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Original article

Prediction of new cyanobacterial drug for treating lung cancer

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A B S T R A C T

Lung cancer causing EGFR kinase protein selected as target and treated against commercially available anticancer drugs and cyanobacterial compounds. The present study was to predict screen and identify the potential high efficient antilung cancer compounds from the marine flora of cyanobacteria. To screen the bioactive compounds against lung cancer causing protein, EGFR kinase, Glide module (Schrodinger suite) was applied. Among the 33 bioactive compounds screened, best Glide docking score of −10.485 was found in Tiglicamide A against EGFR kinase. When this Tiglicamide A was compared with the commercially available drugs like cabazitaxel and apraclonidine through molecular docking, Tiglicamide A was found to be more effective by interacting strongly with lung cancer causing target protein, EGFR kinase. The results of the study support the fact that in silico molecular docking studies using Glide and Hex programs are very useful in predicting lung cancer treating drug. In this study, Tiglicamide A was predicted as the best active cyanobacterial compound derived from *Lyngbya confervoides*.

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1. Introduction

Lung cancer is an uncontrolled cell growth in tissues of the lung. If left untreated, this growth can spread beyond the lung and other parts of the body. Most cancers that start in lung, known as primary lung cancers, are carcinomas that derive from epithelial cells. The main types of lung cancer are small cell lung carcinoma and non-small cell lung carcinoma. The most common cause of lung cancer is long-term exposure to tobacco smoke. The lung cancer is often attributed to a combination of genetic factors, radon gas, and asbestos and air pollution including second-hand smoke [1].

Similar to many other cancers, lung cancer is initiated by activation of oncogenes or inactivation of tumor suppressor genes. Oncogenes are believed to make people more susceptible to cancer. The epidermal growth factor receptor (EGFR) regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion. Mutations and amplification of EGFR are common in non-small cell lung cancer [2].

Common treatments include surgery, chemotherapy, and radiotherapy. The chemotherapy regimen depends on the tumor type [3]. Small cell lung carcinoma (SCLC), even relatively early stage disease, is treated primarily with chemotherapy and radiation. In SCLC, cisplatin and etoposide are most commonly used. Combinations with carboplatin, gemcitabine, paclitaxel, vinorelbine, topotecan, and irinotecan are also used. In advanced non-small cell lung carcinoma (NSCLC), chemotherapy improves survival and is used as first-line treatment, provided the person is well enough for the treatment. Typically, two drugs are used, of which one is often platinum-based (either cisplatin or carboplatin). Other commonly used drugs are gemcitabine, paclitaxel, docetaxel, pemetrexed, etoposide or vinorelbine [4]. Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances. At present commonly used antitumor drugs are cabazitaxel and apraclonidine in which side effects are so common.

Therefore, drug identification from natural resource for the prevention and treatment of cancer is continuing in the last three decades. Numerous types of bioactive compounds have been isolated from marine cyanobacteria. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation. However, developments of marine floral compounds as therapeutic agents are still in the developing stage [5]. Studies have clearly demonstrated that the cyanobacteria are an excellent source of novel drug discovery.

Marine cyanobacteria are considered to be a group of potential organisms which can be the richest sources of known and novel bioactive compounds [6,7]. More than 50% of the marine cyanobacteria are potentially exploitable for extracting bioactive substances which are effective in either killing the cancer cells by inducing apoptotic death.

Identification of new biologically active compounds is required for development of new drugs. Nowadays, molecular docking

Fig. 1. 3D structure of EGFR kinase.

approaches are routinely used in modern drug design to understand drug-receptor interaction. It has been shown in the literature that these computational techniques can strongly support and help the design of novel, more potent inhibitors by revealing the mechanism of drug-receptor interaction [8]. Hence, the present study has planned to evaluate the interaction of the anticancer drugs administered for the target of lung cancer.

At present, commonly used antitumor drugs are cabazitaxel and apraclonidine in which side effects are so common. In lung cancer, EGFR kinase is to be controlled by effective antitumor compounds. Therefore, in the present investigation, suitable drug molecules with high binding affinity, which could be a possible lead molecule derived from cyanobacterial compounds are to be proposed.

2. Material and methods

The lung cancer causing receptor was retrieved from Protein database. [9]. The commercially available drug, apraclonidine and cabazitaxel and cyanobacterial drugs were retrieved from Chemspider database [10], which were later converted into 3D structures using Swiss Pdb viewer [11]. Thirty-three cyanobacterial compounds were screened for the identification of better bioactive compound using Glide module (Schrodinger suite). The potential identified cyanobacterial drug, Tiglicamide A and commercially available drug molecules were docked with the receptor molecule EGFR kinase using Hex software [12].

3. Results and discussion

Lung cancer is caused by EGFR kinase [13]. At present, commonly used antilung cancer drugs are cabazitaxel and apraclonidine in which side effects are so common [14]. EGFR kinase is a protein molecule containing a single chain formed by 327 amino acids (Fig. 1). In lung cancer, EGFR kinase is to be controlled by effective antitumor compounds. Therefore, in the present investigation, suitable drug molecules with high binding affinity, which could be a possible lead molecule derived from cyanobacterial compounds are to be proposed.

4. Drug molecules

Currently, for cancer treatment, adequate potent medicines are not available. Marine cyanobacteria are considered to be the

Table 1
Docking results of EGFR kinase with cyanobacterial compounds using Glide docking.

Cyanobacterial drugs	Source organisms	Glide docking score
Antillatoxin 2	*Lyngbya majuscula*	−4.902
Apratoxin B1	*Lyngbya* sp.	−6.988
Arulide 3	*Lyngbya majuscule*	−5.718
Baslynbiyaside	*Lyngbya* sp.	−6.235
Belamide A2	*Symploca* sp.	−6.542
Basibroamide 1	*Lyngbya* sp.	−7.829
Calothrixin B	*Calothrix*	−7.485
Caylobolide A2	*Lyngbya majuscula*	−8.410
Cryptophycin 226	*Nostoc* sp.	−7.962
Kemopeptinde B	*Lyngbya* sp.	−9.458
Hoamide C	*Phormidium gracile*	−6.003
Homodolastin 16	*Lyngbya majuscula*	−8.171
Isomalgamide B	*Lyngbya majuscula*	−5.634
Lagunamide C	*Lyngbya majuscula*	−6.104
Lynbyabelin C	*Lyngbya majuscule*	−8.102
Lynbaysolide B1	*Lyngbya* sp.	−6.639
Lyngbastatin 6	*Lyngbya majuscule*	−9.065
Majusculamide D	*Lyngbya majuscule*	−7.332
Maleviamide D	*Symploca hydnoides*	−6.664
Malyngamide R	*Lyngbya majuscula*	−6.157
Malyngolide 1	*Lyngbya sordida*	−3.866
Nostocylopeptide	*Nostoc* sp.	−9.230
Obynanaide 2	*Lyngbya confervoides*	−5.277
Pitipeptolide D	*Lyngbya majuscule*	−6.184
Pitiprolamide	*Lyngbya majuscule*	−3.866
Pompanopeptin	*Lyngbya confervoides*	−8.949
Somocystinamide A	*Lyngbya majuscule*	−4.653
Symplocamide A	*Symploca* sp.	−9.879
Symplostatin 2	*Symploca hydnoides*	−9.151
Tasipeptin B	*Symploca* sp.	−6.981
Tasiamide B	*Symploca* sp.	−8.239
Tiglicamide A	***Lyngbya confervoides***	**−10.485**
VeraguamideF	*Symploca hydnoides*	−7.527

Selected drug represented in bold.

potential organisms as rich source of known and novel bioactive compounds, which are effective in either killing the cancer cells or affecting the cell signaling for cancer [15]. Among the various members of marine cyanobacteria, *Calothrix*, *Lyngbya* sp., *Lyngbya confervoides*, *Lyngbya majuscule*, *Lyngbya sordida*, *Nostoc* sp., *Phormidium gracile*, *Symploca* sp. and *Symploca hydnoides* are highly potential organisms having anticancer drug molecules such as Antillatoxin 2, Apratoxin B1, Arulide 3, Baslynbiyaside, Belamide A2, Basibroamide 1, Calothrixin B, Caylobolide A2, Cryptophycin 226, Kemopeptinde B, Hoamide C, Homodolastin 16, Isomalgamide B, Lagunamide C, Lynbyabelin C, Lynbaysolide B1, Lyngbastatin 6, Majusculamide D, Maleviamide D, Malyngamide R, Malyngolide 1, Nostocylopeptide, Obynanaide 2, Pitipeptolide D, Pitiprolamide, Pompanopeptin, Somocystinamide A, Symplocamide A, Symplostatin 2, Tasipeptin B, Tasiamide B, Tiglicamide A and Veraguamide F. When these drug molecules were docked with the lung cancer causing receptor molecule EGFR kinase, Tiglicamide A showed a maximum Glide score indicating effective molecules against receptor tumor causing molecule (Table 1). From this result, it is concluded that among the various cyanobacterial anticancer compounds, Tiglicamide A was identified as the best antilung cancer molecule (Table 2).

Currently, cabazitaxel (Fig. 2) and apraclonidine (Fig. 3) are used as anticancer drugs for lung cancer. In the present study, TiglicamideA (Fig. 4) has been identified as anticancer drug for lung

Table 2
Docking results of EGFR kinase with anticancer drugs.

Lung cancer causing protein	Anticancer drugs	Docking score (e-value)
EGFR kinase	Cabazitaxel	−332.35
	Apraclonidine	−175.91
	Tiglicamide A	**−434.01**