Research Article

Molecular Docking and Statistical Assessment of Macroalgae Halimeda Species against Marine Macro Fouler *Mytilus galvoprovinces* (4CN8)

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ABSTRACT

The purpose of this investigation was to study the inhibitory action of marine macro fouler by macro algae using virtual screening studies in first time. Bioactive compounds from Halimeda spp were utilized for the molecular docking analysis. Protein was obtained from protein data bank and computational docking analysis was performed using Argus lab 4.0.1. There are 39 compounds were screened against *Mytilus galvoprovinces* through computationally. The docking study have revealed moderate to effective inhibition with a range of dock score.6, 9, 12-Octadecatrienoic acid, phenylmethyl ester, (Z, Z, .Z) - compound showed highest and best dock score (-14.0376 kcal/mol) against target biofouling macro fouling protein. Correlation assessments show that there is positive relationship between binding energy, molecular weight and retention time. The present study proves that the macro algae of Halimead spp having high and best antifouling efficiency.

Keywords: Halimeda spp, 4CN8, *In silico*, Correlation, Arguslab, Minitab.

INTRODUCTION

Biofouling is the un welcome progress of aquatic microorganisms, flora and fauna on artificial immersed surface in seawater.[10; 38] The most visible and well-known forms of such fouling are the barnacles, mussels and seaweeds that adorn ships' hulls.[5; 14; 36] They lead to an increase in the drag thereby leading to increased fuel consumption, hull cleaning and removal of paint.[9; 13; 30;] Balanus such as *Mytilus galloprovincialis* cause the most severe fouling problems. Barnacles attach to structures immersed underwater by secreting an adhesive called adhesive protein.[27; 28; 44] After identifying a suitable surface to adhere cyprid larva secretes adhesive protein by a pair of cement ducts, which widens into a muscle sac.[47; 51]The muscular sac is connected to an antenna by another cement duct and pours proteinaceous cement (footprint) into antenna.[11; 12; 21] Cyprid cement flows around and embeds the attachment organs and the cyprid larva is able to attach itself to the surface and metamorphoses into a calcified adult barnacles.[5; 23] The main objective of virtual screening is to help chemist filter out inactive from library of compounds before going ahead for synthesis.[41] Virtual screening has created a good opportunity for assisting researchers in finding new marine natural product.[34] Molecular docking was primarily designed to predict the binding of small drug-like molecules to target proteins.[22] Where drugs could possibly bind and the binding affinities are predicted using simplified free energy calculation methods.[29] Normally most of programs capable of executing this job are high in cost.[48] However, there are some non-commercial free-wares for docking study and the most renowned program is arguslab.[46] The present study was to assess the antibiofouling efficiency of Halimeda spp through *in silico* method.

MATERIALS AND METHODS

Three-dimensional experimentally known protein complexes were obtained from Brookhaven Protein Data Bank (http://www.rcsb.org/). The set of 39 secondary metabolites form macro algae *Halimeda spp* acting as a potential antifoulant were taken into consideration after exhaustive literature survey from[15] GC-MS hexane and methanol extract. The ligand input structure was taken from pubchem and NIST (https://pubchem.ncbi.nlm.nih.gov; https://www.nist.gov). The resulting structure was then saved in ".mol" file formats for molecular docking studies[1; 40] After the preparation of the protein, ligand and the molecular docking studies were performed by ArgusLab 4.0.1. Pearson on correlation study was carried out through Minitab software (Table 1; 2; 3; 4 and fig 1; 2; 3).

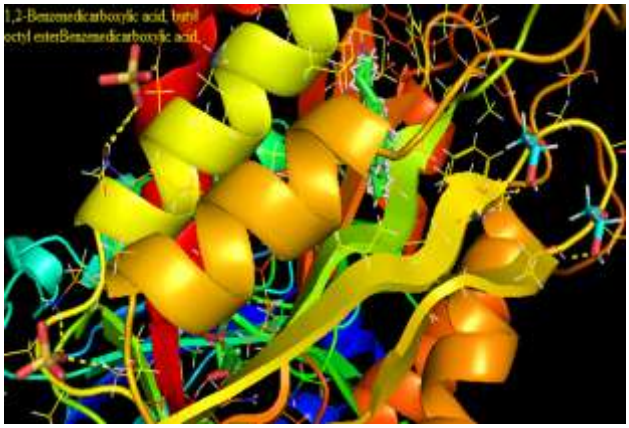


Figure 1: Three dimensional view of 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester vs 4CN8

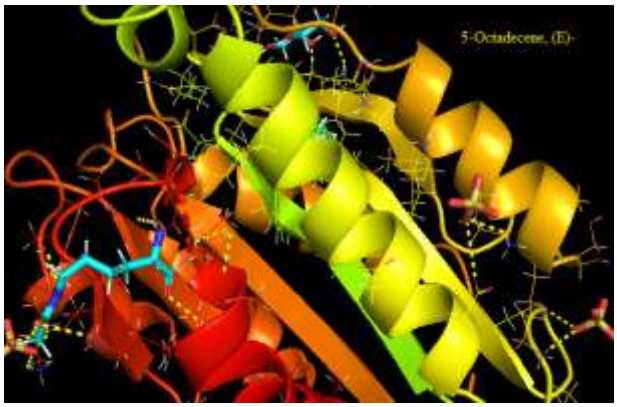


Figure 2: Three dimensional view of 5-Octadecene, (E)- vs 4CN8

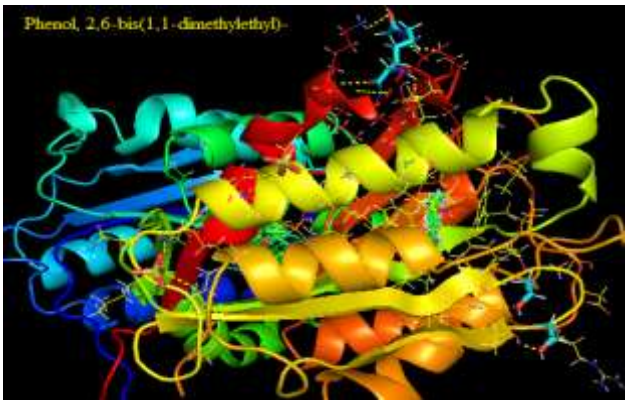
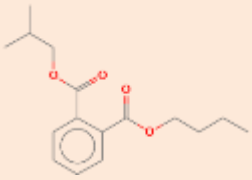
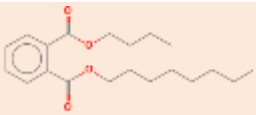
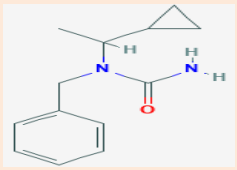
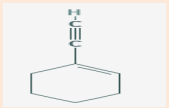
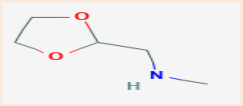
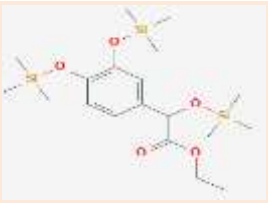
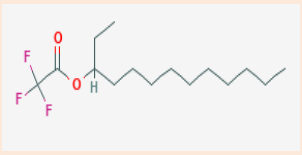
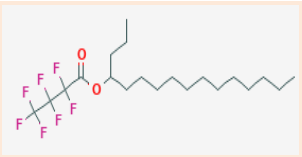
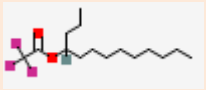
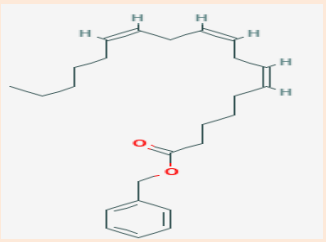


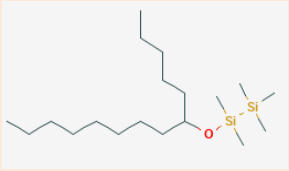
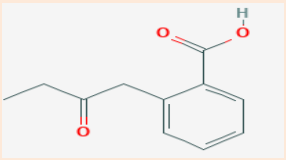
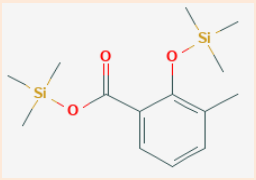
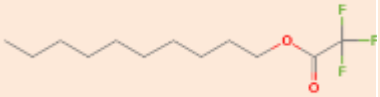
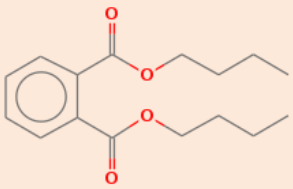
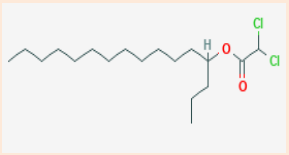
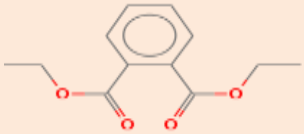
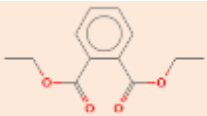
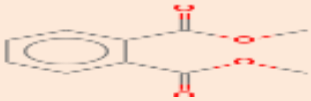
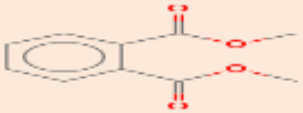
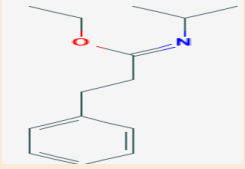
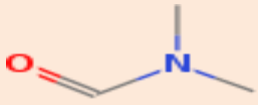
Figure 3: Three dimensional view of Phenol, 2,6-bis(1,1-dimethylethyl)- vs 4CN8

Table 1: Halimeda spp selected compounds (Gadhi et al., 2018)

Sl. No	Retention time	Compound name	Solvents	Formula	Molecular weight g/mol
1	557	Formamide, NN-dimethyl-	Hexane	C_3H_7NO	73.0938
2	816	Octane	Hexane	C_8H_{18}	114.2285
3	888	1-Cyclohexene, 1-ethynyl-	Methanol	C_8H_{10}	106.168
4	937	2-Methylaminomethyl-1,3-dioxolane	Hexane	$C_5H_{11}NO_2$	117.148
5	1216	Decyltrifluoroacetate	Methanol	$C_{12}H_{21}F_3O_2$	254.2891
6	1440	Dimethyl phthalate	Methanol	$C_{10}H_{10}O_4$	194.1840
7	1440	Dimethyl phthalate	Hexane	$C_{10}H_{10}O_4$	194.1840
8	1450	3-Trifluoroacetoxytridecane	Methanol	$C_{15}H_{27}F_3O_2$	296.374
9	1450	4-Trifluoroacetoxytridecane	Methanol	-	-
10	1457	1-Dodecanol	Methanol	$C_{12}H_{26}O$	186.3342
11	1474	Mexiletine	Hexane	$C_{11}H_{17}NO$	179.2588
12	1508	Benzoic acid, 2-(1-oxopropyl)-, methyl ester	Methanol	$C_{11}H_{12}O_3$	192.214
13	1555	Phenol, 2,6-bis(1,1-dimethylethyl)-	Methanol	$C_{14}H_{22}O$	206.3239
14	1556	n-Tridecan-1-ol	Methanol	$C_{13}H_{28}O$	200.3608
15	1580	Benzoic acid, 3-methyl-2-trimethylsilyloxy-, trimethylsilyl ester	Methanol	$C_{14}H_{24}O_3Si_2$	296.513
16	1613	Tetradecyltrifluoroacetate	Methanol	$C_{16}H_{29}F_3O_2$	310.3955
17	1627	N-Isopropyl-3-phenylpropanamide	Hexane	$C_{12}H_{17}NO$	191.274
18	1639	Diethyl phthalate	Methanol	$C_{12}H_{14}O_4$	222.2372
19	1639	Diethyl phthalate	Hexane	$C_{12}H_{14}O_4$	222.2372
20	1669	4-Heptafluorobutyryloxyhexadecane	Methanol	$C_{20}H_{33}F_7O_2$	438.471
21	1694	Ethyl N-isopropyl-3-phenylpropanimidate	Hexane	$C_{14}H_{21}NO$	219.328
22	1729	Phthalic acid, allyl ethyl ester	Methanol	$C_{13}H_{14}O_4$	234.2479
23	1742	6-Dimethyl(trimethylsilyl)silyloxytetradecane	Hexane	$C_{19}H_{44}OSi_2$	344.73
24	1773	Pentafluoropropionic acid, hexadecyl ester	Methanol	$C_{19}H_{33}F_5O_2$	388.4561
25	1787	1-Benzyl-1-(1-cyclopropyl-ethyl)-urea	Methanol	$C_{13}H_{18}N_2O$	218.3
26	1818	5-Octadecene, (E)-	Methanol	$C_{18}H_{36}$	252.4784
27	1854	1-Hexadecanol	Methanol	$C_{16}H_{34}O$	242.4406
28	1855	Carbonic acid, methyl tetradecyl ester	Methanol	$C_{16}H_{32}O_3$	272.4235
29	1954	n-Heptadecanol-1	Methanol	$C_{17}H_{36}O$	256.4671
30	1973	1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester	Methanol	$C_{16}H_{22}O_4$	278.3435
31	2037	Dibutyl phthalate	Methanol	$C_{16}H_{22}O_4$	278.3435
32	2075	3,4-Dihydroxymandelic acid, ethyl ester, tri-TMS	Hexane	$C_{19}H_{36}O_5Si_3$	428.747
33	2136	Phthalic acid, hexyl propyl ester	Hexane	$C_{17}H_{24}O_4$	292.375
34	2235	Phthalic acid, butyl hexyl ester	Methanol	$C_{18}H_{26}O_4$	306.3966
35	2259	Dichloroacetic acid, 4-hexadecyl ester	Methanol	$C_{18}H_{34}Cl_2O_2$	353.368
36	2434	1,2-Benzenedicarboxylic acid, butyl octyl ester	Hexane	$C_{20}H_{30}O_4$	334.4498
37	2668	Phthalic acid, isobutyl undecyl ester	Hexane	$C_{23}H_{36}O_4$	376.537
38	2774	6,9,12-Octadecatrienoic acid, phenylmethyl ester, (Z,Z,.Z)-	Methanol	$C_{25}H_{36}O_2$	368.561
39	3364	Phthalic acid, isobutyl octadecyl ester	Hexane	$C_{30}H_{50}O_4$	474.726

Table 2: Secondary metabolites binding energy and structure

Sl. No	Compound name	Chemical structure	Binding energy kcal/mol
1.	1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester		-10.8255
2.	1,2-Benzenedicarboxylic acid, butyl octyl ester		-13.3894
3.	1-Benzyl-1-(1-cyclopropyl-ethyl)-urea		No
4.	1-Cyclohexene, 1-ethynyl-		-12.3118
5.	1-Dodecanol		-10.8937
6.	1-Hexadecanol		-12.0332
7.	2-Methylaminomethyl-1,3-dioxolane		-4.61537
8.	3,4-Dihydroxymandelic acid, ethyl ester, tri-TMS		No
9.	3-Trifluoroacetoxytridecane		-11.1915
10.	4-Heptafluorobutyryloxyhexadecane		-10.806
11.	4-Trifluoroacetoxytridecane		-10.28
12.	5-Octadecene, (E)-		-13.1201
13.	6,9,12-Octadecatrienoic acid, phenylmethyl ester, (Z,Z,.Z)-		-14.0376

14.	6-Dimethyl(trimethylsilyl)silyloxytetradecane		No
15.	Benzoic acid, 2-(1-oxopropyl)-,methyl ester		-10.0465
16.	Benzoic acid, 3-methyl-2-trimethylsilyloxy-, trimethylsilyl ester		No
17.	Carbonic acid, methyl tetradecyl ester		-10.8994
18.	Decyltrifluoroacetate		-10.3531
19.	Dibutyl phthalate		-10.8821
20.	Dichloroacetic acid, 4-hexadecyl ester		-12.248
21.	Diethyl phthalate		-8.84382
22.	Diethyl phthalate		-8.84382
23.	Dimethyl phthalate		-8.40384
24.	Dimethyl phthalate		-8.49648
25.	Ethyl N-isopropyl-3-phenylpropanimidate		-8.02828
26.	Formamide, NN-dimethyl-		-4.01074

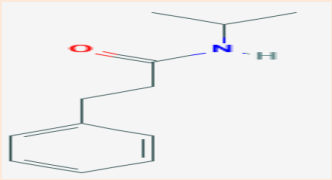
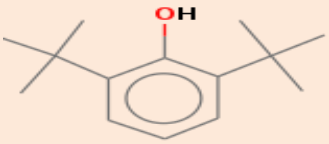
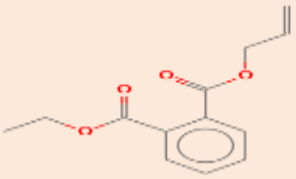
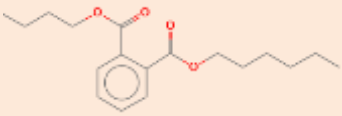
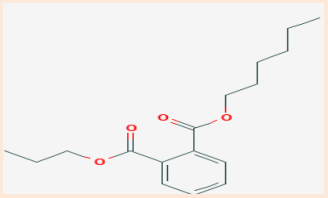
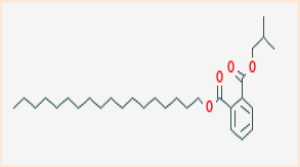
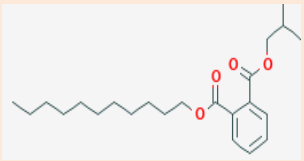
27.	Mexiletine		-9.06274
28.	n-Heptadecanol-1		-11.8473
29.	N-Isopropyl-3-phenylpropanamide		-10.2137
30.	n-Tridecan-1-ol		-11.1991
31.	Octane		-11.6912
32.	Pentafluoropropionic acid, hexadecyl ester		-11.4796
33.	Phenol, 2,6-bis(1,1-dimethylethyl)-		-12.3152
34.	Phthalic acid, allyl ethyl ester		-9.18257
35.	Phthalic acid, butyl hexyl ester		-11.3922
36.	Phthalic acid, hexyl propyl ester		-10.9517
37.	Phthalic acid, isobutyl octadecyl ester		No
38.	Phthalic acid, isobutyl undecyl ester		No
39.	Tetradecyltrifluoroacetate		-11.0112

Table 3: 4CN8 protein details

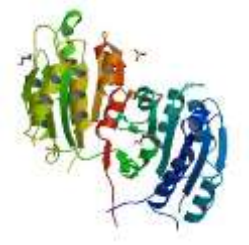
Sl. No	Protein Name	PDB-ID	Method	Organism	Resolution	Structure (3D)
1	Proximal Thread Matrix Protein 1 (PTMP1) from mussel byssus	4CN8	X-ray diffraction	*Mytilus galloprovincialis*	2.45^{0}A	

Table 4: Correlation analysis (Minitab 14.0.1)

	Retention Time	Molecular Weight	Binding Energy
Retention Time	1		
Molecular Weight	0.761647695	1	
Binding Energy	0.116581934	0.213113571	1

RESULTS

They literature collected 39 bioactive compounds were screened against 4CN8 (*Mytilus galloprovincialis*) using molecular docking analysis. In 39 compounds 6,9,12-Octadecatrienoic acid, phenylmethyl ester, (Z,Z,.Z)-showed maximum docking score of -14.0376Kcal/mol followed by the moderate potential recorded in 1,2-Benzenedicarboxylic acid, butyl octyl ester and 5-Octadecene, (E)- have a docking score is -13 Kcal/mol. Then the 1-Cyclohexene, 1-ethynyl-, 1-Hexadecanol, Dichloroacetic acid and 4-hexadecyl ester of ligand show the docking score is -12 Kcal/mol against4CN8 of the target protein followed by 3-Trifluoroacetoxytridecane, n-Heptadecanol-1,n-Tridecan-1-ol,Octane, Pentafluoro propionic acid, hexadecyl ester, Phthalic acid, butyl hexyl ester, Tetradecyl trifluoroacetate expression a potential of inhibition of 4CN8, the score value is -11Kcal/mol. likewise 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester, 1-Dodecanol, 4-Heptafluoro butyryloxyhexadecane, 4-Trifluoroacetoxytridecane, Benzoic acid, 2-(1-oxopropyl)-, methylester, Carbonic acid, methyl tetradecyl ester, Decyltrifluoroacetate, Dibutyl phthalate, N-Isopropyl-3-phenylpropanamide and Phthalic acid, hexyl propyl esterdisplay the docking score is -10 Kcal/mol. The Mexiletine and Phthalic acid, allyl ethyl ester has a docking sore is -9Kcal/mol. Diethyl phthalate, Diethyl phthalate, Dimethyl phthalate, Dimethyl phthalate and Ethyl N-isopropyl-3-phenylpropanimidate have a sore is -8Kcal/mol. The lowest docking scoring -4 kcal/mol recorded in Formamide, NN-dimethyl- against target protein molecule. The Pearson correlation shows the positive correlation between retention time and molecular weight (0.77), retention time and binding energy (0.12), molecular weight and binding energy (0.22) (Table .2).

DISCUSSION

In docking study, lower the docking score is having higher binding efficiency.[48] In 39 compounds, 6, 9, 12-Octadecatrienoic acid, phenylmethyl ester, (Z, Z, Z)-showed maximum docking score of -14.0376 Kcal/mol against 4CN8 (*Mytilus galloprovincialis)* target protein by arguslab, followed by the moderate potential recorded in 1, 2-Benzenedicarboxylic acid, butyl octyl ester and 5-Octadecene, (E)- have a docking score is -13 Kcal/mol. Similarly Raja manikandan et al., 2011 was dock the MUC1 protein against 15 marine(bacteria and fungus) secondary metabolites using arguslab the highest binding energy was recorded as -12.6 Kcal/mol. Raghu., et al2019was investigate *in silico* study using seaweed of Turbinariaconoides (fucoidan) against α-amylase and α-D glucosidase, the highest value was -4Kcal/mol. Ashok and Siva kumari., 3investigate the in-silico study using fucoidan compound against Caspase-3 -NF-kappa-B, Cytochrome C the highest docking score was -12kcal/mol. Dhamodharan., et al 2018 was studied the selected compound against E6 protein, the highest docking value was -8.9Kcal/mol.

CONCLUSION

This is the first report of in-silico study on antifouling using active compounds from the *Halimeda spp* against (4CN8) *Mytilusgallo provincialis*. The present findings also obviously prove the marine antifouling importance of marine seaweed-derived bioactive compounds based on the molecular docking analysis. This study mainly motivated the previous invitro antifouling assessment. Can be further used to designing better potent antifouling compounds. However, wet-lab trials involving chemical synthesis and testing the *in-vivo* using specific cell lines would be required to arrive at ultimate end.

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