1.1 BACKGROUND

Cell proliferation is the basis of development, survival and maintenance of living organisms. Even more critical is the ‘regulation’ of the process of cell proliferation. Aberrant regulation of this phenomenon results in cancer. In fact abnormal cellular proliferation is one of the hallmarks of cancer. Breast cancer comprises of a heterogeneous group of disease that varies in morphology, biology and response to therapy (Rakha et al., 2008). According to the American cancer society survey of 2012, cancer is the second leading cause of death following heart diseases, accounting for 23% of all deaths. A total of 1,638,910 new cancer cases and 577,190 deaths from cancer are projected to occur in the United States of America in 2012. Prostate is the most leading site of cancer in males, which accounts for 241,740 new cases (29% among all the sites diagnosed) and breast cancer is the most leading site of cancer in females which accounts for 226,870 new cases (29% among all the sites diagnosed). However, leading estimated deaths are due to lung and bronchus cancer in both males and females. The lifetime probability of being diagnosed with an invasive cancer is higher for men (45%) than for women (38%). However, women have a slightly higher probability of developing breast cancer before 60 years. Breast cancer ranks first among women ages 20 to 59 years (Cancer facts and figures-2012). In India, oral cancer is the most common, followed by throat and lung cancer (Development of cancer atlas of India, ICMR). In the 1990s, cervical cancer was the number one cause of cancer deaths among women in India, with breast cancer being the second highest. India's first cancer atlas, produced by the Indian Council of Medical Research in 2005, however, confirmed that breast cancer has replaced cervical cancer as the leading site of cancer among women in Indian cities. Breast cancer accounts for 19-34% of all cancer cases among women. This increase has been attributed to changes in lifestyle and food habits (Development of cancer atlas of India, ICMR).

Chemotherapy, surgery and radiotherapy have remained the mainstay of breast cancer treatment. Advances in diagnosis, surgical techniques, radiotherapy and chemotherapy have led to increased survival time for many breast cancer patients. Chemotherapy involves the use of drugs to eliminate uncontrolled proliferation of cancer cells. Yet, chemotherapeutic drugs are also harmful to normal cells which have rapid proliferation rate. The major problem involved in current chemotherapy is the development of drug resistance. Some of the cancer types are intrinsically resistant to various anticancer drugs
while the others develop multidrug resistance upon treatment. Thus, the development of chemoresistance remains a major obstacle for cancer treatment.

Recent reports suggest that initiation and propagation of cancer are increasingly being linked to stem cells. Support for this link comes from the identification of a small population of ‘stem cells’ within tumors of multiple organs, which both functionally and phenotypically resemble the normal tissue-specific stem cells (Visvader and Lindeman, 2008). This small population of cells within tumors has been termed as ‘cancer stem cells’ (CSCs). Cancer stem cells have self renewal, differentiation ability and have the ability to initiate or maintain the tumor (Dalerba et al., 2007). Traditionally, chemotherapy has been based on the ability of cytotoxic drugs to destroy rapidly proliferating cancer cells. Now, it has reported that only rare population of cells having stem cell characteristics drive tumor initiation/maintenance while the rest of cancer cells are non-tumorigenic (Wicha et al., 2006). Hence, chemotherapy directed against the rest of the cancer cells may cause tumor regression but leaves the rare CSCs which may lead to relapse. Therefore, it is hypothesized that frequent relapse of cancer may be due to the inability of current drugs to target CSCs (Nguyen et al., 2012). Hence, the aim of cancer therapy should be specific to cancer stem cells for a complete elimination of tumorigenic cells (Rasheed et al., 2011).

India has one of the richest biodiversity with enriched flora of medicinal plants. India has two (Eastern Himalaya and the Western Ghats) of the 18 hotspots of plant biodiversity in the world. Interestingly, we are seventh among the 16 mega diverse countries, where 70% of the world’s species occur collectively and are rich in our own flora, however, only 65% flora of the country have been surveyed so far (da Silva and Meijer, 2012). In India, medicinal plants are being used as an indigenous cure in folklore or traditional system of medicine for treatment of various kinds of illness including cancer (Khare, 2007). Ayurveda, a traditional sect of Indian medicine based on plant drugs has been successful since early times in using these natural drugs and preventing various tumors. Recently, a greater emphasis has been given towards the research on complementary and alternative medicine that deals with cancer treatment. Recent reports suggest that a variety of anticancer drugs are derived from plant sources, leading to scientific interest in discovery of anticancer drugs from plants (Cragg and Newman, 2009). Secondary metabolites from plants play a very important role in cancer chemotherapy. Sesquiterpene lactones are diverse group of natural compounds present in the medicinal plants. In recent years, the anticancer potential of sesquiterpene lactones attracted a great deal of interest (Ghantous et
al., 2010). For example, sesquiterpene lactones isolated from medicinal plants such as parthenolide, costunolide, Arteminolide C and Helenalin were found to have the ability to induce apoptosis in various cancer cell lines in vitro and effectively inhibited tumor cell growth in vivo (Kreuger et al., 2012). Apoptosis or programmed cell death defines a genetically encoded cell death program, which is morphologically and biochemically distinct from the necrosis (Cotter, 2009). Induction of apoptosis in cancer cells is considered as the one of the strategy for the development of anticancer drugs (Portt et al., 2011). Recent study also suggests that sesquiterpene lactone, parthenolide and its derivatives have the ability to induces apoptosis specifically in acute myelogenous leukemia stem cells and breast cancer stem cells (Guzman et al., 2005, Zhou et al., 2008)

1.2 AIM AND OBJECTIVES

The aim of the current work was to study the selected indigenous medicinal plants bearing sesquiterpene lactones for anticancer activity on human breast cancer cells. The major objectives of the study include:

1) To study cytotoxicity and apoptosis induced by selected indigenous medicinal plants extracts (Withania somnifera and Tinospora cordifolia) on human breast cancer cells.

2) To study the cancer stem cell inhibitory activities of selected indigenous medicinal plant extracts and fractions against human breast cancer cells.

3) Bio-activity guided fractionation of the selected medicinal plant extracts for isolation of the active (anticancer) compounds.

4) Phyto-chemical characterization and decipher the structure of the active compounds.

5) To study the anticancer effects of isolated compounds in human breast cancer cells.

1.3 REFERENCES


