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Computational Analysis of Naturally Occurring Marine Compounds (NOMC) Targeting Gap Junctions and Cell Adhesive Molecules for the Identification of Anticancer Drug Targets

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Abstract

Compounds and metabolites from marine organisms established a new arena for marine pharmacy primarily due to their diverse biological activities. In the long run of anticancer drug development pipeline, some of the naturally occurring marine compounds (NOMCs) appear to be potential candidates and few are commercialized. In the present study, investigation of NOMCs from Marine Algae, Sponges, Corals, Bacteria, Cnardians, and Marine Fish was carried out targeted against Gap junctions (Connexin 26, Connexin 43) and Cell Adhesive molecules (Cadherins, Integrins) via molecular docking studies. The *in silico* effectiveness of NOMCs was studied based upon the interaction with the protein's active site residues with less binding energy. The interacting NOMCs were further filtered to predict the bioavailability and drug likeness properties. Manoalide from Marine Sponges was shown to be a better interacting ligand with low binding energy (-121.693 kcal/mol) and passed all the physicochemical parameters for drug likeness. This work encourages the development of NOMCs with some chemical modifications to augment more efficacy and better activity.

Keywords: Naturally occurring marine compounds (NOMCs), Gap junctions, Cell adhesive molecules, Molecular docking, Anticancer activity

Introduction

Cells do not exist distinct from their environment. Intercellular communication and cell-matrix interactions are vital processes that link a cell to its environment and so play an important role in the life of a healthy cell. Cancer cells commonly exhibit aberrant forms of cell-cell and cell-matrix communication, and this aberrant communication is one factor that allows them to act independently and malignantly. Natural compounds can normalize and protect cell-cell and cell-matrix interactions through their inhibitory effects on PTK, PKC, and NF-kB and through other ways. Although the exact role of some CAMs in cancer progression is still uncertain, we do know that increasing E-cadherin expression and increasing gap junction communication will be useful strategies in cancer treatment. The Marine natural compounds tend to normalize many aspects of cell-to-cell communication and in so doing can inhibit the proliferation, invasion, and metastasis of cancer cells. Thus there is an need to develop modulars using natural compounds to concur the most life taking modifications in cancer biology. Currently there are no approved agents that have come directly from the marine environment, but a very significant number of marine-sourced compounds have either been in clinical trials or are currently in clinical or preclinical trials as anticancer agents [3].The marine microorganisms, seaweeds, soft corals, fungus, sponges, bryozoans, tunicates, annelids, holothurians, molluscs, echinoderms have all been reported to bea source of bioactive molecules (acetogenins, polyketides, terpenes, alkaloids, peptides and many compounds of mixed biosynthesis). To cite a few, sponge derived compounds like Zidovudine (AZT) can fight the AIDS virus, and cytosine arabinoside (Ara-C) is used in the treatment of leukaemias and lymphomas [1, 2 and 4].

In the present study, docking simulation was performed using Biosuite software [6] with Gap junctions (Connexin 26, Connexin 43) and Cell Adhesive molecules (Cadherins, Integrins) as the target and computationally naturally occurring Marine compound were docked into the receptor's binding site. Subsequently, the compounds were screened with ADME/T (absorption, distribution, metabolism, excretion and toxicity) filtering protocol to evaluate their drug likeness.

Materials and Methods

Docking studies and in silico bioavailability analysis were performed for 24 Naturally occurring marine compounds with Gap junctions(Connexin 26,Connexin 43) and Cell Adhesive molecules(Cadherins,Integrins).

Docking studies

Molecular docking was carried out using Biosuite software, installed in a single machine running on Intel Dual-CoreTM processor with 2 GB RAM and 150 GB hard disk with Microsoft VistaTM Ultimate 2006 as the operating system.[7]

Preparation of protein target structures and ligands

The X-ray crystal structure of Gap junctions(Connexin 26,Connexin 43) and Cell Adhesive molecules(Cadherins,Integrins) were retrieved from the Protein Data Bank [8]. The dataset comprised of 182 ligands, out of which 24 inhibitors having known inhibitory activity were chosen from literature [5].The ligand structures were subjected to energy minimization using Hyperchem 8.0.7(without reaction field) and the energy was minimized to Kcal/mol [6].Subsequently, the ligands were geometrically optimized using 3D cleaning utility.

Docking Studies

The Docking simulations were performed by Biosuite Software in which we considered Marine Natural Compounds as ligand against Gap Junction and Cell Adhesive molecules as targets Ligand dataset under study were docked separately into the binding site of the receptor using Biosuite. The binding site was constructed which consist of all residues that have at least one atom within 3.5 Å from any atom in the co-crystallized inhibitor. This generally gives a good representation of the important residues in the binding pocket for a protein target. To determine the optimal geometry of the ligand binding mode is done by iteratively evaluating a number of candidate solutions (ligand conformations) and estimating the energy of their interactions with the targets. The Highest Scoring solutions (best poses of low-energy) are returned for further analysis.

in silico Bioavailability Analysis

Bioavailability analysis is based upon the prediction of various physicochemical properties proposed by Lipinski's Rule of Five (RO5) [10] and Ghose et al, 1999 [11]. Lipophilicity, quantified as WlogP was analyzed using weighted approach with the help of logP plugins of Marvin Sketch. Topological Polar Surface Area (TPSA) was calculated using Polar Surface Area plugin [9]. ADME/T test for the ligand dataset was performed using FAF-Drugs program available at Mobyle portal [12]

Results and Discussion

Gap junctions and Cell adhesive molecules and computationally designed analogues were docked using Biosuite software and the docking energy values were shown in Table-1. Binding energies of the protein-ligand (drug) interactions are important to describe how fit the drug binds to the target macromolecule. In order to validate the docking procedure, the co-crystallized ligands were docked into the binding pocket of different Gap junctions and Cell adhesive proteins and the root mean square deviation (RMSD) were found. These findings supported the docking simulation and reproducibility of the docking algorithm.Docking simulations of all 24 compounds against protein resulted in few best compounds that were evaluated based on the binding compatibility [docked energy (Kcal/mol)] with the receptor. Ligands such as BRYOSTATIN 1 present in Marine Fish have higher binding affinity with the cavity

present in Connexins possessed the better energy value than the others. As KRN 7000 and Manoalide present in Marine Sponges have higher binding affinity with the cavity present in Cadherins and Integrins respectively. From this analysis, it is evident that these compounds may exhibit better interaction than the known inhibitors. Besides the better interaction with the receptor, the compounds should possess acceptable physical properties and chemical functionalities in order to participate in lead optimization and selection of drug discovery process. Lipinski's RO5 and Ghose et al, 1999 profiling for drug likeness were carried out for the dataset. Compounds under study had a molecular weight of less than 500 which suggested better absorption and low level of allergic reactions. Hydrogen bond donors and acceptors were less than 5 and 10. WlogP values of dataset were found to be less than 5 which predicted low level of toxicity, non-specific binding and possible oral administration [13]. Topological polar surface area for the dataset were greater than 60 $Å^2$ and lesser than 140 $Å^2$ indicating a high possibility of complete absorption [14]. Manoalide of Marine Sponges had passed all the physicochemical parameters with better values (Table 2) and have the greater possibility of participation in clinical trials and may exhibit better inhibitory activity.

Conclusion

The Protein-Ligand interactions play a significant role in structural based drug discovery/Designing. In the present work we have taken the receptors Gap junctions and Cell adhesive molecules and assessed a number of Marine natural compounds for complication with it. Table shows the binding affinity values. The protein-ligand interaction plays a prominent role in structure based drug designing. In the present work, Marine natural compounds were docked with the receptors Gap junctions and Cell adhesive molecules. The Manoalide established low binding energy and formed more number of H-bond interactions (-121.693 kcal/mol). Further, *in silico* bioavailability tests were carried out with physicochemical parameters and found that Manolide had better values than known inhibitors. From these results, it is concluded that Manolide could be a potential inhibitor and possessed the entire entire theoretical drug like properties. However, additional *in vitro* studies would help in characterizing the compounds in order to confirm the conclusions. This study also insists the importance of novel molecules showing selective interaction towards Gap junctions and Cell adhesive proteins communication will be useful strategies in cancer treatment and the greater possibility of selective Naturally occurring Marine compounds in cancer therapy.

Keeping the above facts in consideration the experiments can be planned to understand & evaluate New Chemical Entity (NCE) from Marine natural compounds by targeting CAM and Gap junctions by considering various pathways involving the role of CAM and GJIC in cancer biology and also the assessment of the cytotoxiciy profile of Marine natural compounds which can be used as effective alternative anti cancer drug.

Table 1: Docking Results of Marine Natural Compounds as ligand against Gap Junction and Cell Adhesive molecules as targets .

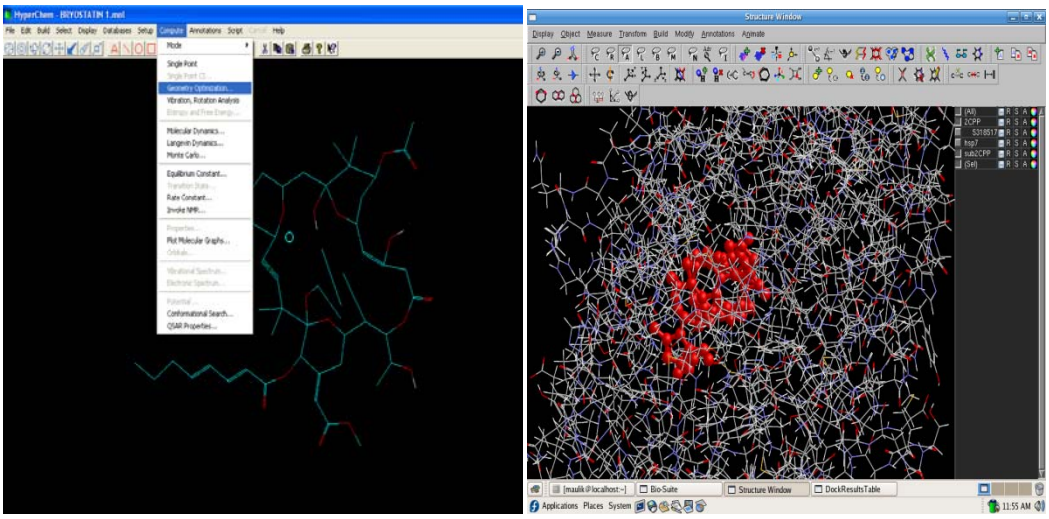
	Connexins		Cadherins		Integrins	
	Connexin 26 P-ID:2ZW3	Connexin 43 2V37	HumanCadherin2O72	MouseCadherin 2QVF	Human Chain Alpha 1KUP	Beta chain 1KUZ
Marine Algae	Dihydroxytetrahydrofuran -100.779	Ascosalipyrrolidinone 1-94.3794	Halomon -110.462	Dihydroxytetrahydrofuran -105.856	No Cavities Found	Dihydroxytetrahydrofuran -79.5276
Marine Sponges	Manoalide -121.693	E7389 -87.1265	KRN 7000 -138.65	KRN 7000 -143.616	KRN 7000 -86.7409	Manoalide -99.3016
Marine Corals	IPL576092 -100.334	IPL576092 -74.4994	IPL576092 -91.3261	IPL576092 -95.9822	No Cavities Found	IPL576092 -66.0466
Marine Bacteria	MC21A -86.5115	MC21A -76.7756	MC21A -92.3896	MC21A -97.5546	No Cavities Found	MC21A -77.6225
Marine Cnardians	Solenolide A -60.391	Solenolide A -60.861	Solenolide A -67.2916	Solenolide A -66.776	Pseudopteroxazole -30.1281	Solenolide A -66.9524
Marine Fish	BRYOSTATIN 1 -124.416	BRYOSTATIN 1 -73.2657	GTS-21 -102.963	BRYOSTATIN 1 -87.0849(1)	BRYOSTATIN 1 -57.994	BRYOSTATIN 1 -71.4809

Table 2: *in silico* bioavailability analysis.

Sr.No		Marine Compound	HD	HA	WlogP	MW	TPSA
1	Marine Algae	Ascosalipyrrolidinone 1	1	4	3.91	385.3	55.40
2		Avrainvilleol	4	4	3.77	404.0	80.92
3		curacin a.mol	0	2	5.68	373.3	46.89
4		Dihydroxytetrahydrofuran	4	9	-2.68	291.2	145.33
5		Halomon	0	0	5.54	401.3	0.00
6	Marine Sponges	Dictyodendrin_B	5	12	--	727.5	207.69
7		Discodermolide	5	9	3.59	593.4	159.54
8		E7389	2	11	1.64	713.4	137.160

9		KRN 7000	7	10	13.31	857.5	168.94
10		Manoalide	2	5	3.40	418.3	75.99
11	Marine Corals	Cavernolide	0	2	5.02	316.2	26.30
12		Homopseudopteroxazole	0	2	7.17	379.3	26.03
13		IPL576092(1)	0	1	5.97	213.2	3.24
14		IPL576092(2)	7	14	-4.07	431.3	224.32
15	Marine Bacteria	Aspermytin A	2	3	2.93	280.2	57.53
16		euplotin	0	4	3.46	292.2	44.76
17		MC21A	2	2	6.34	501.7	40.46
18		Perybysin A	2	3	1.76	252.2	52.99
19		Thiocoraline	6	22	3.22	1157.0	449.82
20	Marine Cnardians	Pseudopteroxazole	0	2	5.13	309.2	26.03
21		Solenolide A	2	9	3.22	556.8	131.89
22	Marine Fish	BRYOSTATIN 1	3	17	--	988.6	229.11
23		GTS-21	0	4	2.76	308.2	43.71
24		squalamine	4	8	7.84	641.5	131.29

Legends: HD-Hydrogen bond donor, HA- Hydrogen bond acceptor, WlogP-Weighted logP, MW-Molecular Weight and TPSA-Topological Polar Surface Area.



(A) (B)

Figure 1: (A) ligands energy minimization using Hyperchem software (B)Docking simulations using Biosuite Software.

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