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Original article

Cryptophycin F – A potential cyanobacterial drug for breast cancer

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ABSTRACT

Cancer is a group of disease characterized by uncontrolled cell divisions leading to abnormal growth of the tissue. Worldwide, breast cancer is the second most common type of cancer after lung cancer. Estrogen and progesterone bind to the receptors and may work with growth factors to cause cancer cell growth and proliferation. Estrogen receptor alpha (ERα) is essential for mammary gland development and also plays a central role in breast cancer development by mediating estrogen induced cell proliferation. 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 breast 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. Hence, the present study is interested to evaluate the interaction of the selected ligands with the breast cancer target receptor. From the study it is concluded that Cryptophycin F, a bioactive compound produced by the *Nostoc* is a promising potential drug for breast cancer.

1. Introduction

Breast cancer is the second most common type of cancer, which starts in the cells of the breast in women and men [1]. Normal breast cells and most breast cancer cells have receptors that attach to circulating estrogen and progesterone. Estrogen and progesterone bind to the receptors and work with growth factors to cause cancer cell growth and proliferation [2]. 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 [3].

ERα is essential for mammary gland development and plays a central role in breast cancer development by mediating estrogen induced cell proliferation. Estrogen receptors are a group of proteins found inside the cells, which are receptors that are activated by the hormone estrogen. Once activated by estrogen, the ER is able to translocate into the nucleus and bind to DNA to regulate the activity of different genes. It is a DNA-binding transcription factor [4]. There are two different forms of the estrogen receptor, usually referred to as α and β, each encoded by a separate gene, *ESR1* and *ESR2* respectively. Estrogen receptors are over-expressed in around 70% of breast cancer cases, referred to as ER-positive.

Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances. Tamoxifen, a chemical drug, is taken orally as a tablet, which interferes with the activity of estrogen. Some of the most common side effects of tamoxifen are blood clots, strokes, uterine cancer, and cataracts. Raloxifene, another chemical drug, infrequently causes serious blood clots to form in the legs, lungs, or eyes. Other reactions experienced include leg swelling/pain, trouble breathing, chest pain, vision changes. The side effects of these drugs make the need for the necessity of new improved drugs [5].

Natural drug formulations for the prevention and treatment of cancer appeared in the last three decades, and the interest on natural sources of potential chemotherapeutic agents is continuing. Almost 60% of drugs approved for cancer treatment are of natural origin. Numerous types of bioactive compounds have been isolated from cyanobacteria. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation. Although marine cynobacterial compounds are underrepresented in current pharmacopoeia, it is anticipated that the marine environment will become valuable source of novel compounds in the future, as it represents 95% of the biosphere [6]. However, development of marine floral compounds as therapeutic agents is still in its infancy.

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Studies have clearly demonstrated that the cyanobacteria are an excellent source of novel drug discovery. Some marine organisms are proved to be the potent sources of drugs. Marine cyanobacteria are considered to be a group of potential organisms, which can be the richest sources of known and novel bioactive compounds including toxins with potential for pharmaceutical applications [7,8]. 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. Cryptophycin is a potent cytotoxin produced by cyanobacteria of the genus *Nostoc*. It is also a promising drug in many cancer therapies.

Thus, identification of new biologically active compounds is urgently required for development of new drugs. To fulfill the demand for new therapeutic drugs and to decrease the average costs involved in development, scientist should consider screening organisms from overlooked microbial source, cyanobacteria.

Nowadays, molecular docking 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 [9]. Hence, the present study has planned to evaluate the interaction of the anticancer drugs administered for the target of breast cancer.

2. Material and methods

The human estrogen receptor ERα structure (1R5K), responsible for breast cancer, was retrieved from Protein database (Pdb). The Pdb structures of commercially available drugs such as Raloxifene and Toremifene were retrieved from Chemspider database. The 2-D structures of the analogue molecules of Arulide 1, Calothrixin B2, Caulerpenye, Cryptophycin F, Isomalgamide K, Malyngamide U, Malyngolide 1, Symplostatin 4 and Usneoidone 2 were retrieved from Chemspider database, which were later converted into 3-D structures using Swiss Pdb viewer. The analogue structures of the above said compounds were screened by using Schrodinger suite program to select a better ligand molecule against ERα receptor. The identified better compounds from Cyanobacteria and commercially available drug molecules were docked with the receptor molecule ERα using Hex software. The efficiency of the three ligands and their binding sites on the receptor were evaluated using Q-site finder.

3. Results

ERα, plays an important role in breast cancer development by mediating estrogen induced cell proliferation. At present commonly used antitumor drugs are Raloxifene and Toremifen in which side effects are so common. In breast cancer, ERα 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.

3.1. Breast cancer receptor molecule

ERα is a protein molecule containing three chains, A, B and C, each one formed by 261 amino acids (Figs. 1 and 2). In breast cancer, ERα is the functional protein and act as the antigen. In the present study, the antigenicity of the ERα molecule was analyzed using VaxiJen and TMHMM tool. The antigenicity of the receptor was 0.5039 which is greater than the threshold value of 0.5 for tumorogenic antigen and the antigen molecule was exomembrane in topology (Fig. 3). From the above facts, it was clear that the ERα is considered as a good antigen and the molecule was more effective tumorogenic antigen.

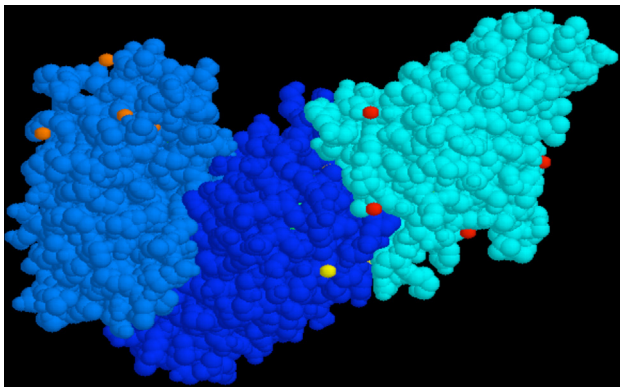

Fig. 1. 3D structure of estrogen receptors alpha (ERα).

3.2. Drug molecules

Currently, Raloxifene and Toremifene are used as anticancer drugs for breast cancer. For cancer treatment, adequate potent medicines are not available. Marine cyanobacteria are considered to be the potential organisms as riche source of known and novel bioactive compounds, which are effective in either killing the cancer cells or affecting the cell signaling for cancer. Among the various members of marine Cyanobacteria, *Calothrix*, *Lyngbya majuscule*, *Nostoc* sp. and *Symploca* sp. are highly potential organisms having anticancer drug molecules and their analogues such as Arulide, Arulide B and C, Arulide 1-3; Calothrixin A, B, B2; Cryptopycin, 1, 5, 6, 16, 24, 38, 175, 176, 226, 326, 327 and 338, B, C, C1, D, E, F, G; Isomalgamide A, B and K; Malyngolide, 1, 2; Malyngamide A, C, H, I, L, M, N, O, O2, P, Q, R, S, T, T2, U, V, v2, W, 2-epi Malyngolide, Malyngolide dimmer and Symplostatin 1–4, Symplostatin analogue 1–3, 4, Symplostatin analogue 1 (Table 1; Figs. 4–12). From this analysis 6 Arulide, 3 calothrixin, 19 Cryptophycin, 3 Isomalgamide, 24 Malyngolide and 9 Symplostatin analogues were identified. When these analogues were docked with the receptor molecule ERα Cryptophycin-F 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 Cryptophycin-F was identified as the best anti breast cancer molecule (Table 2).

Currently, Raloxifene and Toremifene are used as anticancer drugs for breast cancer. In the present study Cryptophycin-F has been identified as anticancer drug for breast cancer, in addition to

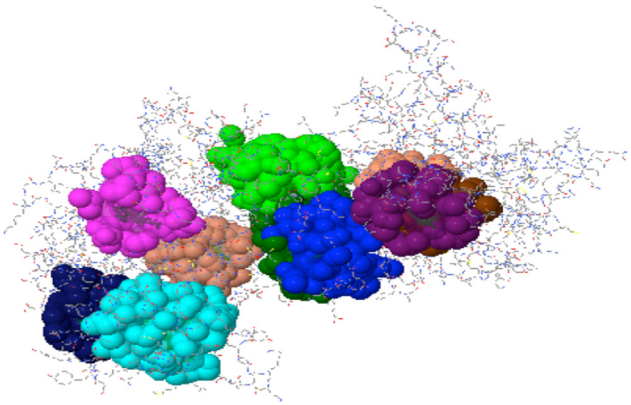

Fig. 2. Ligand binding sites on ERα.