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Research Article

Lyngbyastatin 2-A Potential Drug For Brain, Gastric, Prostate And Ovarian Cancer

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Abstract

Cancer is a group of disease characterized by uncontrolled cell divisions leading to abnormal growth of the tissue. Multidisciplinary scientific investigations are making best efforts to combat this disease, but the perfect cure is yet to be achieved. The side effects of the available drugs make the need for the necessity of new improved drugs. Cyanobacterial resource offers a great scope for discovery of new drugs for cancer. Cyanobacterial novel bioactive compounds with unique biological activities may be useful in finding the potential drugs with greater efficacy, specificity for the treatment of human diseases. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. Nowadays, molecular docking approaches are routinely used in modern drug design to understand drug–receptor interaction. Computational techniques can strongly support and help the design of novel, more potent inhibitors by revealing the mechanism of drug-receptor interaction. The aim of the present study was to predict the anticancer drug from the members of the cyanobacteria. *In silico* molecular docking was carried out between the cyanobacterial bioactive compounds, and four different types of cancer causing receptors. The highest energy value was produced by the Lyngbyastatin-2 with various cancer receptor molecules. From the above results, it is concluded that Lyngbyastatin-2, an ideal cyanobacterial drug can be employed as an alternative drug for treating four different cancers without any side effects.

Keywords: *Lyngbya majuscula*, Lyngbyastatin-2, *Insilico* docking, Brain, Gastric, Prostate and Ovarian cancer

Introduction

A brain tumor is an intracranial solid neoplasm within the brain or the central spinal canal. They are created by an abnormal and uncontrolled cell division, usually in the brain itself, but also in lymphatic tissue, in blood vessels, in the cranial nerves, in the brain envelopes, skull, pituitary gland. Any brain tumor is inherently serious and life-threatening because of its invasive and infiltrative character in the limited space of the intracranial cavity[1]. Gastric cancer is arising from any part of the stomach. It is difficult to cure this cancer unless it is identified in an early stage. It causes over 700,000 deaths worldwide per year. Prognosis is poor with a less than 10% 5-year survival rate, largely because most people with the condition

present with advanced disease. Gastric cancer is the second most common cause of cancer-related death in the world, and it remains difficult to cure in Western countries, primarily because most patients present with advanced disease. In the United States, stomach malignancy is currently the 14th most common cancer [2].

Prostate cancer is a form of cancer that develops in the prostate gland in the male reproductive system. It causes pain, difficulty in urinating and problems during sexual intercourse. Most prostate cancers are slow growing; however, there are cases of aggressive prostate cancers. The cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes. Curative treatment generally involves surgery, various forms of radiation therapy, proton therapy or, less commonly, cryosurgery; hormonal therapy and chemotherapy are generally reserved for cases of advanced disease [3]. Ovarian cancer is a cancerous growth arising from the epithelium of the ovary and the fallopian tube. Most ovarian cancers are classified as epithelial and are believed to arise from the surface of the ovary. However, some evidence suggests that the fallopian tube could also be the source of some ovarian cancers. Since the ovaries and tubes are closely related to each other, it is thought that these fallopian cancer cells can mimic ovarian cancer. Other types may arise from the egg cells [4].

The genus Lyngbya appears to be an emerging source of bioactive peptides. Lyngbyastatins 4–6[5], were identified from the marine cyanobacterium, which was collected off the Florida Atlantic coast [6]. It is possible that the ability to produce a wide range of defensive secondary metabolites has contributed to the high degree biological adaptation observed for cyanobacteria. These secondary metabolites often enable cyanobacteria to compete effectively in a variety of environments, and many have been presented as lead compounds for further drug development[7]. In the present study Lyngbyastatin-2 is identified an ideal drug for various cancers like Brain, Gastric, Prostate and Ovarian through molecular docking.

Material and methods

The various cancer causing receptors were retrieved from Protein database [8]. The following target receptors 1QH4 (brain), 1IVO (ovarian), 1CVI (prostate) and 1BJ7 (gastric) were selected and retrieved from protein databank for each type of cancer. 315 cyanobacterial bioactive compounds were retrieved from Chemspider database[9]. The structures of the above said compounds were screened by using Schrodinger suite program[10] to select a better ligand molecule against various cancer causing receptors Brain, Gastric, Prostate and Ovarian through molecular docking.

Results and discussion

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs [11]. Drug target discovery involves the identification of potential lead molecules against the various cancer causing receptor molecules. When considering the treatments for cancer, chemotherapy, targeted therapies, surgery, radiation and hormonal therapy are the various types that currently exist [12]. But these types of treatments, except for the target-based, are unable to distinguish cancerous cells from the normal and hence, the healthy cells are also commonly damaged in the process of treating the cancer. In this context, considering the above facts, the target based drug discovery is having higher potential over other methods[13]. Towards finding suitable inhibitors for receptor molecules of various cancer diseases, it is essential to find out the binding energy between the ligands and the receptors. This is normally done using molecular docking. This computational technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of drug-receptor interaction [14].

In the present study, molecular docking method is used for the prediction of cancer drug from cyanobacteria. Among the various members of marine cyanobacteria, *Lyngbya confervoides*, organism having high potential anticancer drug molecules. Brain- cancer causing receptor (1QH4) composed 380 amino acid residues with four chains. Gastric cancer causing receptor (1BJ7) composed of 156

amino acids with single chain contain 2 active sites (Figs.1 &2). Prostate (1CV1) cancer causing receptor is formed by 164 amino acid residues with single chain. Ovarian cancer causing receptor (1IVO) contains 622 amino acids with two chains. The Brain, Prostate and Ovarian cancer causing receptor contain 5 active sites. The four different cancer causing receptor molecules were taken for the study. 315 cyanobacterial bioactive compounds were docked against four different cancer receptors. Table 1 represents the active site score of various cancer causing receptors. Table 2 to 5 presented the molecular docking scores of different cancer causing receptors with cyanobacterial bioactive compounds. Among them Lyngbyastatin-2 (Fig.3) have close interaction and maximum energy value with the cancer causing receptors (Table.3 & Fig.4). The recognition and affinity of ligands towards receptors was interpreted from the inter atomic distances and hydrogen bonding formed between the amino acid residues of docked protein-ligand complex structure. The prominent binding pockets and cavities in cancer causing receptors were identified using Glide module. Glide is commercial software used for docking and to predict the binding and active sites of receptors.

Fig1. 3-D structure of gastric cancer causing receptor

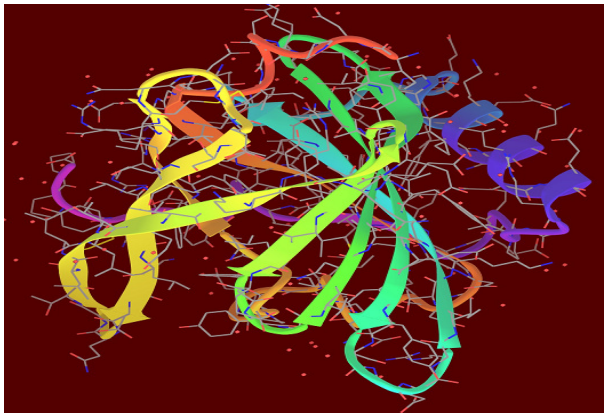


Fig.2.Showing active site of Gastric cancer causing receptor

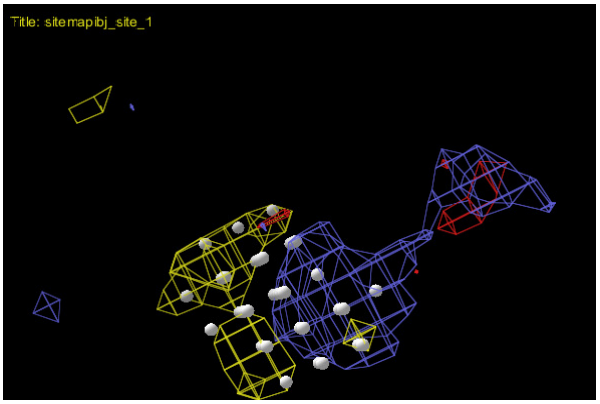


Fig.3.3-D structure of Lyngbyastatin-2

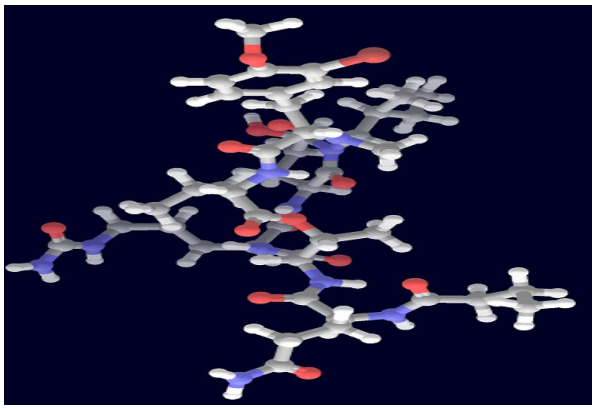


Fig.4.Docking of Gastric cancer causing receptor with Lyngbyastatin-2

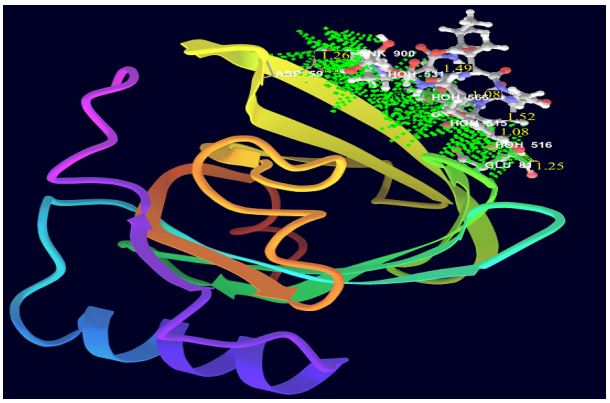
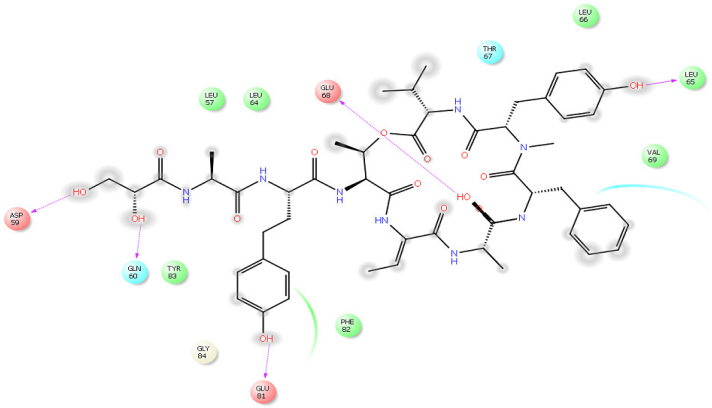


Fig.5. Molecular interaction between active site amino acid residues of gastric cancer causing receptor with Lyngbyastatin-2



The interaction of brain cancer causing receptor amino acid sequence with Lyngbyastatin-2 at inter atomic distance less than 5 Å showed that the interactions between the receptor and ligand had occurred only in the active site pockets.

The pocket of the active site was surrounded by 26 amino acids from which 9 of them were hydrophobic, 10 were charged positive. 4 were polar and 3 were charged negative. The high affinity of the brain cancer causing receptor towards Lyngbyastatin-2 was favored by three hydrogen bonds, formed by Leu-193, His-191 and Lys-196 with ligand molecule Lyngbyastatin-2. The distance of the H-bonds between the above amino acids and the ligand molecules was ranging from 1.09 to 1.51 (Fig.4). The docking study reveals that van der Waals forces play an important role in stabilizing the protein-ligand complex. The van der Waals interaction and hydrogen bonding formed by the reactive amino acid residues of brain cancer causing protein with the ligand molecule lead to binding of receptor molecule and Lyngbyastatin-2.

In docking between gastric cancer causing receptor with selected bioactive compounds, Lyngbyastatin-2 showed highest binding score -6.464462 (Table.3). This receptor contain two active site and the score 0.929 and 0.632. The first active site was identified as the major active site. This active binding site was lined with 13 amino acids from which 7 of them were hydrophobic, 3 were charged negative, two were polar and one was glycine. Among the bioactive compounds, Lyngbyastatin-2 showed 5 hydrogen bonds were ranging from 1.08 to 1.52 during docking (Fig.5).

However due to van der Waals forces and electrostatic attraction, Lyngbyastatin-2 showed highest binding score for which this drug was identified as the best drug for the treatment of gastric cancer.

When cyanobacterial bioactive compounds were docked with prostate cancer causing receptor, only one compound interacted with the major active binding site. It contains five sites and the score were ranging from 0.642 to 1.013. The Lyngbyastatin-2 ligand molecule, which showed highest docking score with the major active site of the receptor molecule, and the score, was -9.535981. This active binding site was lined with 27 amino acids from which 10 of them were hydrophobic, 5 were charged positive, 4 were charged negative, 8 were polar and 4 hydrogen bonds distance were ranging from 1.09 to 1.53.

In the ovarian cancer causing receptor, out of five ligand binding sites, site 2 was identified as the major active site for docking. The interaction score was -9.833242. This active binding site was lined with 22 amino acids from which 20 of them were hydrophobic, 2 were polar and three hydrogen bonds and the distance were ranging from 0.5 to 1.58. In this case also, the receptor-ligand interac-

tion was through the van der Waals forces.

Lyngbyastatins 4-10 were strong cancer inhibitors reported by various authors[15-18]. In the present study also Lyngbyastatin-2 is identified best drug molecule against various cancers.

Thus, from the above results, it is revealed that cyanobacterial drug, Lyngbyastatin-2 produce high docking energy with receptor molecules of different cancers Brain, Gastric, Prostate and Ovarian. Lyngbyastatin-2 could be successfully employed as an ideal and common drug for above said various cancers.

Table.1. Showing active site scores of various cancer causing receptors

Sites	Score
Brain cancer (1QH4)	
Site-2	**1.000**
Site-1	0.986
Site-3	0.741
Site-4	0.633
Site-5	0.542
Gastric cancer (1BJ7)	
Site-1	**0.929**
Site-2	0.632
Prostate (1CV1) cancer	
Site-1	**1.013**
Site-3	0.778
Site-2	0.758
Site-4	0.698
Site-5	0.642
Ovarian cancer (1IVO)	
Site-2	**1.001**
Site-1	0.990
Site-3	0.909
Site-4	0.813
Site-5	0.724

Table.2.Molecular docking score of Brain cancer causing receptor with cyanobacterial bioactive compounds

Bioactive compounds	Glide docking score
17262763(**lyngbyastatin-2**)	**-9.336775**
23314421 (symplocamide A)	-8.638148
27023336(pompanopeptin B)	-8.63066
23076610(lynbyastatin 5)	-8.115151
17214383(lynbyastatin 4)	-8.032714
23310525(lynbyastatin)	-7.880216
24662743(molasamide)	-7.701293
10214176(nostocylopeptide A2)	-7.010625
23076612(lyngbyastatin 7)	-7.006926
28284833 (symplocamide A2)	-6.982444
24687950(kemopeptine A)	-6.825001
28285565(kemopeptide A1)	-6.813872
10193999(symplostatin 2)	-6.753573
27024665(tiglicamide A)	-6.475218
553050(tasiamide)	-6.283545
23339511(lynbaybellin D2)	-6.255719
27024729(lyngbyastatin 8)	-6.21014
27023225(symplocamide A1)	-6.107824
8827454(homodolastin 3)	-6.066642
28283161(lynbaybellin E)	-5.971397
9106209(lynbiabellin D)	-5.933907
10343167(nostocylopeptide A3)	-5.873273
8161464 (cryptopycin F)	-5.844137
9574586 (cryptopycin 226)	-5.822547
8755848 (cryptopycin 5)	-5.695818
28185012(hoiamide D)	-5.652854
8161120 (cryptopycin 6)	-5.425123
24712280(kemopeptinde B)	-5.416525
9939878 (cryptopycin E)	-5.302897
25053061(caylobolide A1)	-5.297093

Table.3.Molecular docking score of Gastric cancer causing receptor with cyanobacterial bioactive compounds

Bioactive compounds	Glide docking score
23310525(**lynbyastatin-2**)	**-6.464462**
23076612(lyngbyastatin 7)	-6.462055
10193999(symplostatin 2)	-6.266507
27023336(pompanopeptin B)	-6.185516
10214176(nostocylopeptide A2)	-5.98038
17262763(lyngbyastatin)	-5.895747
27023335(pompanopeptin A)	-5.752853
10343167(nostocylopeptide A3)	-5.750317
27024665(tiglicamide A)	-5.680098
9290490(somocystinamide A)	-5.565102
23310527 (lyngbyastatin 3)	-5.457926
27024730(lyngbyastatin 9)	-5.453025
24662743(molasamide)	-5.318842
28185012(hoiamide D)	-5.039188
27024666(tiglicamide B)	-4.696442
25053060(caylobolide B)	-4.659205
9574586 (cryptopycin 226)	-4.415653
23076610(lynbyastatin 5)	-4.408319
28285565(kemopeptide A1)	-4.311489
10480304(usneoidone2)	-4.197654
8755848 (cryptopycin 5)	-4.177598
28288392(symplostatin analogue 4)	-4.168782
24614023(symplostatin 4)	-4.16813
9939878 (cryptopycin E)	-4.130397
10478837(somocystinamide A2)	-4.125845
28289545(basilynbiyaside 1)	-4.035665
552745(lynbaysolide B)	-4.025172
8158691 (cryptopycin G)	-3.922089

Table.4.Molecular docking score of Prostate cancer causing receptor with cyanobacterial bioactive compounds

Bioactive compounds	Glide docking score
17262763(**lyngbyastatin-2**)	**-9.535981**
27024665(tiglicamide A)	-9.255723
27024666(tiglicamide B)	-9.08103
28284833 (symplocamide A2)	-9.057345
28285565(kemopeptide A1)	-8.785834
23310525(lynbyastatin)	-8.564532
23076610(lynbyastatin 5)	-8.449634
17214383(lynbyastatin 4)	-8.235247
8161464 (cryptopycin F)	-8.211463
23314421 (symplocamide A)	-8.109519
10214175(nostocyclopeptide A1)	-7.904088
27023335(pompanopeptin A)	-7.79099
10343167(nostocylopeptide A3)	-7.638402
23310527 (lyngbyastatin 3)	-7.62037
27023225(symplocamide A1)	-7.618906
10214176(nostocylopeptide A2)	-7.586817
8163332(tasipeptin B)	-7.484034
27023336(pompanopeptin B)	-7.454147
8755848 (cryptopycin 5)	-7.42916
10279681(dolastin13)	-7.378443
9344966 (cryptopycin 326)	-7.376306
8158691 (cryptopycin G)	-7.221502
8546898 (cryptopycin D)	-7.185972
9939878 (cryptopycin E)	-7.13952
553050(tasiamide)	-7.109793
9290490(somocystinamide A)	-7.022429
27024730(lyngbyastatin 9)	-7.020463
24712280(kemopeptinde B)	-6.752685

Table.5.Molecular docking score of ovarian cancer causing receptor with cyanobacterial bioactive compounds

Bioactive compounds	Glide docking score
17262763(**lyngbyastatin-2**)	**-9.833242**
23310525(lynbyastatin)	-8.590062
23076610(lynbyastatin 5)	-8.299628
23076612(lyngbyastatin 7)	-8.201598
23314421 (symplocamide A)	-7.956847
28284833 (symplocamide A2)	-7.909401
10479838(lynbaybellin D1)	-7.739396
27024731(lyngbyastatin 10)	-7.418468
9106209(lynbiabellin D)	-7.114754
27023336(pompanopeptin B)	-7.037977
10214175(nostocyclopeptide A1)	-6.916479
10481022(lybaybellin F)	-6.782213
10279681(dolastin13)	-6.75329
17214383(lynbyastatin 4)	-6.697888
10193999(symplostatin 2)	-6.624553
10478837(somocystinamide A2)	-6.570385
10481024(lynbaybellin H)	-6.560847
28289559(hoiamide D1)	-6.491422
23339511(lynbaybellin D2)	-6.406228
24614023(symplostatin 4)	-6.382948
24712280(kemopeptinde B)	-6.318806
10480304(usneoidone2)	-6.305421
8755848 (cryptopycin 5)	-6.29287
27024665(tiglicamide A)	-6.256483
23310527 (lyngbyastatin 3)	-6.2415
10481021(lynbaybellin E1)	-6.238544
9290490(somocystinamide A)	-6.233022

Conclusions

The results of the present study clearly showed that Lyngbyastatin-2 is capable of making a strong interaction and binding with various cancer causing receptors Brain, Gastric, Prostate and Ovarian as evidenced by its high binding energy. Based on the results of the above study, it can be concluded that the drug Lyngbyastatin-2 is good drug and hence, it can be employed as an alternative drug for treating above said cancers without producing any side effects. However, further *in vitro* / *in vivo* studies are needed to establish its anticancer potential against variety of cancer types based on the predictions of *in silico* studies

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