1. INTRODUCTION

1. Cancer

Cancer is a malignant neoplasm which is a broad group of diseases involving unregulated cell growth. In this disease, cells divide and grow uncontrollably forming malignant tumors, and invade nearby parts of the body through the lymphatic system or bloodstream. There are over 200 different known cancers that affect humans (Anand et al., 2008). Among them, breast, lung, skin, brain, gastric, prostate, ovarian, blood, cervical and thyroid cancers are more common.

Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk (Sariego, 2010). Lung cancer is characterized by uncontrolled cell growth in the tissues of the lungs and nearby tissue (Horn et al., 2012). Skin cancer arises from the cells of any layer of the skin. Skin cancers are named based on the type of skin cell from which they arise. Basal cell cancer originates from the lowest layer of the epidermis; squamous cell cancer originates from the middle layer, and melanoma, which originates in the pigment-producing cells, melanocytes (Cakir et al., 2012). The brain cancer develops tumors inside the cranium or in the central spinal canal (Striedter, 2006). Gastric cancer is arising from any part of the stomach which is very difficult to cure this cancer unless it is identified in an early stage (Buckland et al., 2009). Prostate cancer is a form of cancer that develops in the prostate gland in the male reproductive system which causes pain, difficulty in urinating and problems during sexual intercourse (Lister, 2009). Ovarian cancer is a cancerous growth arising from the epithelium of the ovary and the fallopian tube (Piek et al., 2008). Blood cancer is caused by malignancy in the blood, lymphatic system, or bone marrow. Blood cancers, start in the bone marrow where blood is produced, and affect the normal production and function of the blood cells (http://www.prokerala.com/health/diseases/cancer/blood-cancer.php). Cervical cancer is arising from cells originating in the cervix of the uterus. One of the most common symptoms of cervical cancer is abnormal vaginal bleeding (Kumar et al., 2007). Thyroid cancer is a malignant neoplasm originating from follicular or parafollicular thyroid cells (Bennedbaek et al., 1999).
2. Receptors causing cancer

Various types of cancers are induced by specific type of enzymes which are called receptors. A receptor is a protein molecule that responds to the specific ligand molecules. The term receptor is also used to include other proteins that are drug targets, such as enzymes. A molecule that binds to a receptor is called a ligand, and can be a peptide (short protein) or another small molecule such as pharmaceutical drugs. Usually, a receptor enzyme molecule has 10 possible ligand binding sites out of which only one functions as active site, and the active site fits with one specific type of ligand molecule (drug). A tighter fit between an active site and the ligand molecule increases the efficiency of the reaction. The active site is the small portion of the enzyme where ligand molecule binds and undergoes a chemical reaction. The active site is usually found in a 3-D groove or pocket of the enzyme, lined with amino acid residues. These residues are involved in recognition of the ligands (drugs).

In breast, ERα is essential for mammary gland development and also plays a central role in breast cancer development by mediating estrogen induced cell proliferation. Estrogen and progesterone bind to the receptors and work with growth factors to cause cancer cell growth and proliferation (Cosman et al., 2003). In lung cancer, EGFR tyrosine kinase is involved in causing non-small-cell lung cancer and therefore EGFR tyrosine kinase is the receptor of the lung cancer (Gazdar, 2009). Heat Shock Protein, (4,5-diarylisoxazole) Hsp90 is upregulated 10-fold in tumour cells suggesting that it helps maintaining tumour cell growth and survival. Hsp90 (5-diarylisoxazole) chaperone is a skin cancer causing receptor protein (Li et al., 2009). The brain cancer is caused by a type of enzyme called brain-type creatine kinase (BB-CK) which is found to be over expressed in a wide range of solid brain tumors. So in brain tumor BB-CK is the enzyme representing the receptor molecule (Virji et al., 1988).

Gastric cancer is caused by Bovine Lipocalin Allergen BOS D 2 and therefore Bovine Lipocalin Allergen BOS D 2 is a receptor molecule causing gastric cancer (Rouvinen et al., 1999). Prostate cancer is caused by the enzyme prostatic acid phosphatase (PAP), produced by the prostate. It may be found in increased amounts in men who have prostate cancer or other diseases. The highest levels of the acid phosphatase are found in metastasized prostate cancer (Jakob et al., 2000).
Therefore Prostatic acid phosphatase (PAP) is the receptor molecule in prostate cancer. The ovarian cancer arises from the ovarian surface epithelium which expresses EGF receptors for the growth and differentiation of the ovarian follicle. There is strong evidence that increased EGF receptor expression is an early event in the ovarian cancer development. These findings suggest that the EGF receptor is the receptor molecule of ovarian cancer (Hudson et al., 2010).

In blood cancer Abelson leukemia Tyrosine Kinase (ABL) is involved in cellular processes and its transforming variants are involved in human leukemias. This abnormality is due to the fusion between Abelson (Abl) tyrosine kinase gene at chromosome 9 and break point cluster (Bcr) gene at chromosome 22. Among them, Abl is considered as the important receptor factor for blood cancer (Nam et al., 1996). Cervical cancer is caused by Epidermal Growth Factor Receptor (EGFR) and it is the receptor molecule for cervical cancer. EGFR functions through dimerization that activates a tyrosine kinase domain to regulate multiple functions such as cell growth, differentiation, gene expression and development (Sogabe et al., 2013). Thyroid cancer is a disease that abnormal cells begin to grow thyroid gland caused by Thyroid Hormone Receptor Alpha 1 (THRA1) which is involved in the proliferative disorder leading to the abnormal growth. The thyroid gland is shaped like a butterfly and is located in the front of neck. Therefore Thyroid Hormone Receptor Alpha 1 (THRA1) is the receptor molecule causing thyroid cancer (Onda et al., 2002).

3. Management of cancer

The most effective management of the cancer is the surgical removal of the cancerous tissue followed by radiation therapy. Hormonal therapy is given with radiation in some cases.

Hormonal therapy and chemotherapy are commonly reserved for cases of advanced disease (Enger et al., 2007). Cancer treatments do not have potent medicines and at the same time in some instances, currently available synthetic drugs are causing more side effects. This makes the need for the necessity of new improved drugs (Anonymous, 2007).

4. Drugs from natural resource

One of the most important treatments currently available for cancer and other diseases is chemotherapy which has limited effectiveness due to some serious life-threatening side effects.
and development of drug resistance cancer cells. The therapeutic efficacy and possible side effects vary among different agents. Some drugs may have excellent efficacy but their side effects are too serious. One effective solution to this problem could be using drugs from natural products. New drug discovery is a long and expensive process and therefore, it is thus worthwhile to pursue a less expensive way for the production of drugs and to decrease their side effects (Feng and Chien, 2003).

Natural products are an important source of new structures leading to drugs in all major disease areas. These products are a valuable source of structural diversity and functional density to identify potential compounds. Therefore, therapeutic effects of natural product-derived drugs are predominantly achieved in antibiotic therapies, oncology and immunoregulation (Hoelder et al., 2012). Almost 60 percent of drugs approved for cancer treatment are of natural origin. Recently, researchers are mainly focusing on drug discovery from natural products due to lack of their side effects (Steven et al., 2010). Since the rate of discovery of compounds from Actinomycetes and Hyphomycetes has decreased recently, it is a high time to turn to cyanobacteria and exploit their potential. Cyanobacteria have been considered as a rich source of secondary metabolites with potential biotechnological applications in the pharmacological field. Production of bioactive compounds with commercial and medical applications has also increased the interest in studying these organisms (Tan et al., 2007). Some of the marine cyanobacteria produce secondary metabolites which show an interesting and exciting range of biological activities ranging from antimicrobial, immunosuppressant, anticancer, anti-HIV, antibacterial, antituberculosis, antiviral and antitumor activities (Gademann and Portmann, 2008; Wase and Wright, 2008; Mayer et al., 2011). During recent decades, researchers have started to pay attention to marine cyanobacteria which are rich in biologically active secondary metabolites. The biosynthetic information on the chemical structures unique to these organisms will be very valuable for finding out new therapeutic agents to suppress cancer (Hakanson et al., 2007; Plinski et al., 2007).

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 cyanobacterial 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 percent of the biosphere (Jimeno et al., 2004). 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 (Jha and Zi-Rong, 2004; Thajuddin and Subramanian, 2005). More than 50 percent of the marine cyanobacteria are potentially exploitable for extracting bioactive substances which are effective in killing the cancer cells by inducing apoptotic death. Thus, identification of new biologically active compounds from cyanobacteria for cancer treatment is urgently required.

The secondary metabolites produced by cyanobacteria exhibit a broad spectrum of biological activities affecting a variety of bacterial, viral, fungal and mammalian targets. Among marine cyanobacteria, the genus *Lyngbya* is considered to be the most prolific producer of over 200 compounds, secondary metabolites including lipopeptides, cyclic peptides and depsipeptides (Blunt and Munro, 2008). Many compounds produced by *Lyngbya spp.* are of significant concern to human and animal health (Osborne et al., 2001). Numerous medical studies in the past revealed that *Lyngbya majuscula* contains a broad spectrum of biologically active compounds and phytochemicals that exert far-reaching nutraceutical and pharmacological effects, inhibiting tumor/cancer growth (Luesch et al., 1999). The advantage of cyanobacteria as a microbial source for drug discovery lies in the economy of their cultivation compared with other microorganisms, as the former require only simple inorganic nutrients for growth. Thus, it seems that the cyanobacteria have the potential for expanded utilization in the drug discovery.

Anticancer drugs are used to target all rapidly proliferating cells, that is, cancer cells, and any normal rapidly dividing cells. One example of a normal cell that is most affected by such drugs is the bone marrow forming cells. The effect of these drugs on normal cells might induce the development of a second cancer. Nevertheless, the benefits of these drugs outweigh the possibility that they will induce the development of a second cancer. The cyanobacterial genus *Oscillatoria* is evenly distributed throughout the ponds having many species mainly marine in nature, rich in secondary metabolites such as flavonoids. The methanolic extract of *oscillatoria* may contain large amount of water soluble vitamins and phycocompounds. Mukund and Sivasubramanian, (2014) studied the anti proliferative potential of methanolic extracts of the cyanobacteria on A549 cells by standard anti-proliferative assays. DNA profiling was studied to investigate any change in DNA of the treated cells.
5. Prediction of drugs for cancer by molecular docking

Drug design is the inventive process of finding new medications based on the knowledge of a biological target (Madsen et al., 2002). The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it (Cohen and Claude, 1996). This type of modelling is often referred to as computer aided drug design. Drugs may be designed that bind to the active region and inhibit this key molecule (Tollenaere, 1996). Current method for structure based drug design is about finding ligands for a given receptor in which a large number of potential ligand molecules are screened. This method is usually referred as ligand-based drug design (Guner and Osman, 2000).

Bioinformatics is seen as an emerging field with the potential to significantly improve drugs, brought to the clinical trials and eventually released to the marketplace. Computer Aided Drug Design is a specialized discipline that uses computational methods to simulate drug receptor interactions and is heavily dependent on bioinformatics tools, applications and databases (Alberto et al., 2006). 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 (Xie et al., 2007).

In the field of molecular modelling and drug identification, docking is a method which predicts the preferred drug (ligand) to a target receptor when bound to each other to form a stable complex. Knowledge of the preferred orientation is used to predict the strength of association or binding affinity between two molecules by using docking scores. Therefore docking is useful for predicting the strength and binding nature of the receptor and ligand molecules (Lengauer and Rarey, 1996). The focus of molecular docking is to computationally simulate the molecular recognition process. The aim of molecular docking is to achieve an optimized conformation for both the receptor (protein) and ligand and relative orientation between receptor and ligand such that the free energy of the overall system is minimized. Thus the protein-ligand interaction plays an important role in determining the suitable drug for the treatment. Docking is frequently used
to predict the binding orientation of small molecule drug candidates to their protein targets in order to, in turn, predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking (Kitchen et al., 2004).

Docking is a process by which two molecules fit together in 3D space. Docking allows virtually screening a variety of compounds and predicting the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme fit together and dock to each other well. The molecules binding to a receptor, inhibit its function, and thus act as drug. The binding ability of the drug with receptor is identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations. The energy value obtained through docking is used as a criterion for the selection of drugs which involves the identification of lead molecules. The lead molecule is one with maximum interaction showing high negative e-value.

Thus in the present investigation, various drug molecules, commonly prescribed by the physicians and various bioactive compounds selected from cyanobacteria, were screened and identified through molecular docking as potential drug molecules for cancers. Among ten cancers brain cancer causing cell line was treated by using cyanobacterial extracts from *Lyngbya majuscula*.

**Scope and objectives**

On the basis of the above facts and information, the present work has been designed and planned to evolve strategy for the identification of potential drugs for various types of cancer through molecular docking with the following objectives.

* To identify the various enzymes causing cancer and to determine the antigenicity of the identified enzymes causing various cancers,

* to find out the possible ligand binding sites from the enzymes,
* to screen the cyanobacterial secondary metabolites available in the database and to identify the effective of cyanobacterial secondary metabolites, acting as a drug, for various cancers through molecular docking.

* to compare the synthetic drugs with cyanobacterial bioactive compounds through molecular docking.

* to find out best drug molecules for various cancers and to conduct in vitro studies to find out cell line activity against the extract of any one cyanobacterial organism.