, posing serious cardiovascular complications. Liver X alpha receptor (LXRα) is highly expressed in liver, function as cholesterol sensors with important roles in regulating cholesterol homeostasis. The leaves of *Corchorus trilocularis* possess anti-atherosclerotic property along with its anti hyperglycemic activity. The Genetic Optimization for Ligand Docking (GOLD) software resulted in identifying the best compound that interacts with the receptor. The present study was carried out to evaluate the anti-atherosclerotic activity of the ethanolic leaf extract of *Corchorus trilocularis* against LXRα by using GOLD software. Phytochemical molecules were retrieved from the pubchem database and the 2D chemical structures were generated from Simplified Molecular Input Line Entry Specification (SMILES) notation by using the Chemsketch Software. 3-Dimensional structure of LXRα was retrieved using Protein Data Bank. 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. Among the twelve phytochemicals, 10-Methyl-E-11-tridecen-1-ol propionate has the GOLD score of 28.33. From the *in-silico* docking results, it is quite evident that phytochemicals of *Corchorus trilocularis* leaves have the great potential against atherosclerosis and may act as better leads and in turn prevent atherosclerosis. ADME and toxicity was predicted by using ADMET structure-activity relationship database.

**INTRODUCTION:** Atherosclerosis is a chronic disease characterized by lipid deposition and inflammation in arterial inner wall [1]. Atherosclerosis is one of the major risk factors for coronary artery disease.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(9).3839-44

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(9).3839-44

There are a number of genetic, metabolic, and environmental factors involved in the formation and evolution of the atherosclerotic plaque. A well-known risk factor in humans is hyper-cholesterolemia, *i.e*., elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDLc) [2] and other important contributors to this disease include inflammation, oxidative stress and insulin resistance [3, 4]. Liver X Receptors (LXRs) $\alpha$ and $\beta$ are nuclear hormone receptors that regulate multiple genes involved in reverse cholesterol transport (RCT) and are potential drug targets for

atherosclerosis [5]. LXR*α* is highly expressed in liver, and at lower levels in the intestine, macrophages, kidney and other organs, while LXR *β* is expressed ubiquitously [6]. Traditionally, natural products, including plants, animals and minerals have been used since ancient times and in folklore for the treatment of many diseases and illnesses [7]. Medicinal plants have historically proven their value as a source of molecules with therapeutic potential, and nowadays still represent an important pool for the identification of novel drug leads [8].

Many countries follow the traditional medicine as one of the most important health care systems [9]. 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 [10]. *Corchorus trilocularis* L. (Tiliaceae) is one of the most common plants in India and is available throughout the year. The plant has been reported to possess various activities such as anti-inflammatory [11], antidiabetic [12] and demulcent properties [13].

In traditional folklore medicine in India, *Corchorus trilocularis* is also used for the treatment of syphilis [14]. Twelve different bioactive constituents have been identified from the ethanolic leaf extract of *Corchorus trilocularis* by gas chromatography mass spectrometry analysis [15].

In modern drug designing, molecular docking provides useful information about drug receptor interactions and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule [16]. Further computational prediction of pharma-cokinetic parameters like Absorption, Distribution, Metabolism and Excretion (ADME) and toxicity studies have become increasingly important in drug selection and promotion process and are promising tools for early screening of potential drug candidates [17]. Therefore, the present study was aimed to investigate the molecular interaction between the phytochemicals in the ethanolic leaf extract of *Corchorus trilocularis* and the LXRα for preventing atherosclerosis through *insilico* docking by using GOLD [18]. *In-silico* screening ADMET profiles of phytochemicals by using ADMET structure-activity relationship database (ADMET SAR) [19].

## MATERIALS AND METHODS:

**Liver X Alpha Receptor (LXR*α*) 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:** Twelve phytochemicals identified from ethanolic leaf extract of *Corchorus trilocularis* were screened against LXRα. List of phytoconstituents 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 [20].

**TABLE 1: PHYTOCONSTITUENTS FROM THE ETHANOLIC EXTRACT OF *C. TRILOCULARIS* LEAVES**

| S. no. | Name of the compound |
|---|---|
| 1 | 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6- methyl- |
| 2 | 3,7,11,15-Tetramethyl-2-hexadecen-1-ol |
| 3 | trans-2-Undecen-1-ol |
| 4 | E-7-Tetradecenol |
| 5 | n-Hexadecanoic acid |
| 6 | Phytol |
| 7 | 9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)- |
| 8 | Docosanoic acid, ethyl ester |
| 9 | 9-Tetradecen-1-ol, acetate, (E)- |
| 10 | 10-Methyl-E-11-tridecen-1-ol propionate |
| 11 | Squalene |
| 12 | Vitamin E |

**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 twelve compounds derived from *Corchorus trilocularis* 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 (Gold Mine) and visualization of docking results. The ligand molecule which shows highest binding affinity with the receptor molecule was chosen as best drug.

**ADMET Prediction:** AdmetSAR provides the latest and most comprehensive manually curate data for diverse chemicals associated with known ADMET profiles. This database is having twenty two qualitative classification and five 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 [21]. The admetSAR tool was employed for the *in-silico* screening of ADMET profiles for the active compounds derived from the ethanolic extract of *Corchorus trilocularis* leaves.

**RESULTS AND DISCUSSION:** The molecular docking analysis of the twelve compounds derived from ethanolic extract of *Corchorus trilocularis* 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) [22]. 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**.

**TABLE 2: GOLD DOCKING SCORE OF PHYTO-CONSTITUENTS PRESENT IN *CORCHORUS TRILOCULARIS* LEAVES**

| S. 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 | 9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)- | - | - | 3.18 |
| 3 | Docosanoic acid, ethyl ester | 1 | 3.030 | 21.75 |
| 4 | E-7-Tetradecenol | 1 | 2.584 | 26.99 |
| 5 | n-Hexadecanoic acid | - | - | 21.03 |
| 6 | Phytol | - | - | 15.88 |
| 7 | Squalene | - | - | -4.58 |
| 8 | trans-2-Undecen-1-ol | - | - | 22.33 |
| 9 | Vitamin E | 1 | 2.529 | 12.11 |
| 10 | 10-Methyl-E-11-tridecen-1-ol propionate | 2 | 2.973 | 28.33 |
| 11 | 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6- | 2 | 2.254 | 22.62 |
| 12 | 9-Tetradecen-1-ol, acetate, (E)- | - | - | 26.13 |

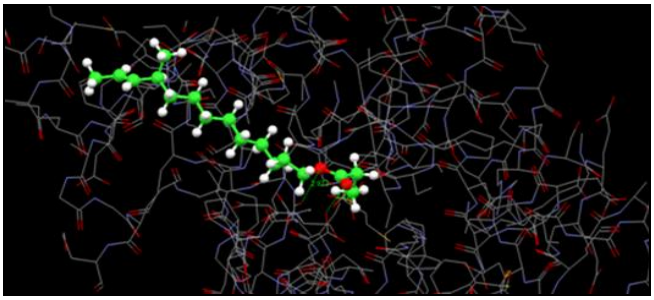

**FIG. 1: DOCKING OF 10-METHYL-E-11-TRIDECEN -1-OL PROPIONATE WITH LIVER X ALPHA RECEPTOR**

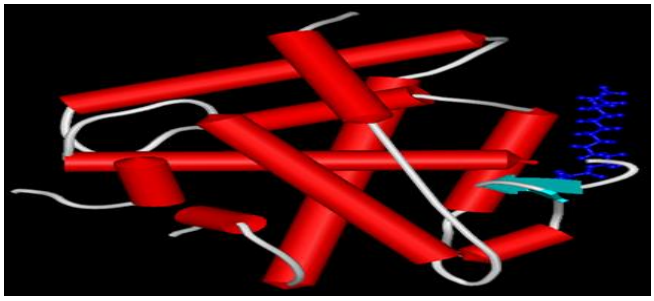

**FIG. 2: DOCKING SCHEMATIC PATTERN 2: PROTEIN - SCHEMATIC, LIGAND - BALL AND STICK**

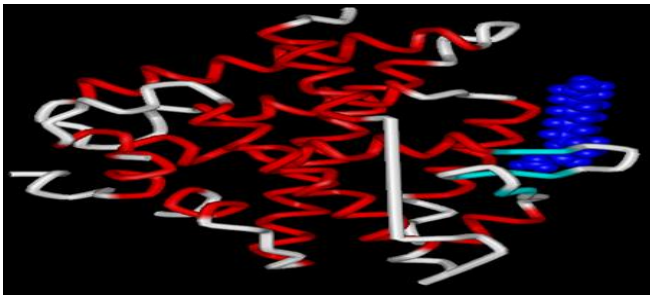

**FIG. 3: DOCKING SCHEMATIC PATTERN 3: PROTEIN - TUBE, LIGAND – BALL AND STICK**

The results indicate that compound 10-Methyl-E-11-tridecen-1-ol propionate has the highest affinity to bind with LXRα with GOLD score of 28.33. The compounds E-7-tetradecenol, 9-tetradecen-1-ol, acetate, 4H-Pyran-4-one,2,3-dihydro-3, 5-dihydro xy-6-methyl-, trans-2-Undecen-1-ol, Docosanoic acid, ethyl ester and *n*-Hexadecanoic acid shows relatively good binding affinity with the GOLD score of 26.99, 26.13, 22.62, 22.33, 21.75 and 21.03 respectively.

Phytol, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol and Vitamin E shows comparatively less binding affinity with the GOLD scores of 15.88, 15.88 and 12.11 respectively. 9, 12, 15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)- and Squalene shows the least affinity with the GOLD scores being 3.18 and -4.58. The docking of 10-Methyl-E-11-tridecen-1-ol propionate with LXRα is shown in **Fig. 1**. The different Docking schematic patterns for 10-Methyl-E-11-tridecen-1-ol propionate with LXRα are given as **Fig. 2** and **3**.

From the *in-silico* docking results, it is quite evident that *Corchorus trilocularis* compounds have the great potential against atherosclerosis.

The implementation of ADMET profiling of drug candidates, in conjunction with biological efficacy and safety optimization, has dramatically reduced pharmacokinetic failures in clinical trials and leads to the development of effective compounds in the process of drug design [23]. ADMET properties, as derived from admetSAR server, reveal that in case of absorption, the active phytochemicals for different types of models such as BBB penetration, P-glycoprotein substrate, renal organic cation transporter, and the human intestinal absorption and $CacO_2$ permeability showed positive results which strongly support the ability of phytochemical to act as drug. Absorption prediction profile for active compounds from *Corchorus trilocularis* L. are given in **Table 3**.

**TABLE 3: ABSORPTION PREDICTION PROFILE FOR ACTIVE COMPOUND FROM *CORCHORUS TRILOCULARIS* LINN.**

| Parameter | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blood-Brain Barrier | + | + | + | + | + | + | + | + | + | + | + | + |
| Human Intestinal Absorption | + | + | + | + | + | + | + | + | + | + | + | + |
| Caco-2 Permeability | + | + | + | + | + | + | + | + | + | + | + | + |
| P-glycoprotein Substrate | 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 |
| Renal Organic Cation Transporter | NI | NI | NI | NI | NI | NI | NI | NI | NI | NI | NI | NI |

+: positive, -: negative, NS: Non-substrate, S: Substrate, NI: Non-Inhibitor

Cytochrome P450 (CYP) is a group of isozymes involves in the metabolism of drugs, fatty acids, steroids, bile acids and carcinogens. Almost 75% of phase I drug metabolism depends on the association of CYP enzymes. In case of metabolism, various CYP substrate and inhibitor models are designed and the outcome shows that these active phytochemicals are non-substrate and non-inhibitor of CYP enzymes. The vitamin E alone shows to act as substrate for CYP450 3A4 Substrate. Metabolism prediction profile for active compounds from *Corchorus trilocularis* Linn. are given in **Table 4**. In terms of toxicity, all the phytochemicals are found to be non toxic. Toxicity prediction profile for active compounds from *Corchorus trilocularis* L. are given in **Table 5**.

**TABLE 4: METABOLISM PREDICTION PROFILE FOR ACTIVE COMPOUND FROM *CORCHORUS TRILOCULARIS* LINN.**

| Parameter | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CYP450 2C9 Substrate | 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 |
| CYP450 3A4 Substrate | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| CYP450 1A2 Inhibitor | NI | I | I | NI | NI | NI | I | I | NI | NI | NI | NI |
| CYP450 2C9 Inhibitor | 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 |
| CYP450 2C19 Inhibitor | 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 |

NS: Non-substrate; NI: Non-Inhibitor; I: Inhibitors; S: Substrate

**TABLE 5: TOXICITY PREDICTION PROFILE FOR ACTIVE COMPOUND FROM *CORCHORUS TRILOCULARIS* L.**

| Parameter | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Human Ether-a-go-go Related Gen Inhibition | WI | WI | WI | WI | WI | WI | WI | WI | WI | WI | WI | WI |
| AMES Toxicity | T | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| Carcinogens | NC | C | C | NC | C | C | NC | NC | NC | C | C | NC |
| Fish Toxicity | LT | 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 |
| Honey Bee Toxicity | HT | HT | HT | HT | HT | HT | HT | HT | HT | HT | HT | HT |
| Biodegradation | RB | RB | RB | RB | RB | R | RB | RB | RB | RB | RB | NRB |
| Acute Oral Toxicity | III | III | III | III | III | III | III | IV | III | III | III | III |

+: positive, -: negative, NS: Non-substrate, S: Substrate, NI: Non-Inhibitor, I: Inhibitor, WI: Weak Inhibition, NT: Non-Toxic, NC: Non- Carcinogen, C: Carcinogen, HT: High Toxic, RB: Readily Biodegradable, NRB: Not Readily Biodegradable

**CONCLUSION:** The molecular docking analysis of the twelve compounds from ethanolic extract of *Corchorus trilocularis* leaves with the LXRα using the GOLD software revealed their potential to interact with the receptor. To the best of our knowledge, this is the first report of the prospective anti-atherosclerotic activity of *C. trilocularis* leaves.

From this study, best compound (10-Methyl-E-11-tridecen-1-ol propionate) has been identified for treatment and management of atherosclerosis. This *in-silico* studies helps us to move on for *in-vivo* procedure to confirm the above biological activity. Further experimental studies are needed to determine and clarify their underlying mechanism.

**ACKNOWLEDGEMENT:** The authors are grateful to the University Grant Commission, New Delhi, India for providing UGC-BSR fellowship.

**CONFLICT OF INTEREST**: The authors have declared that there is no conflict of interest associated with this publication.

## REFERENCES:

1. Lusis J: Atherosclerosis. Nature 2000; 407(6801): 233-241.
2. Pearson TA, Blair SN and Daniels SR: AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. Circulation 2002; 106: 388-391.
3. Libby P, Ridker PM and Maseri A: Inflammation and atherosclerosis. Circulation 2002; 105: 1135-1143.
4. Van Gaal LF, Mertens IL and De Block CE: Mechanisms linking obesity with cardiovascular disease. Nature 2006; 444: 875-880.
5. Odd KG, Martin R and Sleph P: Pharmacological Characterization of a novel liver X Receptor agonist with partial LXRα activity and a favorable window in nonhuman primates. Journal of Pharmacology and Experimental Therapeutics 2015; 352: 305-314.
6. Miller A, Crumbley C and Prüfer K: The N-terminal nuclear localization sequences of liver X receptors alpha and beta bind to importin alpha and are essential for both nuclear import and transactivating functions. Int J Biochem Cell Biol 2009; 41(4): 834-43.
7. Dias DA, Urban S and Roessner U: A historical overview of natural products in drug discovery. Metabolites 2012; 2(2): 303-336.
8. Atanasova AG, Waltenbergerb B and Pferschy-Wenzig EM: Discovery and resupply of pharmacologically active plant derived natural products. A review. Biotechnol Adv 2015; 33(8): 1582-1614.
9. Houghton PJ: The role of plants in traditional medicine and current therapy. J Altern Complement Med 1995; 1(2): 131-43.
10. Scott T: Exploring the universe of ayurvedic botanicals to manage bacterial infections. Clin Nutr Insights 1998; 6(17): 1-3.
11. Ahirrao RA, Borse LB, Pawar SP, Rane BR, Desai SG and Alagawadi KR: Evaluation of anti-inflammatory activity of *Corchorus trilocularis* Linn. Seed oil. Adv Pharmac Toxic 2009; 10 (1): 117-200.
12. Gupta PK, Jain S, Kaushik A and Alok S: Evaluation of anti-diabetic activity of *Corchorus trilocularis* leaves in streptozotocin induced diabetic rat. International Journal of Pharmaceutical Sciences and Research 2017; 8(7): 3075-3080.
13. Senthilkumar M, Gurumoorthi P and Janardhanan K: Some medicinal plants used by Irular, the tribal people of mrudhamalai hills, Coimbtore, Tamil Nadu. Natural Product Radiance 2006; 5(5): 382-388.
14. Ishtiaq CM and Khan MA: An ethanomedicinal inventory of plants used for family planning and sex diseases in Samahni valley, Pakistan. Ind J of Traditional knowledge 2008; 7 (2): 277-283.
15. Dhanalakshmi R and Manavalan R: Bioactive Compounds in leaves of *Corchorus trilocularis* L. by GC-MS Analysis. Int. J. Pharm Tech Res 2014; 6(7): 1991-1998.
16. Vijesh AM, Arun M and Isloor: Molecular docking studies of some new imidazole derivatives for antimicrobial properties. Arabian Journal of Chemistry 2013; 6: 197-204.
17. Moroy *et al*.: Toward *in-silico* structure-based ADMET prediction in drug discovery. Drug Discov Today 2012; 17: 44.
18. Jones G, Willett P, Glen RC, Leach AR and Taylor R: Development and validation of a genetic algorithm for flexible docking. J Mol Biol 1997; 267(3): 727-48.
19. Cheng F, Li W, Zhou Y, Shen J, Wu Z and Liu G: AdmetSAR: A Comprehensive source and free tool for assessment of chemical ADMET properties. J Chem Inf Model 2012; 52: 3099-105.

20. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T and Hutchison GR: Open Babel: An open chemical toolbox. J Cheminform 2011; 3: 33.
21. Balakin KV, Ivanenkov YA, Savchuk NP, Ivashchenko AA and Ekins S: Comprehensive computational assessment of ADME properties using mapping techniques. Curr Drug Discov Technol 2005; 2(2): 99-113.
22. Nissink JW, Murray C, Hartshorn M, Verdonk ML, Cole JC and Taylor R: A new test set for validating predictions of protein-ligand interaction. Proteins 2002; 49: 457-71.
23. Tsaioun K, Blaauboer BJ and Hartung T: Evidence-based absorption, distribution, metabolism, excretion (ADME) and its interplay with alternative toxicity methods. ALTEX 2016; 33(4): 343-358.

**How to cite this article:**
Dhanalakshmi R, Manimekalai P and Manavalan R: *In-silico* molecular docking studies on the phytoconstituents of *Corchorus trilocularis* (L.) for its antiaherosclerotic activity and ADMET prediction. Int J Pharm Sci & Res 2018; 9(9): 3839-44. doi: 10.13040/IJPSR.0975-8232. 9(9).3839-44.