Research Article

First Report on *in-silico* Analysis of Halimeda SPP against Breast Cancer (BRCA1) and its Evolutionary Relation

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ABSTRACT

Breast cancer (BRCA1) is a serious problem in the world causing illness and mortality in women. The current study investigated the anticancer potential of the macro-algae Halimeda species against breast cancer protein using arguslab and drug discovery of without clinical trial and constructed a Phylogenetic tree to identify similar organisms and it is evolution. Breast cancer protein retrieved from the Protein Data Bank, Phytochemicals have been collected from PubChem and evaluated anti-breast cancer activity using arguslab 4.0.1 software. Sequences gathered from National Centre for Biotechnology Information and Phylogenetic tree was constructed. There are 41 compounds employed against BRCA1, three ligands showed around -13 binding energy (5-Octadecene, (E)-, n-Heptadecanol-1, 6, 9, 12-Octadecatrienoic acid and phenylmethyl ester, (Z,Z,.Z)-) followed by 4 ligands showed activity of -12 (Phthalic acid, butyl hexyl ester, n-Tridecan-1-ol, Carbonic acid, methyl tetradecyl and 1,2-Benzenedicarboxylic acid, butyl octyl ester), 9 ligands exhibit ed -11 docking score, 7 ligands revealed -10 docking score, 8 ligands expressed -9 docking score, few compounds are below -9 and only seven compounds had no interaction with the tested compound. The correlation analysis shows the retention time positively associated with molecular weight and binding energy.

Keywords: Arguslab 4.0.1; BRCA1 gene; Halimeda spp; Human being; MEGA-X; Minitab 14.1.

INTRODUCTION

Cancer is one of the leading causes of death, globally, and thus poses a significant impact on worldwide health. Breast cancer is one of the common cancers prevailing in women in the developed and developing countries. Up to normal growth of cancer cell and lost breast cells viability. Worldwide advancement in diagnostic and treatment measures, morbidity and mortality rates are high due to breast cancer. It is a second form of cancer next to lung cancer leads to cause death predominantly.[2, 3, 32, 34] Most medicinal plants are widely used to cure inflammatory conditions, diabetes, parasitic infections, neuralgia and cancer.[1] Seaweeds act as a source of more than 2400 natural products in the world.[21, 34] Seaweeds are one of the major sources of potential molecules hold the pharmacological activities like anti-inflammatory, anti-microbial, anti-tumour and other activities.[34, 37] *Halimeda* species of seaweed is a source of many bioactive phenolic and other secondary metabolic compounds.[11, 34, 35] There is no much a docking study in *Halimeda species*. Aim of the present study was to screen the effective bioactive compound against breast cancer in *Homo sapiens* and assess the evolutionary relationship between other organisms. *Halimeda* species is used against breast cancer protein.

MATERIALS AND METHODS

Protein preparation

The crystal three-dimension structure of the BRCA1 BRCT domain (3PXB) from *Homo sapiens* was collected from the protein data bank (Table 1).

Table 1: Breast cancer structure and other PDB details

Sl. No	Protein Name	PDB-ID	Method	Organism	Structure
1	BRCA1 BRCT domain (Breast cancer)	3PXB	X-ray diffraction (2.5 A°)	*Homo sapiens*	

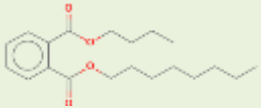
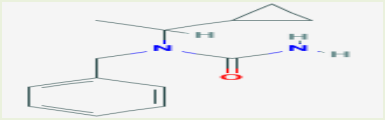
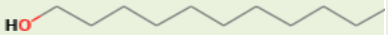
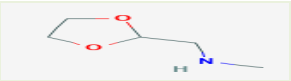
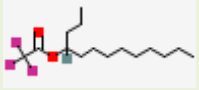
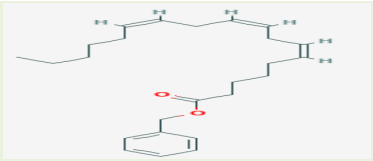
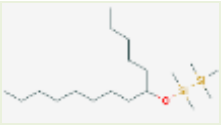
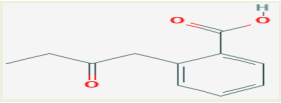
Compound preparation

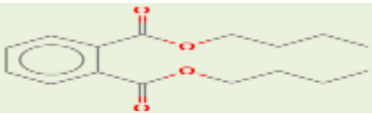
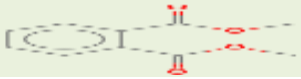
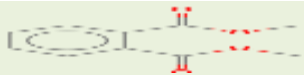
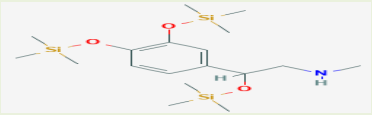
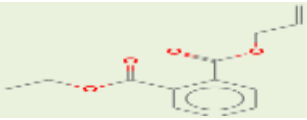
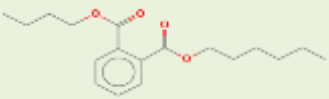
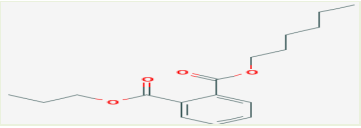
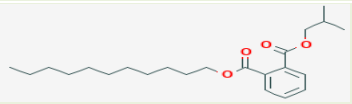
There are 41 compounds were collected from the previous work of[11] (Table 2). The structures of the phytochemicals from the Halimeda species were elucidated from the National Institute of Standards and Technology (NIST) and Pubchem. Two-dimension structure collected from NIST and Pubchem. The SDF format obtained from Pubchem converted through simplified molecular-input line-entry system (SMILE) to convert (Table 3).

Table 2: The GC-MS analysis of Halimedaspp from Red sea[11]

Sl.No	Retention Time	Solvent	Compound Name (Halimeda spp)	Molecular formula	Molecular Weight g/mol
1	1973	Methanol	BUTYL ISOBUTYL PHTHALATE	$C_{16}H_{22}O_4$	278.3435
2	2434	Hexane	1-O-butyl 2-O-octyl benzene-1,2-dicarboxylate	$C_{20}H_{30}O_4$	334.4498
3	1787	Methanol	MMICPGUPDRJGHH-UHFFFAOYSA-N	$C_{13}H_{18}N_2O$	218.3
4	888	Methanol	1-ethynylcyclohexene	C_8H_{10}	106.168
5	1457	Methanol	Dodecan-1-ol	$C_{12}H_{26}O$	186.3342
6	1854	Methanol	Hexadecan-1-ol	$C_{16}H_{34}O$	242.4406
7	937	Hexane	ZCCPVTVGEQLONB-UHFFFAOYSA-N	$C_5H_{11}NO_2$	117.148
8	2075	Hexane	HDFZMIKRLKMIBX-UHFFFAOYSA-N	$C_{19}H_{36}O_5Si_3$	428.747
9	1450	Methanol	YSOIFBQBQKWBAM-UHFFFAOYSA-N	$C_{15}H_{27}F_3O_2$	296.374
10	1669	Methanol	XKNWOOPYRXMIGS-UHFFFAOYSA-N	$C_{20}H_{33}F_7O_2$	438.471
11	1450	Methanol	IKOHXWSQVVBFIV-UHFFFAOYSA-N	$C_{15}H_{27}F_3O_2$	296.37g
12	1818	Methanol	(5E)-5-Octadecene	$C_{18}H_{36}$	252.4784
13	2774	Methanol	(6Z,9Z,12Z)-6,9,12-Octadecatrienoic acid benzyl ester	$C_{25}H_{36}O_2$	368.561
14	1742	Hexane	VDRMTSVGVDNSOQ-UHFFFAOYSA-N	$C_{19}H_{44}OSi_2$	344.73
15	1716	Hexane	6-Hydroxymethylmexiletine	$C_{11}H_{17}NO_2$	195.26
16	1508	Methanol	benzoic acid 2-{1-oxopropyl}-methyl ester	$C_{11}H_{12}O_3$	192.214
17	1580	Methanol	MMUCIJOPDDWEJV-UHFFFAOYSA-N	$C_{14}H_{24}O_3Si_2$	296.513
18	1855	Methanol	Methyl tetradecyl carbonate	$C_{16}H_{32}O_3$	272.4235
19	1216	Methanol	Fluoroacetate - Decyltri	$C_{12}H_{21}F_3O_2$	254.2891
20	2037	Methanol	Di-n-butyl phthalate	$C_{16}H_{22}O_4$	278.3435
21	2259	Methanol	1-Propyltridecyl dichloroacetate	$C_{18}H_{34}Cl_2O_2$	353.368
22	1639	Hexane	phthalic acid diethyl ester	$C_{12}H_{14}O_4$	222.2372
23	1639	Methanol	Anozol	$C_{12}H_{14}O_4$	222.2372
24	1440	Hexane	Avolin	$C_{10}H_{10}O_4$	194.1840
25	1440	Methanol	Solvanom	$C_{10}H_{10}O_4$	194.1840
26	1694	Hexane	Ethyl (1Z)-N-[(Z)-1-methylethyl]-3-phenylpropanimidoate	$C_{14}H_{21}NO$	219.328
27	557	Hexane	N,N-dimethyl-2-pyridinecarboxamide	$C_{19}H_{36}O_5Si_3$	73.0938
28	1474	Hexane	1-(2,6-dimethylphenoxy)propan-2-amine	$C_{11}H_{17}NO$	179.2588
29	1954	Methanol	HEPTADECYL ALCOHOL	$C_{17}H_{36}O$	256.4671
30	1627	Hexane	3-phenyl-N-(propan-2-yl)propanamide	$C_{12}H_{17}NO$	191.274
31	1556	Methanol	Tridecyl alcohol	$C_{13}H_{28}O$	200.3608
32	816	Hexane	n-octane	C_8H_{18}	114.2285
33	1773	Methanol	1-Hexadecanol, pentafluoropropionate	$C_{19}H_{33}F_5O_2$	388.4561
34	2007	Hexane	GXPIVEGQEQCSBV-UHFFFAOYSA-N	$C_{18}H_{37}NO_3Si_3$	399.700
35	1555	Methanol	2,6-Di-t-butylphenol	$C_{14}H_{22}O$	206.3239
36	1729	Methanol	1-O-ethyl 2-O-prop-2-enyl benzene-1,2-dicarboxylate	$C_{13}H_{14}O_4$	234.2479
37	2235	Methanol	Butyl hexyl phthalate	$C_{18}H_{26}O_4$	306.3966
38	2136	Hexane	ICADHACGSCAYCF-UHFFFAOYSA-N	$C_{17}H_{24}O_4$	292.375
39	3364	Hexane	COMSPPGIKGWQMS-UHFFFAOYSA-N	$C_{30}H_{50}O_4$	474.726
40	2668	Hexane	YXEXTSNCBSZCCV-UHFFFAOYSA-N	$C_{23}H_{36}O_4$	376.537
41	1613	Methanol	Tetra – decyltri - fluoroacetate	$C_{16}H_{29}F_3O_2$	310.3955

Table 3: Arguslab 4.0 result and compound structure of Halimedaspp

Sl. No	Compound Name	Compound structure	Docking energy value (3PXB) kcal/mol
1	BUTYL ISOBUTYL PHTHALATE		-10.9242
2	1-O-butyl 2-O-octyl benzene-1,2-dicarboxylate		-12.9216
3	MMICPGUPDRJGHH-UHFFFAOYSA-N		-10.2338
4	1-ethynylcyclohexene		-10.8962
5	Dodecan-1-ol		-10.8198
6	Hexadecan-1-ol		-11.9297
7	ZCCPVTVGEQLONB-UHFFFAOYSA-N		-4.65349
8	HDFZMIKRLKMIBX-UHFFFAOYSA-N		No
9	YSOIFBQBQKWBAM-UHFFFAOYSA-N		-11.0085
10	XKNWOOPYRXMIGS-UHFFFAOYSA-N		-9.97859
11	IKOHXWSQVVBFIV-UHFFFAOYSA-N		-11.2755
12	(5E)-5-Octadecene		-13.5652
13	(6Z,9Z,12Z)-6,9,12-Octadecatrienoic acid benzyl ester		-13.0333
14	VDRMTSVGVDNSOQ-UHFFFAOYSA-N		No
15	6-Hydroxymethylmexiletine	-	No
16	benzoic acid 2-{1-oxopropyl}-methyl ester		-10.1622
17	MMUCIJOPDDWEJV-UHFFFAOYSA-N		No
18	Methyl tetradecyl carbonate		-12.211
19	Fluoroacetate - Decyltri		-11.2725

20	Di-n-butyl phthalate		-11.1291
21	1-Propyltridecyl dichloroacetate		-11.295
22	phthalic acid diethyl ester		-9.35111
23	Anozol		-9.35111
24	Avolin		-9.17018
25	Solvanom		-9.17018
26	Ethyl (1Z)-N-[(Z)-1-methylethyl]-3-phenylpropanimidoate		-7.87049
27	N,N-dimethyl-2-pyridinecarboxamide		-4.01012
28	1-(2,6-dimethylphenoxy)propan-2-amine		-9.07201
29	HEPTADECYL ALCOHOL		-13.2969
30	3-phenyl-N-(propan-2-yl)propanamide		-10.116
31	Tridecyl alcohol		-12.2851
32	n-octane		-9.73012
33	1-Hexadecanol, pentafluoropropionate		-10.0597
34	GXPIVEGQEQCSBV-UHFFFAOYSA-N		No
35	2,6-Di-t-butylphenol		-11.9309
36	1-O-ethyl 2-O-prop-2-enyl benzene-1,2-dicarboxylate		-9.67913
37	Butyl hexyl phthalate		-12.7095
38	ICADHACGSCAYCF-UHFFFAOYSA-N		-11.027
39	COMSPPGIKGWQMS-UHFFFAOYSA-N		No
40	YXEXTSNCBSZCCV-UHFFFAOYSA-N		No
41	Tetra – decyltri - fluoroacetate		-11.291

In-silico analysis

Arguslab 4.0.1 software used for docking study and PyMOL used for the 3D view of docked protein with the compound. Breast cancer protein from Homo sapiens (3PXB) was docked with Halimeda spp derived compounds (Table 3; Fig 2; Fig 3).

Phylogenetic tree

MEGA-X used to assess and derive an evolutionary tree. FASTA protein sequence of breast cancer blast in the National Centre for Biotechnology Information (NCBI) and derived similar in other organisms (Fig.1).

Statistical analysis

Through Minitab 14.1 software the correlation were carried between retention time, molecular weight and binding energy (Table 4).

Figure 1: Phylogenetic tree of Breast cancer gene using MEGA-X

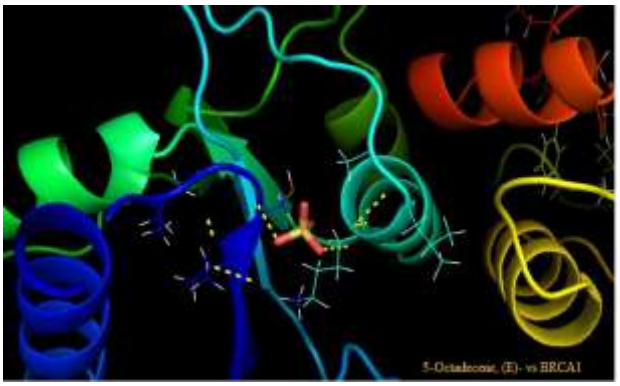


Figure 2: Three Dimension of BRCA 1 against 5-Octadecene, (E)-

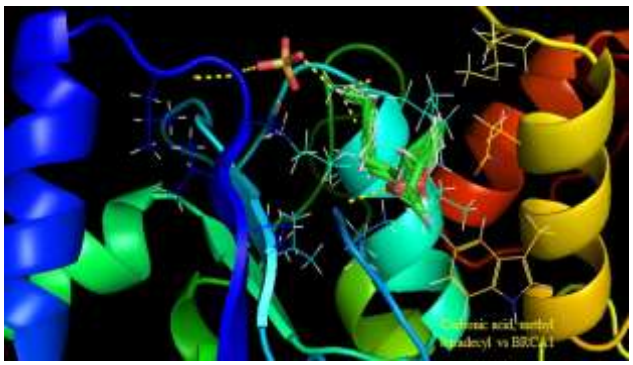


Figure 3: Three Dimension of BRCA 1 against Carbonic acid, methyl tetradcyl

Previous works in Halimeda spp

In Halimeda spp in the world following works are present in the world (Table 5).

Table 4: Correlation analysis using MINITAB 14.1

	Retention Time	Molecular Weight	Binding Energy
Retention Time	1		
Molecular Weight	0.635624	1	
Binding Energy	0.117286	-0.02014	1

Table 5: Previous works in Halimedaspp in world

Sl. No	Details (Halimedaspp)	Reference
1	Potential medicinal	Stirk et al., 2003
2	Aqueous extract	Fallarero et al., 2003
3	Metabolites	Gu et al., 2004
4	Human leukemic	Huang et al., 2005
5	Liver injury	Filho et al., 2009
6	Anti proliferative	Puc et al., 2009
7	Photosynthetic and anticancer	Folmer et al., 2010
8	Alkaloids	Guven et al., 2010
9	Human therapy	EbadaandProksch ., 2011
10	Spectroscopic	Ovenden et al., 2012
11	Antitumor activity	Pejin et al., 2013
12	Isolation and characterization of bioactive proteins	Ahmad et al., 2014
13	Structure and function	Young et al., 2015
14	Anti-tumor	Alghazeer et al., 2016
15	Isolation	Andriani et al., 2016
16	Innovation and sustainable utilization	Chye et al., 2017
17	Natural product against cancer	Wali et al., 2019

RESULTS

Docking BRCA1 vs *Halimeda spp*

There are 41 bioactive compounds were screened against breast cancer protein BRCA1 using Arguslab. In 41 compounds, three compounds showed around -13 docking energy values (5-Octadecene, (E)-, n-Heptadecanol-1 and 6,9,12-Octadecatrienoic acid, phenylmethyl ester, (Z,Z,.Z)-) followed by 4 compounds showed around -12 docking values (1,2-Benzenedicarboxylic acid, butyl octyl ester, Phthalic acid, butyl hexyl ester, n-Tridecan-1-ol and Carbonic acid, methyl tetradecyl), 9 compounds showed around -11 docking energy values (Phthalic acid, hexyl propyl ester, Phenol, 2,6-bis(1,1-dimethylethyl)-, 1-Hexadecanol, Dichloroacetic acid, 4-hexadecyl ester, Tetradecyltrifluoroacetate, 4-Trifluoroacetoxytridecan, Decyltrifluoroacetate, Dibutyl phthalate and 3-Trifluoroacetoxytridecane), 6 compounds showed around -11 docking values, 8 compounds showed around -9 docking values and others are below -9 docking energy values and no docking energy values (Table 3).

Phylogenetic relationship

Percentage identification among protein sequence of Homo sapiens BRCA1 gene with wild organisms like (*Pan troglodytes, Pongo abelii, Macaca mulatta, cerocebusatys, Mandrillus leucophaeus, Aotusnan cymaae and Piliocolobus tephrosceles*). A *Pan troglodytes* 75% with *Homo sapiens*, followed by *Pongo abelii* 75 % similar with *Pan troglodytes*, same *Macaca mulatta* 75 % relation with *Pongo abelii*. Percentage similarity study in MEGA shows breast cancer gene highly similar with *Pan troglodytes, Pongo abelii, Macaca mulatta, ceroce busatys, Mandrillus leucophaeus, Aotus nancymaae and Piliocolobus tephrosceles (Fig.1).*

Statistics

The correlation analyses were carried out using Minitab 14.1 software. It was observed that there was a strong positive correlation between retention time and molecular weight (0.64) and low positive correlation between the retention time and binding energy (0.12). There negative correlation observed between molecular correlation and binding energy (-0.020). According to the correlation study reveals that there is relationship between retention time and binding energy.

DISCUSSION

The present study shows around 25 compounds are expressing low docking energy with high activity against the protein. Lower the docking score higher is the binding efficiency blocking the activity of a particular protein was reported by.[28; 29] fungal metabolites used against breast cancer and Phthalic acid showed good activity in-silico approach.[29] Ikpeme et al., 2016 studied breast cancer activity and the phylogenetic relationship between domestic animals. Naganathan et al., 2016 used vitex spp against breast cancer and 38 compounds in 2 species were showed activity against cancer cell. Mittal et al., 2018 did in-silico analysis using cannabidiol, nimbin and acetogenin and showed high activity. Formononetin was employed against breast cancer and it showed some good activity.[32]

CONCLUSION

This is a first Insilico studyfrom macro algae of Halimedaspp against BRCA1 breast cancer. Phylogenetic reveals that there is a relation between wild animals to the human being. Study shows that Halimedaspp having high potential against breast cancer. So, the above compounds can be used to cure cancer activity. It is utilizable for further can be employed in drug design and synthesis.

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