Introduction
1. Introduction

During mitosis parent cell divides into two daughter cells (Robert and Hine, 2008). They are generally considered to be the part of larger cell cycle whereby each daughter cell produced is genetically identical to the parent cell (Griffiths et al., 2012). But in certain cases mutations leads to unregulated cell division termed as cancer. To be more precise, cancer is a genetic disease caused due to the uncontrolled growth of cells (Carmaeia, 1993). Inspite of the advancements in diagnosis and treatment, this disease still remains as a threat and a challenge for the mankind with the report of increased mortality rate. (Kotnis et al., 2005). There is an estimated case of 2.5 million cancer patients existing with about 8,00,000 new cases reported and 5,50,000 deaths occurring every year (Nandakumar, 1990-96). In India, this disease has become one of the ten leading causes of death. Further, there is also an estimation of 3 million new cases reported at any particular point of time with 1 million cases added every year (Pankaj, 2013). In 2008 itself, approximately 12.7 million cancers were diagnosed and in 2010 nearly 7.98 million people died (Jemal et al., 2011). Thus, the overall effect of all types of cancers accounts for approximately 13% of all deaths each year. The mortality rate for each cancer is reported by World Health Organization with the most common being the lung cancer (1.4 million deaths), followed by stomach cancer (740,000 deaths), liver cancer (700,000 deaths), colorectal cancer (610,000 deaths), and breast cancer (460,000 deaths) (WHO, 2010). (Figure. 1) The above data indicates that in invasive cancer the leading cause of death in the developed world and the second leading cause of death in the developing world (Jemal et al., 2011).

1.1. Cancer types

On a broader scale, this killer disease has been classified based on the region of attack like lungs, breast stomach, gall bladder, cervix, mouth, esophagus and colon (Imran et al., 2011). But apart from this, there are 200 more types of cancers identified till
date (Cancer Research, 2012). In India, particularly the population has been reported to get affected by cancers of the lungs, breast, colon, rectum, stomach and liver (Imran et al., 2011).

**Figure.1.** Mortality rate from malignant cancer per 100,000 inhabitants in 2004 (WHO, 2009, 2010)

To begin with, even though lung cancer was quite scarce in the beginning of the century which has become the deadly killer disease by 1971. The report from National Cancer Registry Program of the Indian Council of Medical Research from urban and rural areas confirms varying degrees of incidence in different areas (ICMR, 1988-89). Second, breast and cervical cancer are confined to females. Of this, the former exhibited an alarming increase of 12% in India from 1985-2001 which again represented 57% raise of cancer burden for the country (Yip et al., 2006, Hadjiiski et al., 2006). Quite interestingly, cervical cancer is much less reported in Indian population due to better diagnosis, treatment and life style. Third, the oral cancer is quite common in Indian population (ICMR, 1992) which results in the increase in incidence of oral sub-mucous fibrosis; especially among youngsters. This disease occupies fourth place after lung, stomach and liver cancers in males. Moreover, it settles at fifth place next to cervix, breast, stomach and lung cancer in females (Park, 1997).
1.2. Carcinogens

The agents which generally cause cancer are known as carcinogens. All these agents alter the functions of the genes and finally leads to uncontrolled cell divisions. Agents could be either chemical, environmental, biological or an amalgamation of all these. What generally happens is that all these carcinogens interact with DNA of the normal cells resulting into a series of cascading events responsible for tumor formation (Carmaeia, 1993). Thus from a broader perspective, cancer could strike through either external or internal factors. The external factors include radiation and chemical compounds. Regarding radiations, the factors include X-ray, UV-radiation, gamma radiation, Radium-226, Plutonium-238 and Plutonium 239. For chemical compounds, tobacco based cancer is due to intake of tar which could be because of both active and passive smoking. The other listed chemical compounds which causes cancer includes arsenic, asbestos, benzene beryllium, cadmium, hexavalent chromium (VI) compounds, lead, ethylene oxide and Nickel (Sasco et al., 2004, Rowlands et al., 2009). The infectious agent which causes cancer could be from virus, bacteria or parasites. The virus involved in causing cancer is termed as oncovirus. Some of them are human papilloma virus (cervical carcinoma), Epstein-Barr virus (B-Cell lymph proliferative disease and nasopharyngeal carcinoma), Kaposi’s sarcoma herpesvirus (Kaposi’s sarcoma), hepatitis B and hepatitis C viruses (hepatocellular carcinoma) and Human T-cell leukemia virus-1(T-cell leukemias) (Pagano et al., 2004). There are reports of bacterial infection based cancer due to Helicobacter pylori resulting in gastric carcinoma. Also parasitic infection based cancer caused by Chistosoma haematobium (Samaras et al., 2010).

Further, the internal factors include inherited mutations, hormones and immune conditions. Majority of these cancers are non-hereditary (sporadic cancers) while hereditary cancer are due to inherited genetic defects. Less than 0.3% of the population is carriers of genetic mutations. The best example is the breast cancer genes (BRCA1 and BRCA2) with more than 75% risk, ovarian cancer and hereditary non-polyposis colorectal cancer (Roukos, 2009; Cunningham et al., 2010). Even hormones are also reported to develop cancer by promoting cell proliferations in breast, endometrium, prostate, ovary, thyroid, bone and testis (Henderson et al., 2000).
All these factors discussed above leads to mutations which ultimately results in gene damage (Kinzler *et al.*, 2002). Recently many diagnostic are designated to identify causes based on symptoms, medical imaging and screening tests. The generated results from these were further subjected to microscopic examination followed by treatment through chemotherapy, radiation therapy and surgery. As far as cancer is concerned, the survival of the individual is purely based on the tumor location and the stage of disease during treatment. Even though cancer can strike at any stage of life, but still later stage is quite vulnerable (Jemal *et al.*, 2011).

Irrespective of many factors cited for causing cancer like radiation, chemicals, genetic mutations, virus, and hormones but still, for certain cases the factors are uncertain and could also be an amalgamation of all of them. Cancer accounts for more death worldwide than AIDS, malaria, and tuberculosis combined. According to World Economic Forum (WEF), cancer is among one of the three greatest risks to the global economy due to escalating cost of care, the threat to productivity from death and disability and the effects of costs on household impoverishment (http/cancerresearch).

### 1.3. Anti-Cancer Research

This field gained its momentum in 1971 in order to develop strategies for prevention, diagnosis, treatments and cure (Sharon, 2008). The research ranges from molecular bioscience, as well as clinical trials to evaluate and compare applications of the various cancer treatments. The applications mainly include surgery, radiation therapy, chemotherapy, hormone therapy and immunotherapy. From mid 1990, the emphasis in clinical cancer research has shifted towards therapies derived from biotechnology research such as immunotherapy and gene therapy (http/cancerresearch). Currently, many fields have converged to reason out the causes of cancer and identify better treatments. These fields include molecular biology, biochemistry and cell biology. With the advent of new technologies came biotechnology which assisted in understanding the causes of cancer. The latest entrant in to this arena is bioinformatics which is a multidisciplinary field in turn a combination of biology, computer science, mathematics and statistics which has simultaneously assisted in understanding the cancer from sequential and structural perspective (Jana *et al.*, 2009).
With the sequencing of human genome in 2003, thrust was on for the understanding of cause and to identify better treatment against cancer. Thus recently bioinformatics gained its importance in cancer research and therapy which mainly includes database searches; analysis of genes and proteins; and gene expression analysis to study the drug response and tumor response (Gordon, 2009). In addition to this, biophysical methods have assisted in presenting proteins in 3D structures for better structure based analysis (Erbel et al., 2011). All these structures are elucidated using X-ray, NMR and electron microscopy methods and later on deposited in Protein Data Bank for further analysis (RCSB). This knowledge assists in understanding of protein structure and function which ultimately helps in protein-protein interactions and molecular simulations and drug design. Moreover, they also provide us with an option to introduce mutations to elucidate the functional significance of individual residues and their structural stability (Muñoz et al., 2008). To summarize, achieving successful anticancer drug requires the amalgamation of research disciplines like pharmacology, genomics, biochemistry, comparative genomics, functional genomics, proteomics and bioinformatics.

1.4. Cancer Targets

Identification of cancer drug targets requires the understanding of biochemical pathways that gets affected in the cancer genome. Thus many targets were reported which includes p53, chk1/2, actin, kinesin Eg5, tubulin, CDK1, HMGa, CDC25, Topoisomerase i/iiCDK2, CDK4, Cdc7 to name a few. All these reported targets are associated with different stages of cell division and are considered to be a potential drug targets which when gets blocked plays a vital role in controlling and curing different types of cancers (Onyango, 2004). Of all these types mentioned above, especially tubulin protein will be extensively investigated from sequential and structural perspective to understand the drug interactions, effect of residual substitutions, protein-protein interactions, protein structural flexibility and molecular simulations.

1.5. Objectives of the present study

1. The present study is aimed at modelling of Homo sapiens α- and β- tubulin by comparative modelling.
2. To investigate the significance of eight residual deletions observed in α- and β-tubulin from sequential, structural and docking perspective.

3. To investigate the bulkiness, flexibility and the rigidness of the peptide segments associated with the lateral interactions in α- and β-tubulin.

4. To identify the potential lead molecules for human β-tubulin through virtual screening of Seaweed Metabolites against taxol binding site.

5. To understand the role of amino acid substitutions in human β-tubulin that brings in drug resistance.

6. To study the interactions of potential chemical compounds from lower and higher plants including marine flora with the wild and the mutant human β-tubulin proteins.