Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Research Article **DOI:10.26479/2019.0501.71**

PHYTOCHEMICALS OF *AVICENNIA* SPECIES: PREDICTION OF TOXICITY THROUGH QSAR MODELLING AND LEAD COMPOUND IDENTIFICATION ON TNF-α THROUGH MOLECULAR DOCKING

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ABSTRACT: The objective was to predict toxicity on daphnids, fish and rat oral exposure through quantitative structure activity relationship (QSAR) modelling as well as binding affinity and energy value of common phytochemicals present in *Avecennia* sp. compared to synthetic drug (Ibuprofen) on tumour necrosis factor-α (TNF-α) through molecular docking and interaction study. The QSAR modelling was done for toxicity evaluation by using T.E.S.T. (Version 4.1) and the virtual screening to know receptor-ligand binding affinity and energy value by using the software, PyRx (Version 0.8). The TNF-α (receptor) was obtained (PDB ID: 2az5) from the European Protein Data Bank (PDBe) and the information on selected fifteen ligands (phytochemicals) and one synthetic ligand (Ibuprofen) were taken from PubChem database. QSAR modelling resulted all the compounds showed toxic to *D. magna* and *P. promelas* but non-toxic to rat oral exposure. In the docking result, among established 15 phytocompounds, Lupeol (ligand) was observed favourable binding energy value (-10.7 Kcal/mol) on the TNF-α receptor followed by Taraxerone (-10.1 Kcal/mol) compared to Ibuprofen (-6.7 Kcal/mol). In conclusion, phytoligand Lupeol of *Avicennia* sp. showed the activity of lead molecule, which may inhibit the activity of TNF-α and prevent inflammation. The future study is suggested the toxicological and pharmacological assay to validate the present predictive data.

KEYWORDS: Predictive toxicity, QSAR modelling, Molecular docking; TNF-α; Ligands.

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1. INTRODUCTION

The mangroves are halophytic plant species, which are found in the intertidal zones between land and sea of tropical and sub-tropical region of the world [1, 2]. Among several mangrove species, three types of *Avicennia* sp. such as *A. alba*, *A. marina* and *A. officinalis* are common mangrove plants that found in the Sundarban delta. The ethnomedicinal uses of this genus have been reported for the treatment of many diseases viz. rheumatism, pregnancy, ulcer, smallpox, etc. [3]. According to Shilpi et al. [4] and Simlai and Roy [5], several parts such as leaf, bark, stem, seeds, roots and fruits of this mangrove have been experimented for the treatment of various diseases. The mangroves like *Avicennia alba* Blume (a variant to *A. marina*), *A. marina*, *A. nitida* and *A. officinalis* have been reported worldwide for medicinal use against the treatment of many diseases. Moreover, there are several reports available for ethnomedicinal uses of different species of *Avicennia* plants for the treatment of pain and inflammation [6, 7, 8, 9, 10, 11, 12, 13, 14]. Acute toxicity studies are major toxicity endpoints on different organisms that supported the ecotoxicological research. The toxicity endpoints can also be studied to determine predictive value through QSAR (quantitative structure activity relationships) modelling software [15, 16, 17] and T.E.S.T. (Toxicity Estimation Software Tool) is an easy predictive tool based on the two-dimensional molecular descriptor [18]. It is used for toxicity evaluation, which is an important parameter during drug design, compounds derrived from synthetic or natural products. Tumour necrosis factor (TNF-α) is a pro-inflammatory cytokine protein, which increases during inflammation and causes several diseases such as infection, injury, joint disorders, etc. [19]. Also, it was noted oxidative stress during progression of these diseases. In this context, several synthetic medicines are used for pain relief and targeting specific immune and inflammatory pathways by inhibition of TNF-α [19, 20]. It was reported that synthetic drugs have potent side effects when used for the inhibition of pro-inflammatory cytokines such as TNF-α, etc. [19, 21, 22, 23]. To prevent side effects, researchers are showing interest for medicines from plant origin or phytomedicines to target inflammatory mediators without any adverse effects [19]. According to Dragos et al. [19], there are several plant species used to relief pain and prevent inflammation, oxidative stress, etc. According to several researchers, study of molecular docking and interaction or structure based virtual screening to detect activity as effector or inhibitor on macromolecule (receptor) by using natural compounds or synthetic drugs as ligands [24, 25, 26, 27, 28]. Basically, the virtual screening helps to identify the proper phytochemical present in crude extracts as lead compound, which in future is suitable for new drug design. However, crude extract of plant may have allosteric or inhibitory properties on several receptors, but identification of lead compound is more potential to know effector or inhibitor on target receptor. According to Vyas et al. [29], virtual screening is a tool to design a drug faster and easy identification of lead compound(s) for diseases prevention. In general, virtual screening with phytochemicals (ligands) are the main research interest in the recent pharmaceutical arena. The objective of the present study was to know

the predictive toxicity through QSAR modelling as well as binding affinity and energy value of different established phytochemicals present in *Avecennia* sp. compared to synthetic drug (Ibuprofen) against TNF-α through molecular docking and interaction.

2. MATERIALS AND METHODS

The present computational prediction is based on predictive toxicity and molecular docking to determine the efficacy of phytocompound(s) in comparison with synthetic drug.

Evaluation of predictive toxicity through QSAR modelling tool

The QSAR modelling tool was used to estimate the median lethal concentration (LC_{50}) of *Daphnia magna* and *P. promelas* and rat oral median lethal dose (LD_{50}) values of established phytochemicals of *Avecennia* sp. In the present predictive study, Toxicity Estimation Software Tool (T.E.S.T.), Version 4.1 was used [18]. The predicted values for LC_{50} and LD_{50} along with correlation coefficient values were obtained.

Selection of compounds

Two types of ligands such as phytoligands and synthetic ligand were selected for the present study. These phytoligands were categorized as phytosteroids (Oleic acid, β-sitosterol, Campesterol and Stigmasterol), tannins (Lapachol, Catechin, Chlorogenic acid, Gallic acid and Ellagic acid), terpenoids (Lupeol, Taraxerol, Taraxerone, Betulinic acid, Betulinaldehyde and Ursolic acid) and Ibuprofen respectively as synthetic drug for anti-inflammatory properties. All these phytochemicals were selected as per several reports by Kar et al. [13], Thatoi et al. [14], Bell and Duewell [30], Majumdar and Patra [31], Majumdar et al. [32], Ghosh et al. [33], Sutton et al. [34], Ito et al. [35], Sharaf et al. [36], Jia et al. [37], Subrahmanyam et al. [38], Feng et al. [39], Han et al. [40], [41], Mahera et al. [42], Sura et al. [43], Mahera et al. [44] and Ramanjaneyulu et al. [45].

Selection of protein

The crystal structure of protein TNF-α (PDB ID: 2az5) was downloaded from the European protein data bank (http://www.ebi.ac.uk/pdbe/). As per experimentation by He et al. [46], the deposited X-ray diffraction crystallographic structure of the TNF-α (2.1Å resolution) was taken. The three-dimensional (3-D) ribbon structure is depicted in Figure 1 after visualizing in MGL tool developed by The Scripps Research Institute [47]. An inhibitory molecule [6,7-Dimethyl-3-[(Methyl{2-[Methyl({1-[3-(Trifluoromethyl) Phenyl]-1H-Indol-3-YL} Methyl)Amino] Ethyl} amino)Methyl]-4H-Chromen-4-One] attached in chain A and C (307) was obtained in the protein structure.

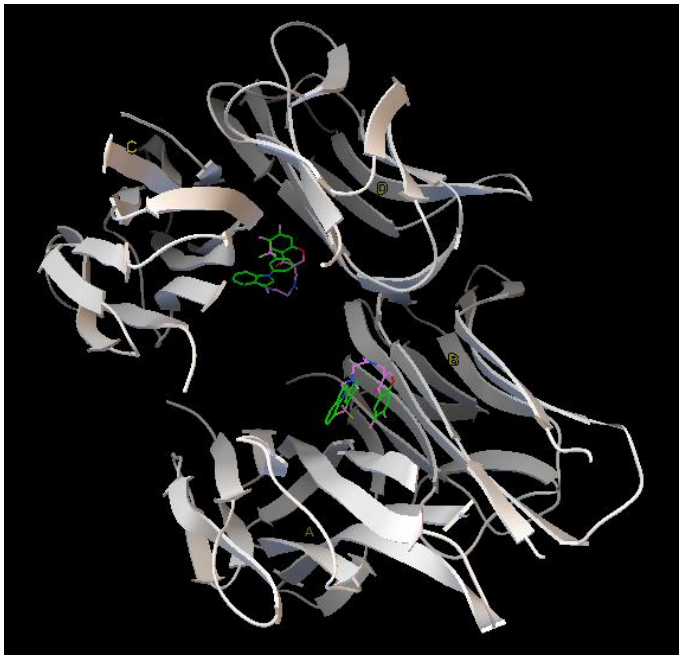

Figure 1: Three-dimensional (3D) ribbon structure of tumour necrosis factor-α [(PDB ID: 2az5) attached with inhibitory ligands (6,7-Dimethyl-3-[(Methyl{2-[Methyl({1-[3-(Trifluoromethyl)Phenyl]-1H-Indol-3-YL}Methyl)Amino]Ethyl}amino)Methyl]-4H-Chromen-4-One) in Chain A and Chain C (307) as line structures]

Molecular docking and interaction for receptor-ligand binding

Prior to virtual screening, for all the selected compounds, the CAS (chemical abstract service) number and canonical SMILES (simplified molecular-input line-entry system) string were taken from the PubChem database (www.ncbi.nlm.nih.gov/pubchem) and .pdb file of each ligand was obtained from CORINA online server (http://www.mol-net.de) after inserting SMILES (Table 1). All the 3-D structure of compounds (ligands) are exhibited in Figure 2. The molecular docking was done for receptor-ligand binding by using PyRx software (Version 0.8) developed by Trott and Olson [48]. The molecular docking was visualized by using molecular graphics laboratory (MGL) tool, developed by The Scripps Research Institute [47] and the 3-D structure of lead compound(s) was taken from MGL tool. The grid box of the docking site on this target protein was recorded with the dimensions of X: 71.6928, Y: 67.4813 and Z: 71.3257 Å, with a grid spacing of 0.375 Å, centered on X: -13.6907, Y: 71.6033 and Z: 26.9992 Å. The present tool predicts docking result by obtaining energy value for each studied ligand. The docking results of structural complexes of each ligand/receptor binding were visualized in MGL tool for identifying specific contacts between the atoms of the test ligand and amino acids of the target receptor.

Table 1: Information on established phytochemicals of *Avecennia* sp. and synthetic drug

Sl. No.	Ligands	CAS no.*	Canonical SMILES*
Phytochemicals			
Phytosteroids			
1.	Oleic acid	112-80-1	CCCCCCCCC=CCCCCCCCC(=O)O
2.	β-sitosterol	83-46-5	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
3.	Campesterol	474-62-4	CC(C)C(C)CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C
4.	Stigmasterol	83-48-7	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
Tannins			
5.	Lapachol	84-79-7	CC(=CCC1=C(C2=CC=CC=C2C(=O)C1=O)O)C
6.	Catechin	7295-85-4	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
7.	Chlorogenic acid	327-97-9	C1C(C(C(CC1(C(=O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O
8.	Gallic acids	149-91-7	C1=C(C=C(C(=C1O)O)O)C(=O)O
9.	Ellagic acids	476-66-4	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O
Terpenoids			
10.	Lupeol	545-47-1	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C
11.	Taraxerol	127-22-0	CC1(CCC2(CC=C3C4(CCC5C(C(CCC5(C4CCC3(C2C1)C)C)O)(C)C)C)C)C
12.	Taraxerone	514-07-8	CC1(CCC2(CC=C3C4(CCC5C(C(=O)CCC5(C4CCC3(C2C1)C)C)(C)C)C)C)C
13.	Betulinic acid	472-15-1	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C(=O)O
14.	Betulinaldehyde	13159-28-9	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C=O
15.	Ursolic acid	77-52-1	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1C)C)C(=O)O
Synthetic drugs			
1.	Ibuprofen	15687-27-1	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O

*Obtained from PubChem compound database; NF = Not found

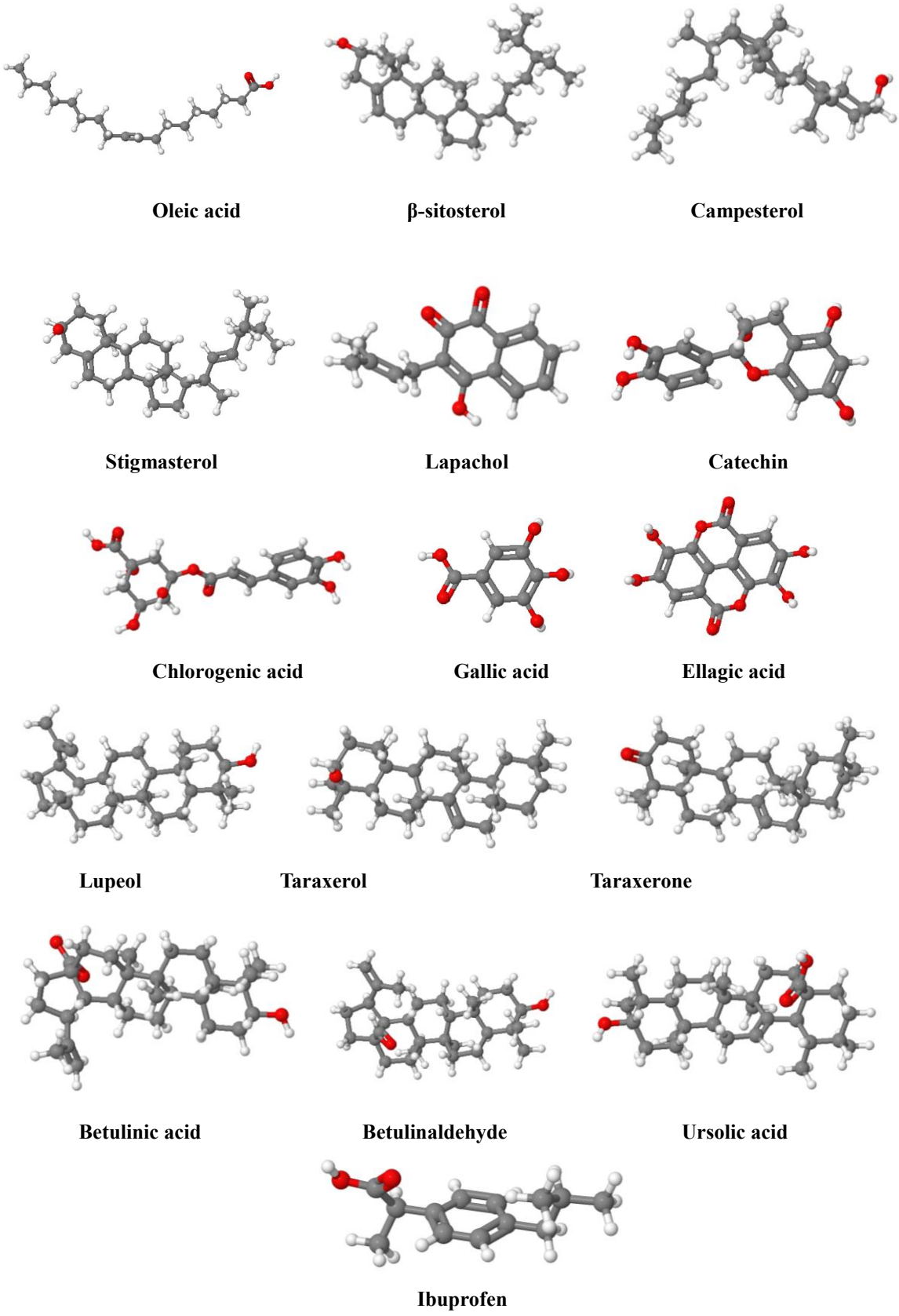

Figure 2: 3-D structures of different phytochemicals and synthetic drug

3. RESULTS AND DISCUSSION

The acute toxicity prediction data of *D. magna* and *P. promelas* (LC_{50}) and rat oral LD_{50} value for above mentioned phytochemicals and synthetic drug is tabulated in Table 2. For *D. magna*, the predicted LC_{50} data (mg/l) for Lupeol (0.14), Stigmasterol (0.043), Taraxerol (0.15), Ursolic acid (0.21), β-sitosterol (0.07), Campesterol (0.14), Lapachol (0.67), Ellagic acids (2.77), Chlorogenic acid (3.54), Oleic acid (1.16) and Gallic acids (3.54) as well as Ibuprofen (0.72) were obtained. For *P. promelas*, the predicted LC_{50} data (mg/l) for Lupeol (0.20), Stigmasterol (0.13), Taraxerol (0.26), Ursolic acid (0.76), β-sitosterol (0.17), Campesterol (0.30), Lapachol (0.56), Ellagic acids (0.29), Chlorogenic acid (3.21), Oleic acid (0.14) and Gallic acids (3.21) as well as Ibuprofen (2.57) were obtained. In case of oral rat LD_{50} data (mg/kg), Lupeol (610.81), Stigmasterol (250.97), Taraxerol (1531.47), Ursolic acid (1778.59), β-sitosterol (894.28), Campesterol (953.08), Lapachol (211.71), Ellagic acids (1513.19), Chlorogenic acid (3249.45), Oleic acid (12911.86) and Gallic acids (3912.42) as well as Ibuprofen (1713.58) were obtained. For correlation coefficient (R^2) value (%) at significant level, it was observed that phytochemicals such as Lupeol (91), Stigmasterol (96), Taraxerol (95), Ursolic acid (96), β-sitosterol (96), Campesterol (95), Lapachol (92), Ellagic acids (91), Chlorogenic acid (94), Oleic acid (95) and Gallic acid (94) as well as Ibuprofen (92) for *D. magna*, Lupeol (78), Stigmasterol (72), Taraxerol (86), Ursolic acid (73), β-sitosterol (77), Campesterol (78), Lapachol (83), Ellagic acids (80), Chlorogenic acid (88), Oleic acid (94) and Gallic acid (88) as well as Ibuprofen (89) for *P. promelas* and Lupeol (82), Stigmasterol (85), Taraxerol (73), Ursolic acid (77), β-sitosterol (86), Campesterol (78), Lapachol (85), Ellagic acids (80), Chlorogenic acid (90), Oleic acid (80) and Gallic acid (84) as well as Ibuprofen (83) for rat respectively. The phytocompounds such as Taraxerone, Betulinaldehyde, Betulinic acid and Catechin were unable to predict toxicity due to unidentified CAS number in the database of T.E.S.T. software. Present *in silico* approach through QSAR modelling for phytocompounds and synthetic chemical at lower to higher trophic level is done to detect predictive toxicity supported by several researchers [49, 50, 51]. On the other hand, an *in silico* approach with special reference to QSAR modelling is an important predictive mathematical model, which has a relationship between the biological activity and the two-dimensional or three-dimensional compounds descriptors [49, 51, 52, 53]. This study is supported several ecotoxicological endpoints for aquatic animals and terrestrial mammals [54, 55, 56, 57]. Lipnick [58] explained that QSAR modelling is very important tool for testing of new chemicals to meet regulatory requirements at priority level. In the present observations, all the compounds showed toxic to *D. magna* and *P. promelas* but non-toxic to rat may be due to improved metabolic activities in mammal.

Table 2: Predictive toxicity data on different organisms through QSAR modelling of selected phytocompounds of *Avecennia* sp. and synthetic drug

Sl. No.	Compounds	*Daphnia magna* 48h LC_{50} (mg/L)	R^2 value	*Pimephales promelas* 96h LC_{50} (mg/L)	R^2 value	Oral rat LD_{50} (mg/Kg)	R^2 value
Phytochemicals							
1.	Lupeol	0.14	91%	0.20	78%	610.81	82%
2.	Taraxerone	NF	NF	NF	NF	NF	NF
3.	Stigmasterol	0.043	96%	0.13	72%	250.97	85%
4.	Taraxerol	0.15	95%	0.26	86%	1531.47	73%
5.	Ursolic acid	0.21	96%	0.76	73%	1778.59	77%
6.	Betulinaldehyde	NF	NF	NF	NF	NF	NF
7.	Betulinic acid	NF	NF	NF	NF	NF	NF
8.	β-sitosterol	0.070	96%	0.17	77%	894.28	86%
9.	Catechin	NF	NF	NF	NF	NF	NF
10.	Campesterol	0.14	95%	0.30	78%	953.08	78%
11.	Lapachol	0.67	92%	0.56	83%	211.71	85%
12.	Ellagic acids	2.77	91%	0.29	80%	1513.19	80%
13.	Chlorogenic acid	3.54	94%	3.21	88%	3249.45	90%
14.	Oleic acid	1.16	95%	0.14	94%	12911.86	80%
15.	Gallic acid	3.54	94%	3.21	88%	3912.42	84%
Synthetic drug							
1.	Ibuprofen	0.72	92%	2.57	89%	1713.58	83%

NF = not found in T.E.S.T. database; R^2 = Correlation coefficient

Another part of results indicated that the molecular docking and interaction of the established phytochemicals of *Avecennia* sp. with a target protein tumor necrosis factor (TNF-α) (PDB ID: 2az5) was energetically favourable. The energy values were observed lowest for Lupeol (-10.7 Kcal/mol) followed by Taraxerone (-10.1 Kcal/mol) while highest for Gallic acid (-5.7 Kcal/mol) compared to known synthetic drug as Ibuprofen (-6.7 Kcal/mol). In case binding affinity, suitable values were observed for Lupeol followed by Taraxerone when compared to Ibuprofen. All the binding energy values for all ligands are tabulated in Table 3. The close contact residues were found Tyr151, Tyr59, Tyr159, Ile155 and Leu57 at chain C for Lupeol while the contact residues obtained between chain A and C with Leu57 and Val123 for Taraxerone. One hydrogen bond contact with Gln149 residue for Lupeol at chain C and no hydrogen bond contact in Taraxerone was observed. In case of

Ibuprofen, close contact residues such as Tyr59 and Leu57 were observed at chain A. The contact amino acid residues and hydrogen bonding for rest of the phytoligands are tabulated in Table 3.

Table 3: Binding energy values of selected phytochemicals of *Avecennia* sp. and synthetic drug against TNF-α receptor (PDB ID: 2az5)

Sl. No.	Ligands	Binding energy (Kcal/mol)	Hydrogen bond number and contact residues	Close contact residues
Phytochemicals				
1.	Lupeol	-10.7	1 and Gln149	Tyr151, Tyr59, Tyr159, Ile155 and Leu57 at chain C
2.	Taraxerone	-10.1	---	Leu57 and Val123 at chain B and C
3.	Stigmasterol	-9.7	1 and Tyr151	Tyr59, Leu57 and Val123 at chain C
4.	Taraxerol	-9.6	---	Leu57, Leu167 and Val123 at chain A and Leu57 and Tyr59 at chain C
5.	Ursolic acid	-9.5	---	Val123, Leu157 and Tyr59 at chain A and C
6.	Betulinaldehyde	-9.2	---	Tyr59, Val123 and Leu57 at chain A
7.	Betulinic acid	-8.7	---	Tyr151, Tyr59, Tyr159, Ile155 and Leu57 at chain C
8.	β-sitosterol	-8.6	---	Val123, Leu57, Tyr59 and Tyr151 at chain A
9.	Catechin	-8.5	4 and Gln125, Arg82	Gln125, Leu93 and Phe124
10.	Campesterol	-8.4	---	Leu57, Val123, Tyr59
11.	Lapachol	-8.1	---	Gly121, Val123, Leu57 and Tyr59 at chain C
12.	Ellagic acid	-7.6	---	Tyr151, Tyr59, Leu57 and Ley157 and chain A
13.	Chlorogenic acid	-7.3	3 and Gln125, Arg82 and Asn92	Arg82, Leu93 and Val91
14.	Oleic acid	-6.1	---	Leu57 and Tyr59 at chain C
15.	Gallic acid	-5.7	2 and Gln125 and Arg82	Leu57, Leu157 and Leu93
Synthetic drug				
1.	Ibuprofen	-6.7	---	Tyr59 and Leu57 at chain A

The 3-D structures of docking pose and interaction for two phytoligands and one synthetic ligand are exhibited in Figure 3, 4 and 5.

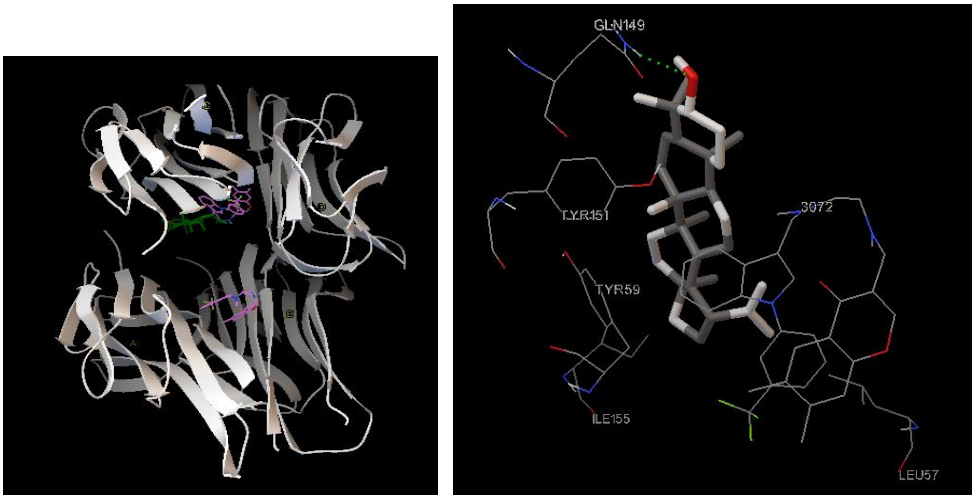

Figure 3: Lupeol docking pose and interaction

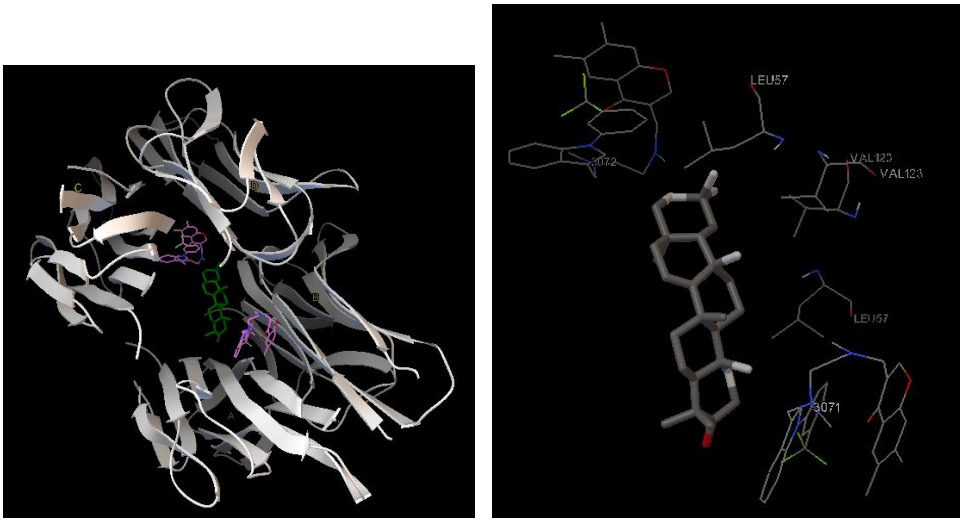

Figure 4: Taraxerone docking pose and interaction

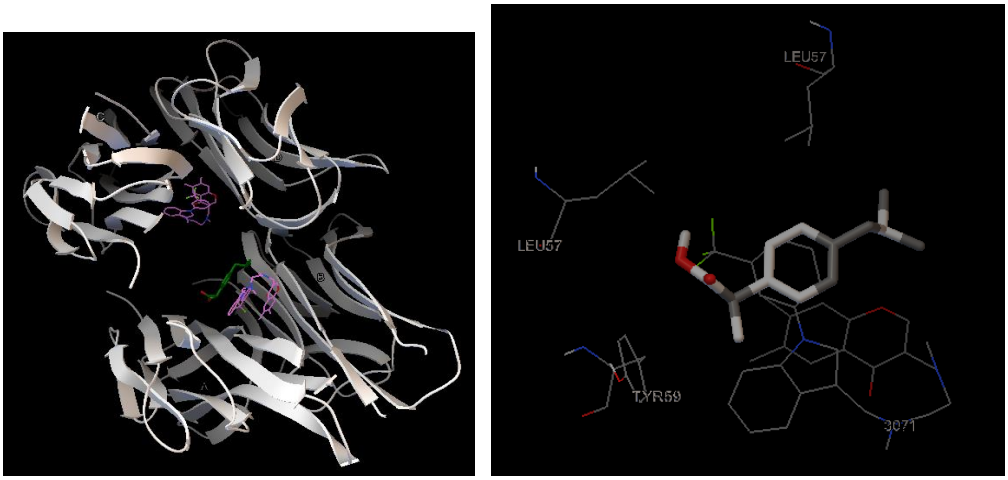

Figure 5: Ibuprofen docking pose and interaction

The present molecular docking and interactions or structure based virtual screening of phytoligands and synthetic ligand was done to detect receptor-ligand binding site, which supported by several researchers [59, 60]. The receptor TNF-α and phytoligands binding had been carried out with bioactive compounds of several medicinal plants for new drug discovery [59, 60, 61]. Also, it was studied that crude extract of *Avicennia* sp. used for the prevention of inflammation [11, 14, 62] but which phytocompound is acting suitable to prevent inflammatory disease is unclear. For this reason, virtual screening is an important tool to detect exact lead compound. In the present virtual screening, among established 15 phytocompounds, Lupeol phytocompound (ligand) was observed favourable binding energy value (-10.7 Kcal/mol) against the TNF-α receptor with one hydrogen bond contact at GLN149 followed by Taraxerone (-10.7 Kcal/mol) between chain A and C with Leu57 and Val123 contact residues without hydrogen bonding. Other 14 ligands were obtained below energy value than Lupeol. However, a synthetic inhibitory molecule namely Ibuprofen has already been established for synthetic drug, having anti-inflammatory properties to decrease TNF-α production [63]. According to He et al. [46] and Cambridge Center C [64], TNF-α receptor as pro-inflammatory cytokine and a synthetic compound 6,7-Dimethyl-3-[(Methyl{2-[Methyl({1-[3-(Trifluoromethyl) Phenyl]-1H-Indol-3-YL}Methyl)Amino]Ethyl}amino)Methyl]4H Chromen-4-One had potential inhibitory effect on TNF-α receptor. It was observed Lupeol has one hydrogen bonding and contact residue same as inhibitory molecule in chain C of Leu57 in the active site. The phytocompound Lupeol of *Avecennia* sp. may be considered potent anti-inflammatory drug due to strong binding affinity as well as one hydrogen bonding and close contact residue involved in chain C of Leu57. Therefore, overactivity of TNF-α may be inhibited by phytoligand Lupeol present in *Avecennia* sp. and may be prevented inflammation. But recent *in silico* approach by Ganeshpurkar and Saluja [65] the phytoligand Rutin inhibited the activity of TNF-α and binding found in the active site. A similarity was obtained that both phytocompounds are flavonoids and flavonoids are well-known anti-inflammatory phytocompounds [66].

4. CONCLUSION

The QSAR modelling and virtual screening tools are the suitable, faster computational screening to detect predictive toxicity at food chain level and lead compound(s) for new drug discovery. Based on present predictive results, toxicity was observed for both daphnids and fish but not for rat oral dose and the dock score values were predicted that Lupeol has good binding affinity towards TNF-α (PDB ID: 2az5) compared to other phytoligands and synthetic ligand. The binding interaction for this phytoligand was observed active site TNF-α receptor when compared to established synthetic ligand. This phytoligand Lupeol of *Avicennia* sp. may be considered as lead molecule to inhibit the activity of TNF-α and may prevent inflammation. However, it is suggested further pharmacological and toxicological functional assay with this phytoligand to detect the molecular mechanism of anti-inflammation and toxicity evaluation to validate the present computational predictions.

ACKNOWLEDGEMENT

The authors convey thanks to all the developers of studied software, data bank for protein and organic compounds, etc. used in the present computational predictions.

CONFLICT OF INTEREST

Authors declare none.

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