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In-Silico Screening of Novel Compounds from Lentinus Tuberregium Edible Mushroom Against Breast Cancer Cell Line

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ABSTRACT

Breast cancer is the most common cause of death among women. Hence discovery of novel molecules to inhibit the breast cancer protein is critical research. Molecular docking, an in-silico techniques been used for the identification of protein-ligand interactions for the current study on breast cancer. Autodock, the common and accurate software for molecular docking was used in the current study. In this study, two compounds 5α,8α-epidioxy-24 ε-methylcholesta-6,22-dien-3β-ol and Ergosta-5,7,22-trien-3β-ol from the mushroom Lentinus tuberregium was docked with breast cancer biomarkers like VEGFR2, Human Estrogen Receptor, IL17A and PI3K. Among them Ergosta-5,7,22-trien-3β-ol showed least binding energy of -8.94 kcal/mol against VEGFR2, followed by 6.78 kcal/mol against IL17A, -6.52 kcal/mol against human estrogen receptor and -4.79 kcal/mol against PI3K. The other ligand 5α,8α-epidioxy-24 ε-methylcholesta-6,22-dien-3β-ol was also found to be potential inhibitor with a binding energies of -6.99 kcal.mol, -6.22 kcal/mol, -6.06 kcal/mol and -3.61 kcal/mol against human estrogen receptor, VEGFR2, IL17A and PI3K respectively. The control drug Abemaciclib, showed a binding energies higher than the ligands. In addition, ADMET studies also revealed that the ligands are safer and no toxic effects. From this current study, the reported ligands from mushroom can be potential and novel inhibitors for drug targets of breast cancer and can be used for the treatment of breast cancer.

Keywords: Breast cancer; Autodock 4.2; ADMET; Binding energy; Ergosta-5,7,22-trien-3 β-ol; 5 α; 8 α-epidioxy-24; ε-methylcholesta-6,22-dien-3β-ol; Abemaciclib.

INTRODUCTION

Cancer is the highly fatal disease that results when cellular changes cause uncontrolled growth and division of cells (Pruitt 2016). Cancer affects all age groups, and all genders, but as per a study, more women get affected by cancer than men, though the survival rates differ. The highest incidence of cancer in women is breast cancer, with a mortality rate of 11.6% globally in the year 2018 (Bray et al., 2018). Many proteins have been reported to be responsible for breast cancer, interleukin 17A (IL17A), a pro-inflammatory cytokine has been proven to increase the NF-kB mediated inflammatory pathway (Fabre et al., 2019). Other main target reported in breast cancer is PI3K. Activation of PI3K can lead to diverse functions like cell proliferation, differentiation and survival, and hence could be a major protein (Baselga 2011). Human estrogen receptor is again proved to have a positive role in cancer progression (Roy and Vadlamudi 2012). VEGFR2, other important protein in breast cancer proved to promote cancer cell survival and proliferation (Guo et al., 2010). Inhibiting the effect of these proteins will provide an effective way to reduce the occurrence of cancer and the same has undertaken here as a study.

Docking was performed with the compounds isolated from an edible mushroom that is mainly grown in Asia and Africa "Lentinus tuberregium", against breast cancer proteins (Kumar et al. 2012). Two main compounds were extracted from the mushroom, namely 5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol and Ergosta-5,7,22-trien-3 β-ol. The compounds were patented for their anti-cancer activity proved by *in vitro* studies on colorectal, ovarian and breast cancer cell line.

In-silico study was performed to identify the inhibitors for specific breast cancer drug targets for the ligands. For molecular docking, AutoDock been widely used free software (Ferreira et al., 2015). Docking methodology paves way for drug discovery by reducing the time and cost of *in vitro* drug development methods. Autodock 4.2, open source software mainly run on Lamarckian genetic algorithm and evaluated by least binding energies and the most flexible conformations between the protein and the ligand. It also provides details about the hydrogen, van der walls and hydrophobic interactions between the protein and the ligand and hence the protocol been used for this current study (Ördög et al.,2008).

This is the first study involving docking of the ligands 5 α,8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol and Ergosta-5,7,22-trien-3 β-ol with breast cancer associated proteins, IL17A, PI3K, VEGFR2 and human estrogen receptor. Both the ligands showed good binding with the proteins, indicating their potential to inhibit the proteins. Abemaciclib, approved by Food and Drug Administration (FDA) was chosen as the control and all the proteins were docked with the control drug (Johnston et al., 2019). The ligands showed a good binding energy in comparison to the control drug and interacted with the active site amino acids of the protein. Thus these ligands can be a natural alternative to the chemically synthesized drug for breast cancer.

MATERIALS AND METHODS

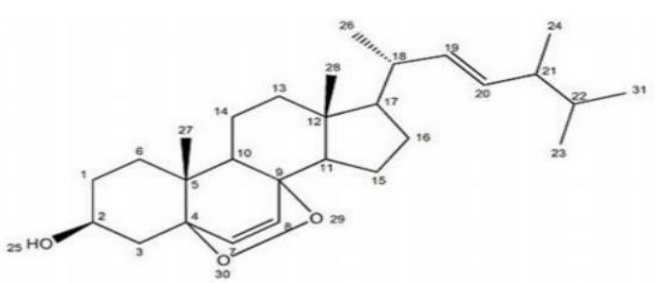
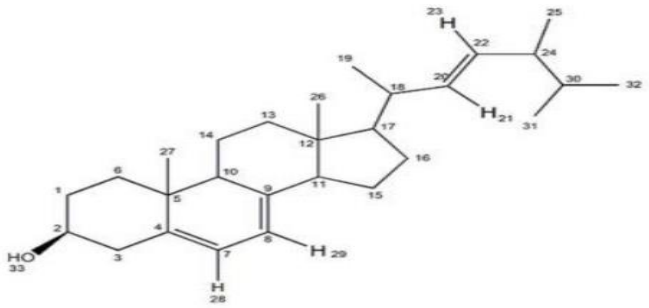
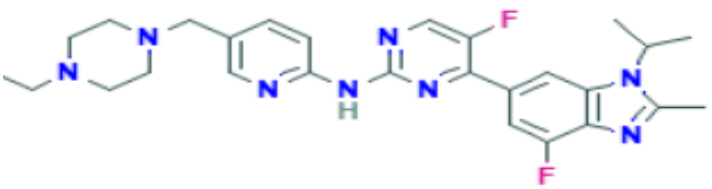
Protein preparation

The three dimensional structure of protein dataset was selected from VEGFR2 (PDB ID: 4AGC), human estrogen receptor (PDB ID: 2IOG), IL17A (PDB ID: 4HR9) and PI3K (PDB ID: 3QAR) were obtained from Protein Data Bank (PDB). PDB, a primary protein structure database were experimental protein structures are deposited (Rose et al., 2016). All the water molecules and heteroatoms in the proteins were removed using PyMol software. The proteins were then prepared by adding polar hydrogen atoms and kollman charges using Autodock 4.2. The protein structures were then saved in the autodock readable PDBQT format (Seeliger and de Groot 2010).

Ligand preparation

Two ligands 5α,8α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol and Ergosta-5,7,22-trien-3 β-ol were chosen for docking studies (Hunter, 1997). The structure of the ligands was drawn using Chemsketch software. Chemsketch, a freeware developed by Advanced Chemistry Development, Inc., (http: //www. acdlabs. com). The structure was saved as mol file and converted to PDB using NCI/CADD group (https://cactus.nci.nih.gov/index.html). Energy minimization of the ligands was performed using Swiss PDB viewer (Guex and Peitsch, 1997). Gasteiger charges and rotatable bonds were added to the ligands and finally the ligand structure in the PDB format was converted to PDBQT format and saved for further docking studies. The structure of control drug Abemaciclib, a drug used in for treating cancer was obtained from PubChem. The control drug also prepared in the same protocol as the other ligands and saved in the PDBQT format for docking with the protein (Madeswaran et al., 2012). The structure of the ligands and the control were shown in Table 1.

Table 1: Structure of ligands and control drug.

Ligand	Structure
5 α,8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol	
Ergosta-5,7,22-trien-3 β-ol	
Abemaciclib	

Active site determination

The ligand binding pocket of the proteins VEGFR2, PI3K and human estrogen receptor alpha were obtained from PDBSum. In our previous study, the active site of IL17A was determined using CASTp and the same was utilized now or this study (Laskowski, 2001; Dundas et al., 2006).

Molecular docking

The docking of proteins with the ligands and the control drug were performed using Autodock 4.2. The X, Y and Z coordinates of the grid box was adjusted to 40*40*40 for all the proteins (Adejoro et al. 2016). Only the X, Y and Z centers were adjusted to certain size for each protein. Lamarckian genetic algorithm (LGA), a combination of genetic algorithm and local search algorithm was used to predict the docked conformations of the ligands (Forli et al. 2016).

Visualization

The docking results was analyzed by weak interactions between the ligand and the protein using Discovery studio. It provides the information about amino acids involved in the protein ligand interaction, hydrogen bonds formation and other interactions between the protein and the ligand (Jamal et al., 2012).

ADME(T) prediction

The adsorption, distribution, metabolism, excretion and toxicity (ADMET) are the major parameters to be considered to analyze the drug potential of a molecule. The ADMET properties for the ligands were evaluated using the online software tool predicting small-molecule pharmacokinetic properties using graph-based signatures (pkCSM) (http://biosig.unimelb.edu.au/pkcsm/). It is a free web based server for rapid screening of various pharmacokinetic properties of a drug.

RESULTS AND DISCUSSION

Four proteins VEGFR2, PI3K, human estrogen receptor and IL17 are known to be involved in the pathogenesis of cancer were chosen for docking studies.The active site of the proteins VEGFR2, PI3K and human estrogen receptor were obtained from the protein ligand interactions depicted in PDBSum (Figure 1). Since no ligand interactions are available in PDBSum for IL17A, CASTp was used for studying the active site amino acids. In our previous study, the active site of IL17A was determined using CASTp and the same was used here (Hari 2019) (Figure 2).

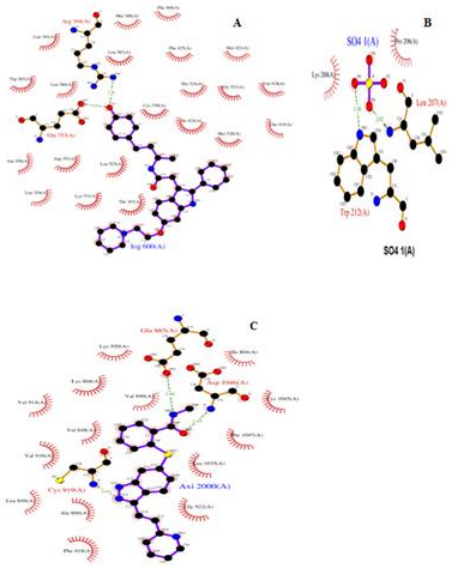


Figure 1: A) Ligand binding amino acids of Human estrogen receptor alpha. B) Ligand binding amino acids of PI3K. C) Ligand binding amino acids of VEGFR2.

Figure 2: Active site pocket of IL17A determined by CASTp. Amino acids highlighted in blue are active site amino acids.

Docking

Molecular docking is a powerful technique performed for structure based drug design using known or predicted active sites or binding site information through in-silico approaches (Brooijmans and Kuntz, 2003). In the current research work, the docking results of protein drug targets and the ligand showed that ergosta-5,7,22-trien-3 β-ol showed the least binding energy of -8.94 kcal/mol against VEGFR2. Many amino acids in the active site of VEGFR2 was found to interact with the ligand ergosta-5,7,22-trien-3 β-ol. Active site amino acids that interacted with the ergosta-5,7,22-trien-3 β-ol include Leu 840, Glu 885, Val 848, Val 916, Gly 922, Leu 1035, ASP 1046 and Phe 1047. The binding energy and the interacting atoms are shown in table. 5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol interacted with human estrogen receptor with a binding energy of -6.99 kcal/mol and the interactions were compared with amino acid in the active site of 2IOG obtained from PDBSum. In docking analysis, mainly the weak intermolecular interactions like hydrogen bonds and hydrophobic interactions plays a key role in formation of protein-ligand and also in complex stabilization (Lu et al., 2009). The drug efficacy was improved with the formation of key weak interactions in binding involved the active sites of protein (Desiraju, 2005). In this case, the results showed that the ligand interacted well with the active site amino acids, Arg 394, Met 388, Trp 383, Phe 404, Leu 354, Glu 353, Phe 425, Met 421, His 524, Ala 350, Asp 351, Thr 347, Cys 530, Lys 531, Met 528, Gly 521, Ile 424 through hydrogen bonds.

Ergosta-5,7,22-trien-3 β-ol also showed a good binding with human estrogen receptor with a binding energy of -6.52 kcal/mol and interacted with the active site amino acids. They include Trp 383, Arg 394, Leu 354, Glu 353, Phe 425, Asp 351, Cys 530, Lys 531, Met 528. Against IL17A protein ergosta-5,7,22-trien-3 β-ol gave a binding energy of -6.78 kcal/mol. The amino acids in the active center of the protein that interacted with the ligand include Tyr 44, Trp 51, Leu 53, Trp 67, Val 119 through hydrogen bonds. 5α,8α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol interacted with VEGFR2 and IL17A with a binding energies of -6.22 kcal/mol and -6.06 kcal/mol respectively. The ligand formed interaction with all the amino acids in the active site of the protein. The interactions are Glu 885, Ile 804, Asp 1046, Phe 1047, Cys 1045, Lys 868, Leu 1035, Gly 922, Cys 919, Val 848, Ala 866, Lys 920, Val 914, Val 916 and Leu 840. All the active site amino acids obtained using PDBSum were found to interact with the ligand. With IL17A, the ligand formed bond with many amino acids in the active center of the protein. These include Pro 63, Leu 53, Ala 69, Val 119, Ser 118, Val 117, Ile 96, Ile 66 and val 65 through hydrogen bonds.

Both Ergosta-5,7,22-trien-3 β-ol and 5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol did not show a good effect against PI3K. The binding energy was -4.79 kcal/mol for Ergosta-5,7,22-trien-3 β-ol against PI3K. Ligand 5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol showed a binding energy of -3.61 kcal/mol. The ligands were found to interact with the amino acids that were not in the active site of the protein. Even after a series of grid changes according to the active site of the protein, the ligand did not bind to the active site amino acids, hence a conformation with the least binding energy was taken to consideration.

In order to compare the efficacy of the ligand, control drug Abemaciclib was docked with all protein drug targets. Abemaciclib, a common and specific drug was widely used for breast cancer treatment. The drug showed binding energies of -4.92 kcal/mol, -1.5 kcal/mol, -4.08 kcal/mol and -4.04 kcal/mol against VEGFR2, PI3K, human estrogen receptor and IL17A respectively. In summary, the docking results proved the reported ligand was more efficient than the control drug Abemaciclib.

The docking results of 5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol with the proteins are shown in Figure 3, Figure 4 depicts the results of docking of the ligand Ergosta-5,7,22-trien-3 β-ol against the breast cancer proteins. The control Abemaciclib's interaction with the proteins is shown in Figure 5. The binding energies of the protein-ligand and the amino acids involved in the interaction are given in Table 2 and Table 3 respectively.

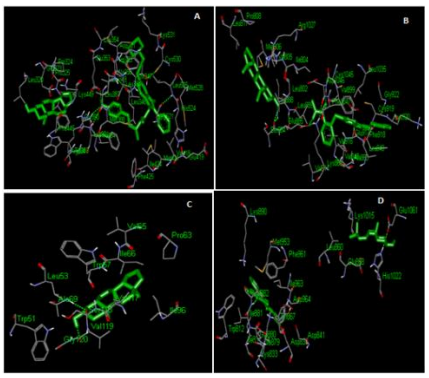


Figure 3: Interactions of 5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol with A) Human estrogen receptor B) VEGFR2. C) IL17A, D) PI3K.

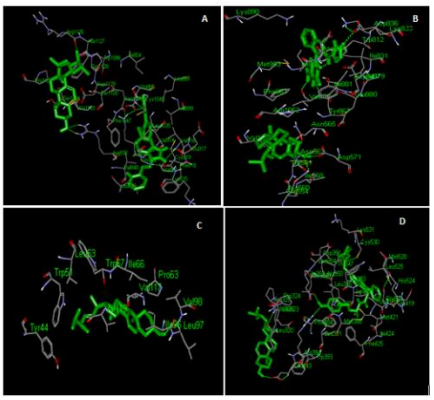


Figure 4: Interactions of with ergosta-5,7,22-trien-3 β-ol with A) VEGFR2 B) PI3K C) IL17A D) human estrogen receptor.

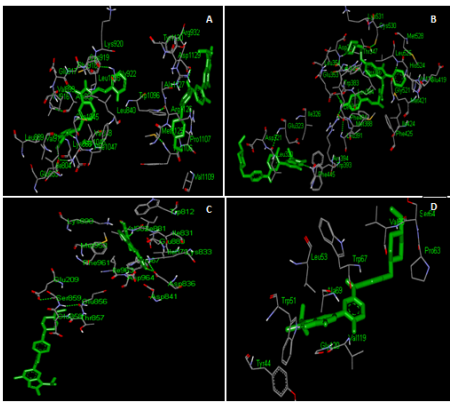


Figure 5: Interactions of Abemaciclib with A) VEGFR2 B) human estrogen receptor C) PI3K D) IL17A.

Table 2: Binding energies of protein-ligand interaction studies.

Protein	Binding energies (kcal/mol)		
	5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol	Ergosta-5,7,22-trien-3 β-ol	Abemaciclib
VEGFR2	-6.22	-8.94	-4.92
PI3K	-3.61	-4.79	-1.5
Human estrogen receptor alpha	-6.99	-6.52	-4.08
IL17A	-6.06	-6.78	-4.04

Table 3: List of amino acids involved in the binding of proteins with the ligands.

Protein	Ligand interacting amino acids		
	5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol	Ergosta-5,7,22-trien-3 β-ol	Abemaciclib
VEGFR2	Leu 811, Pro 808, Met 806, Ser 884, Ile 888, Glu 885, Leu 889, Val 805, Ile 804, Leu 802, Arg 1027, Asp 1046, Phe 1047, Cys 1045, Val 889, Lys 868, Leu 1035, Gly 922, Cys 919, Val 848, Glu 917, Ala 866, Phe 918, Lys 920, Val 914, Val 916, Leu 840	Val 899, Leu 1035, Cys 919, Lys 920, Gly 922, Leu 840, Val 848, Lys 868, Val 914, Glu 885, Val 916, Glu 917, Leu 889, Phe 1047, Arg 932, Ala 1103, Ser 1104, Ser 1100, Asp 1129, Pro 1128, Pro 1107, Asp 1046, Arg 1126, Ala 1127, Trp 1096, Ile 804	Lys 920, Cys 919, Phe 918, Glu 917, Val 899, Val 916, Cys 1045, Leu 889, Val 914, Glu 885, Arg 932, Tyr 1130, Asp 1129, Pro 1128, Trp 1096, Ala 1103, Ala 1127, Arg 1126, Lys 863, Val 846, Ile 804, Leu 1035, Gly 922, Cys 919, Lys 920, Met 1125, Tyr 1106, Pro 1107, Val 1109

PI3K	Lys 890, Met 953, Phe 961, Ile 963, Val 882, Ile 881, Trp 812, Glu 880, Ile 879, Lys 833, Phe 961, Ile 963, Asp 964, Tyr 867, Asp 836, Asp 841, Leu 860, Glu 858, His 1022, Lys 1015, Glu 1061	Lys 890, Met 953, Phe 961, Arg 1052, Val 1057, Ile 881, Val 882, Trp 812, Glu 880, Tyr 867, Phe 961, asp 841, Ile 963, Asp 964, Asp 836, Arg 1056, Asn 555, Asp 562, Val 1057, Thr 561, Ala 560, Ile 558, Gln 554, Asp 571	Lys 890, Lys 833, Ile 831, Ile 879, Asp 841, Glu 880, Tyr 867, Asp 841, Asp 841, Phe 961, Met 953, Ile 963, Asp 964, Lys 890
Human estrogen receptor	Leu320, Glu 323, Pro 324, Pro 325, Ile 326, Phe 445, Ly 449, Trp 393, Arg 394, Leu 387, Met 388, Leu 384, Trp 383, Leu 387, Phe 404, Leu 354, Glu 353, Ile 424, Phe 425, Gly 521, Met 421, His 524, Glu 419, Ala 350, Asp 351, Leu 349, Leu 346, Thr 347, Cys 530, Lys 531, Met 538, Leu 525, Val 418, Gly 521, Phe 425, Ile 424, Met 421, His 524, Val 418, Glu 419	Leu 320, Glu 323, Pro 324, Pro 325, Ile 326, Trp 393, Arg 394, Leu 384, Trp 383, Leu 354, Glu 353, Ile 424, Phe 425, Asp 351, Leu 349, Leu 346, Cys 530, Lys 531, Met 528, Phe 404, Val 418, met 421, Glu 419	Phe 445, Leu 320, Glu 323, Asp 321, Ile 326, Arg 394, Trp 393, Phe 404, Met 388, Leu 387, Glu 353, Leu 349, Leu 354, Asp 351, Ala 350, Lys 531, Trp 383, Ala 350, Lys 531, Trp 383, Ala 350, Leu 349, Thr 347, Leu 346, Lys 531, Cys 530, Leu 525, Met 528, His 524, Gly 521, Phe 425, Ile 424, Met 421
IL17	Tyr 44, Trp 51, Leu 53, Trp 67, Val 119, Val 117, Pro 63, Val 98, Ile 96, Leu 97	Pro 63, Trp 51, Leu 53, Ala 69, Gly 120, Val 119, Ser 118, Val 117, Ile 96, Ile 66, Val 65	Ser 64, Pro 63, Val 65, Trp 67, Ala 69, Leu 53, Trp 51, Tyr 44, Gly 120, Val 119

Pharmacokinetic properties

The ADMET properties of the ligands were predicted using pkCSM online portal for predicting the pharmacokinetics of the ligands. pkCSM is an easy, user friendly and very rapid online portal for predicting the ADMEt properties of drugs. It provides the complete list of absorption, distribution, metabolism, excretion and toxicity of the ligands (Pires et al., 2015). For the ligand Ergosta-5,7,22-trien-3β-ol, the results showed that the ligand is absorbed by the intestine and was shown not to contain any Salmonella typhimurium reverse mutation assay (AMES) toxicity. The LD50 value (oral rat acute toxicity) was shown to be 2.323 mol/ kg. The ADMET properties of 5α,8α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol showed 94.696 % intestinal absorption and had no AMES toxicity. The LD50 value for the ligand was 2.217 mol/ kg. Table 4 shows the results from pKCSM for the ligand Ergosta-5,7,22-trien-3 β-ol and 5 α,8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol.

Table 4: Pharmacokinetic properties of the ligands.

Property	**Model**	**Predicted result**	
		5 α, 8 α-epidioxy-24 ε-methylcholesta-6,22-dien-3 β-ol	**Ergosta-5,7,22-trien-3 β-ol**
Absorption	Water solubility	-6.153 log mol/L	-7.092 log mol/L
	Caco2 permeability	1.597 log Papp in 10-6 cm/s	1.297 log Papp in 10-6 cm/s
	Intestinal absorption (human)	94.70%	96.40%
	Skin Permeability	-2.706 log Kp	-2.759 log Kp
	P-glycoprotein substrate	No	No
	P-glycoprotein I inhibitor	Yes	Yes
	P-glycoprotein II inhibitor	No	Yes
Distribution	VDss (human)	0.362 log L/kg	0.326 log L/kg
	BBB permeability	0.688 log BB	0.797 log BB
	CNS permeability	-1.647 log PS	-1.376 log PS
Metabolism	CYP2D6 substrate	No	No
	CYP3A4 substrate	Yes	Yes
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitior	No	No
	CYP2C9 inhibitior	No	No
	CYP2D6 inhibitior	No	No
	CYP3A4 inhibitior	No	No
Excretion	Total Clearance	0.758 log ml/min/kg	0.564 log ml/min/kg
	Renal OCT2 substrate	No	No

Toxicity	AMES toxicity	No	No
	Max. tolerated dose (human)	-0.751 log mg/kg/day	-0.242 log mg/kg/day
	hERG I inhibitor	No	No
	hERG II inhibitor	Yes	Yes
	Oral Rat Acute Toxicity (LD50)	2.217 mol/kg	2.323 mol/kg
	Oral Rat Chronic Toxicity (LOAEL)	1.303 v log mg/kg_bw/day	1.142 log mg/kg_bw/day
	Hepatotoxicity	No	No
	Skin Sensitisation	Yes	No

CONCLUSION

The ligands from Lentinus tuberregium are patented for the *in vitro* anticancer properties. Hence to analyze the specific protein ligand interaction in breast cancer, four key proteins VEGFR2, human estrogen receptor, IL17A, PI3K that are associated with the pathogenesis of breast cancer were chosen. The ligand-protein interaction studies using Autodock showed that both the ligands have potential ability to inhibit the above breast cancer protein. Among the ligands Ergosta-5,7,22-trien-3 β-ol been reported with least binding energy of -8.94 kcal/mol and interacted with the active site amino acids, indicating its potential ability to inhibit cancer proteins. The pharmacokinetic properties of the ligands were predicted using pkCSM. The results indicated that the ligands are absorbed in the intestine, had Blood Brain Barrier (BBB) permeability and are nontoxic. These results indicate that these ligands are safe which can be proved by further *in vivo* studies. Hence, the reported ligands can be acts as lead compounds and used as a potential alternative drug for available breast cancer drugs.

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