Introduction
Nature has been the rich source of medicinal products for the past millions of years. With the advent of many useful drugs from plant sources, plants have formed the basis of indigenous traditional medicine systems, dating from around 2600 BC in Mesopotamia. Egyptian record on medicinal plants “Ebers Papyrus”, the Chinese “Materia Medica”, the documentation of the Indian Ayurvedic system “Charaka Samhita and Sushruta Samhita” and the contributions of Greeks, Romans and Arabs all point out the importance of plants and plant derived products in the ancient traditional medical practices, that formed the basis for treatments still used today (Cragg and Newman, 2013). Research on natural products, that to be used in the treatment of cancer is on high demand, especially with the focus on those derived from plant species. Naturally derived compounds are considered to have less toxic side effects compared to current treatments (Greenwell and Rahman, 2015).

In 2030 the number of cancer deaths is projected to increase 11.5 million globally. In order to manage or arrest the carcinogenic process the use of medicinal plant products as an alternative or in combination to conventional allopathic medicine is highly encouraged. Several herbal products have already been evaluated in clinical studies and are still under investigation to find out the tumouricidal properties against different types of cancers. The Indian Ayurvedic system of medicine incorporates herbs into its treatment regime. The holistic approach in the Ayurveda treatment claimed to provide an effective alternative to individual plant isolates in the treatment of cancer. The well known Ayurvedic classics Charaka and Sushruta samhitas, describe cancer as inflammatory or non-inflammatory swelling and mention them as either Granthi (minor neoplasm) or Arbuda (major neoplasm) (Desai et al., 2008).

Recent statistics shows that globally breast cancer is the most commonly occurring cancer among women. Breast cancer comprises twenty three percent of the approximate 1.7 million female cancers that are newly diagnosed each year. In the last 5 years ~ 6.2 million women were diagnosed with breast cancer, making breast cancer the single most prevalent cancer around the globe (Braithwaite et al., 2016). The TNM system, where T is the size of tumour, N denotes whether or not the tumour has spread to lymph nodes and M the
metastatic status of the tumour to distant sites of the body is used to assess breast cancer staging. Stage zero is a marker condition or precancerous condition. In stage one to three there is the presence of tumour within breast and lymph nodes. The stage four is the most severe condition where it has already reached the blood stream and metastatic progression to distant organs has occurred. At this stage the cancer is managed by combinations of all treatments such as surgery, chemotherapy, radiation therapy and targeted therapies. The survival rate is about ten percent with treatment and five percent without treatment (Carlson et al., 2009).

At the time of diagnosis most cancer patients already have disseminated disease either in the form of undetectable micrometastases. The features of primary tumour cells will persist in the metastases. To survive the metastatic cascade the cancer cells should have the crucial characteristics like heterogeneity, plasticity and genetic instability. The metastatic cells evolve from the primary tumours and may develop resistance to current therapeutic approaches and establish themselves in a new microenvironment. This process is of central importance from a drug discovery perspective (Lehembre and Regenass, 2012).

In the last few years Complementary And Alternative medicine (CAM) has been developed as one of the major aspects of cancer therapy in order to alleviate the side effects of drugs and for relieving the pain in breast cancer patients (Mansky and Wallerstedt, 2006). It is essential to find other adjuvant methods for breast cancer therapy and CAM may be valuable for optimizing the conventional therapy. To find out the effect of CAM in breast cancer patients several studies were already been done. Medicinal plants can be used in combination with conventional medicine as a supportive therapy to improve Health-Related Quality of Life (HRQoL). It has been shown that the use of some types of CAM in breast cancer patients has dramatically increased and is gaining in popularity. For example as an anthroposophical medicine, mistletoe is one of the most important herbal drugs and is potentially effective against cancer. Using mistletoe extract for cancer therapy especially breast cancer is recommended due to its minimal side effects and the fact that these side effects are not life threatening (Marvibaigi et al., 2014). The natural products used in the mainstay
of cancer therapy are nature selected. Mother Nature has taken about three billion years to refine her chemistry and today we are only scratching the surface in exploring Nature’s molecular diversity (Cragg and Newman, 2013).

**Relevance and objectives of the study**

Agents that are able to block metastatic process of tumour cells have wide potential as anticancer agents therefore, it is essential to search for novel antimetastatic agents with minimal side effects. Hence there is an incitement to find out newer drugs with less toxic effects to prevent metastasis (George and Kuttan, 2016). In the present study we have taken an effort to find out the effects of selected natural products from the medicinal plants on the breast cancer development and progression in order to assess the therapeutic efficacy of these products in a catastrophic complication like metastatic cancer progression using syngeneic mouse 4T1 breast tumour model, in mice with normal immune function. To our knowledge, when introduced orthotopically this tumour model has the capacity to metastasize in a way that is similar to or can mimic the breast cancer metastasis in humans and is found to be the only system of its kind (Tao et al., 2008).

There was a strong literature background for the selection of the natural products used in the study. Source plants of these selected natural products are well renounced for its uses in the traditional medicines. These plants are already been in use for various disease treatments including cancer in the indigenous systems of traditional medicine including Ayurveda system in India. In the present study we also tried to analyse the effect of these selected products in the allied aspects of cancer treatment like anti-inflammatory, antiangiogenic, immunomodulatory or the usefulness in combination with conventional radiotherapy and chemotherapy.

We analysed the effect of selected plant products on the immune system that are not previously been examined for its immunomodulatory effects because the functional involvements of immune system in resisting or eradicating budding
neoplasias, late-stage tumours, and micrometastases have great impact on tumour growth and development (Hanahan and Weinberg, 2011).

Other important aspects we analysed were inflammation and angiogenesis that are closely related to tumour initiation and progression. Inflammation plays decisive roles in every single step of tumourigenesis, from initiation through tumour promotion, all the way to metastatic progression with significant effects on different stages of tumour development like malignant conversion, invasion etc (Grivennikov et al., 2010). Formation of new blood vessels from pre-existing vasculature is an indispensable process in the tumour initiation, invasion and metastasis (Bhat and Singh, 2008).

As part of our study we also tried to find out whether any of the selected plant products can be used in combination to the existing therapeutic approaches. Radiation therapy is one of the prime treatment modality of breast cancer. But the cancer initiating tumour cells present in the hypoxic tumour environment will form a major hurdle for the therapeutic success. Likewise chemotherapy using agents like cyclophosphamide in cancer treatment, has been shown to have bladder toxicity in the form of hemorrhagic cystitis, immunosuppression, alopecia and at high doses cardiotoxicity. Agents those are able to alleviate these negative results of conventional therapy will be of great significance in the battle against cancer.