ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of DEVELOPMENT RESEARCH

International Journal of Development Research
Vol. 4, Issue, 1, pp. 174-183, January, 2014

Full Length Research Article

CANCER DEATH RATES - NECESSITATES A NEED FOR NATURAL MEDICINE

Vidya, S., Vinola Jenifer, S., Jeyasudha, A., Babu, V., Thiyagarajan, C. and *Thiruneelakandan, G.

Department of Microbiology, Srimad Andavan Arts and Science College, Trichy, India

ARTICLE INFO

Article History:
Received 11th October, 2013
Received in revised form
30th November, 2013
Accepted 21st December, 2013
Published online 25th January, 2014

Key words:
Oncogenes,
Cancer Metastasis,
Marine source,
Apoptosis,
Microtubules,
Angiogenesis.

ABSTRACT

This review highlights the urgent need of natural medicine to counter the side effects and to reduce the death rates of cancer. The modern drugs fail to meet the expectations of the novel drug due the properties of the cancer cells. Moreover the present day treatments are patient specific rather than type of tumor stage specific, hence new diagnostic tools are needed towards the cancer diagnosis. Nowadays marine source are gaining more and more importance because of its potentiality. So search of marine drugs for new therapeutic uses is an efficient approach to drug discovery.

INTRODUCTION

Despite incredible improvements in health since 1950, there are still a number of diseases are challenging the human community, which should have been easy to solve. 36 million deaths each year are caused by non communicable diseases, such as cardiovascular disease, cancer, diabetes and chronic lung diseases. Among this cancer is one of the most daunting public health challenges. Half of all cancer deaths each year are due to lung, stomach, liver, colorectal and female breast cancers (WHO, 2004). An estimated 12.7 million new cancer cases occurred in 2008. In men, lung cancer was the most common cancer (16.5% of all new cases in men). Breast cancer was the most common cancer diagnosed in women (23% of all new cases in women).An estimated 169.3 million years of healthy life were lost globally because of cancer in 2008 (Soerjomataram *et al*., 2012). The following Figure Estimates of worldwide burden of cancer in 2008 (Ferlay *et al*., 2008) (Figure 1). The Union for International Cancer Control (UICC) and the International Agency for Research on Cancer (IARC) announced that 1.5 million lives which would be lost to cancer, could be saved per year if decisive measures are taken to achieve the World Health Organization's (WHO) '25 by 25' target; to reduce premature deaths due to non-communicable diseases (NCDs) by 25% by 2025.

Corresponding author: Thiruneelakandan, G.
Department of Microbiology, Srimad Andavan Arts and Science College, Trichy, India

Molecular Basis of Tumor Characters

In order to eradicate cancer it is mandatory to understand the molecular mechanisms; it is indispensable to identify the genes whose alterations accumulate during cancer progression as well as the genes whose expression is responsible for the acquisition of metastatic potential in cancer cells. Alterations in three types of genes are responsible for tumorigenesis: oncogenes, tumor-suppressor genes and stability genes.

Oncogenes

A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens. The first oncogenes were discovered through the study of retroviruses, RNA tumor viruses whose genomes are reverse-transcribed into DNA in infected animal cells (Varmus, 1988). Oncogenes encode proteins that control cell proliferation, apoptosis, or both. They can be activated by structural alterations resulting from mutation or gene fusion, (Konopka *et al*., 1985). Translocations and mutations can occur as initiating events (Finger *et al*., 1986) or during tumor progression, whereas

Fig. 1. worldwide burden of cancer in 2008

Table 1. Incidence and Mortality of cancer (excluding non-melanoma skin cancer) Worldwide based on 2008 Survey

Estimated numbers (thousands)	Men		Women		Both sexes	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	6617	4219	6044	3345	12661	7564
More developed regions	2964	1522	2591	1222	5555	2744
Less developed regions	3653	2697	3453	2122	7106	4819
WHO Africa region (AFRO)	253	209	318	226	571	435
WHO Americas region (PAHO)	1276	611	1233	568	2509	1179
WHO East Mediterranean region (EMRO)	214	169	214	144	428	313
WHO Europe region (EURO)	1812	1038	1610	822	3422	1860
WHO South-East Asia region (SEARO)	742	567	910	565	1652	1132
WHO Western Pacific region (WPRO)	2316	1621	1755	1016	4071	2637
IARC membership (22 countries)	3129	1655	2856	1376	5985	3031
United States of America	745	294	692	271	1437	565
China	1622	1222	1194	736	2816	1958
India	430	321	518	312	948	633
European Union (EU-27)	1324	693	1119	540	2443	1233

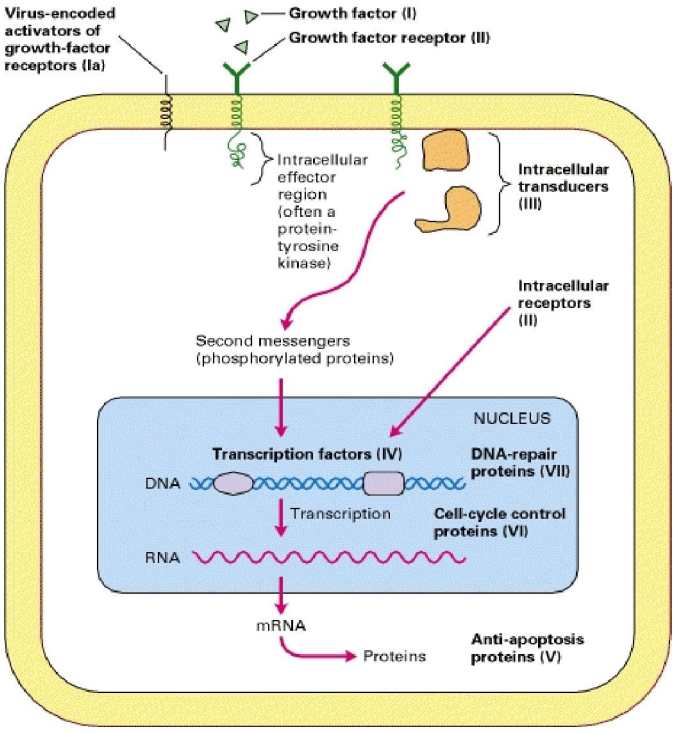

Fig. 2. Virus-encoded proteins that activate growth-factor receptors (Ia) also can induce cancer (Lodish *et al*., 2000).

amplification usually occurs during progression. There are seven types of proteins that participate in controlling cell growth. Cancer can result from expression of mutant forms of these proteins: growth factors [I], growth factor receptors [II], signal-transduction proteins [III]), transcription factors [IV], pro- or anti-apoptotic proteins [V], cellcycle control proteins [VI], and DNA repair proteins [VII]. Mutations changing the structure or expression of proteins in classes I – IV generally give rise to dominantly active oncogenes. The class VI proteins mainly act as tumor suppressors; mutations in the genes encoding these proteins act recessively to release cells from control and surveillance, greatly increasing the probability that the mutant cells will become tumor cells. Class VII mutations greatly increase the probability of mutations in the other classes. Virus-encoded proteins that activate growth-factor receptors (Ia) also can induce cancer (Lodish *et al*., 2000) Figure 2.

Tumor-Suppressor Genes

Tumor suppressor genes play a critical role in regulation when cells are allowed to divide and increase in number. When DNA damage is detected in a cell, some tumor suppressor genes can stop the cell from multiplying until the damage is repaired. Also, specific tumor suppressor genes can stimulate cells with damaged DNA to commit "cell suicide". When tumor suppressor genes don't function correctly, the cells with

DNA damage continue to divide and can accumulate further DNA damage that can eventually lead to the formation of a cancer cell.

MECHANISM OF METASTASIZING

The term “Metastasis “was first used by Joseph Claude Recamier, a French physician, in 1892 to describe the secondary growths which occurred in the brain of a woman with mammary carcinoma. Now, "metastasis" is widely defined as the ability of tumor cells to leave their site of origin and migrate to other locations in the body, where a new colony is established. Metastasis is facilitated by cell-cell interactions between tumor cells and the endothelium in distant tissues. Tumor cells in circulation interact also with platelets and leukocytes that further contribute to tumor cell adhesion, extravasation, and the establishment of metastatic lesions. Hematogenous cancer metastasis is a multistep cascade encompassing process, starting with local invasion of tumor cells at primary tumors, survival in systemic circulation, extravasation in secondary sites, and ending with establishment of growing metastatic lesions. The metastatic capacity of tumor cells correlates with their ability to exit from the blood circulation, to colonize distant organs, and to grow in distant organs (Chambers *et al*., 2002).

Poor outcomes of current therapies, in particular poor prognosis for patients in advanced stages of solid tumours, have opened the possibility that tumour cells include a population of cells responsible for the initiation of tumour development, growth and its ability to metastasize and reoccur. Because these cells share some similarities with stem cells, they are referred to as Cancer Stem Cells (CSCs). CSC are undifferentiated cells characterised by three major features: [WHO, 2004] potential to differentiate into several or all types of cells that are produced by the original tumour; [Soerjomataram *et al*., 2012] self - renewal ability; and [Ferlay *et al*., 2008] capacity to maintain the 'stem cell pool' and the most mature tumour elements for unlimited time periods (Schulenburg *et al*., 2010). CSC could originate from tissue-specific stem cells and bone marrow stem cells, and somatic cells that undergo trans-differentiation processes, or can result from the fusion or horizontal gene-transfer processes. The self-renewal and differentiation ability of CSC gives rise to all tumour cell types, and thereby produces tumour heterogeneity. This relatively new perspective, the so-called "cancer stem cell" concept, casts new light on the origins of cancer.

The relationship and differences between normal and malignant stem cells remain unclear. In many instances, normal stem cells, tumour stem cells and metastatic stem cells share some common traits. Neoplastic stem cells were indeed shown to express similar antigen pattern and to display similar functional properties in comparison with normal stem cells. Moreover, it has been shown that for the maintenance and activation of both, normal stem cells and tumour stem cells, the Wnt/beta-catenin signalling, Notch and PTEN pathways are crucial (Kitamura *et al*., 2009). Furthermore, growth of both, normal and neoplastic stem cells, is often mediated by the same cytokines (Reya *et al*., 2001). Importantly, cancer/metastatic stem cells might be discerned from embryonic stem cells by their propensity to differentiate into the cell types within a particular organ (tumour). Therefore, it is tempting to believe that tumour arises from tissue stem cells, and that cellular components bearing stem-like properties govern tumour formation. If cancer arises from rare population of cells with stem-like characteristics, then it is plausible to presume that these stem cells differ from "normal" stem cells in high rate of mutations. It is widely accepted that stem cells undergo multiple mutations that are also required for carcinogenesis, most probably due to their long-lived nature (Wicha *et al*., 2006). Deregulation of self-renewal mechanisms (e.g. Wnt/beta-catenin, Notch and Hedgehog signalling pathways), which drive the stem cell expansion, might be the early key event precipitating the formation of CSCs in the particular tissue during the onset of carcinogenesis. This hypothesis is further corroborated by the fact that oncogenes may affect different stem cells and progenitor cells resulting in phenotypic differences in tumours, whereby it was shown that transgenes encoding components of the Wnt/beta-catenin signalling pathway preferentially induce mammary cancers from progenitor cells (Li *et al*., 2003). Activation of oncogenes and inactivation of some tumour-suppressor genes as the consequence of genomic instability might drive transformation of normal stem cells to CSCs. Several genes including AKT, TRAIL and CXCL12 are recognised as candidate genes for cancer stem cell progression and latent metastasis (Zhang *et al*., 2009). At last, cancer/metastatic stem cells might exhibit higher expression levels of some genes (e.g. CXCR4, SDF1, VEGF), anti-apoptotic proteins (Bcl-2 family inhibitors of apoptosis) and transporter proteins (BCRP and P-glycoprotein), and might remain in the G0 phase accounting for their resistance to chemotherapy.

Initiation of metastasis process is inherent to CSCs, the metastatic progression should be thus studied as an independent and "parallel" process in tumorigenesis governed by the so-called EMT (epithelial to mesenchymal transition) that occurs among tumour cells. The majority of tumours are epithelial but exert mesenchymal characteristics. During tumour invasion, tumour cells move from the primary tumour site and, similarly to the cells in epithelia during normal embryonic development, lose epithelial characteristics and cell-to-cell contacts, and acquire the mesenchymal gene expression (Thiery, 2002). Such cells are then capable of invading distant sites. The changes occurring in the cell-to-cell adhesions forces as well as in the cytoskeletal cortex association to plasma membranes are therefore central to the invasion, migration and intravasation of tumour cells.

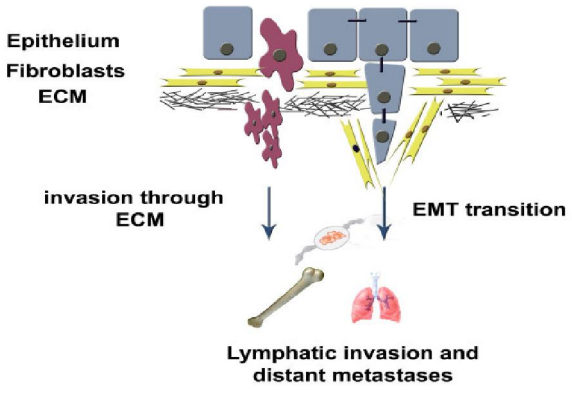

Figure 3. The epithelial-mesenchymal transition (emt) of cancer cells

According to this, epithelial cells might be somehow "induced" to become metastatic by several factors such as chemokine CCL5 (Karnoub *et al*., 2007) and transcription factors FOXC2, Twist, Snug, Snail and ZEB1 (Kurrey *et al*., 2009; Mani *et al*., 2008) that were shown to drive the EMT programme. The EMT process might account for some similarities found between embryonic stem cells and the stem cell-like traits in neoplastic cells. One must, however, always have in mind that not every EMT-inducing factor discovered will necessarily elicit a stem-like profile. The Epithelial-Mesenchymal Transition (EMT) occurs at the primary tumour site where epithelial cells lose tight junctions and apico-basal polarity. The remodelling of the cytoskeleton occurs as well. The invasion process through the Extracellular Matrix (ECM) is frequently led by so called tumour-associated fibroblasts. EMT can induce stem-cell-like properties in cells. The question still remains whether the existing cancer stem cells or rather those cells that escaped the primary tumour and acquired the stem cell like phenotype through the EMT process induce distant metastasis (Sandra *et al*., 2011).

THE MAIN STEPS IN THE FORMATION OF A METASTASIS

Metastasis is a multi-step process encompassing the [i] local infiltration of tumor cells into the adjacent tissue, [ii] transendothelial migration of cancer cells into vessels known as intravasation, [iii] survival in the circulatory system, [iv] extravasation and [v] subsequent proliferation in competent organs leading to colonization (Eger and Mikulits, 2005). Metastasis is known as a very inefficient process (Chambers *et al*., 2002) and (Mehlen and Puisieux, 2006), because a coordinated choreography of the multiple events is required to prevent failure of the complex process that otherwise runs into the elimination of emigrating cancer cells at any of the many steps on the way (Chambers *et al*., 2002). Although the dissemination from a primary tumor of 1 cm size (roughly corresponding to 1 × 109 cancer cells) can infiltrate the circulatory system with one million cancer cells per day (Fidler, 2005), subsequent colonization is very limited due to incompatible distal sites. Consequently, <0.1% of disseminated cancer cells successfully develop distal metastasis (Fidler, 1970) and (Mack and Marshall, 2010). Albeit, dormant solitary tumor cells or micrometastases, which represent undetectable cancer cell populations due to either a cell cycle arrest or a balance between proliferation and apoptosis (Mack and Marshall, 2010), might eventually outgrow to clinically detectable macrometastases many years post anti-cancer treatment (Mack and Marshall, 2010), (Almog, 2010) and (Willis *et al*., 2010). Fig represents main steps in formation of metastasis (Fidler, 2003).

DRUGS AVAILABLE IN CANCER TREATMENT AND ITS SIDE EFFECTS

Cancer treatment depends on the cancer type, where it began, and whether it's spread (plus general health and personal choices). Often more than one treatment's used. Options include surgery, immunotherapy, hormone therapy and targeted therapy, as well as: Chemotherapy, Radiotherapy and Photodynamic therapy. Table represents the drugs for Chemotherapy and its side effects.

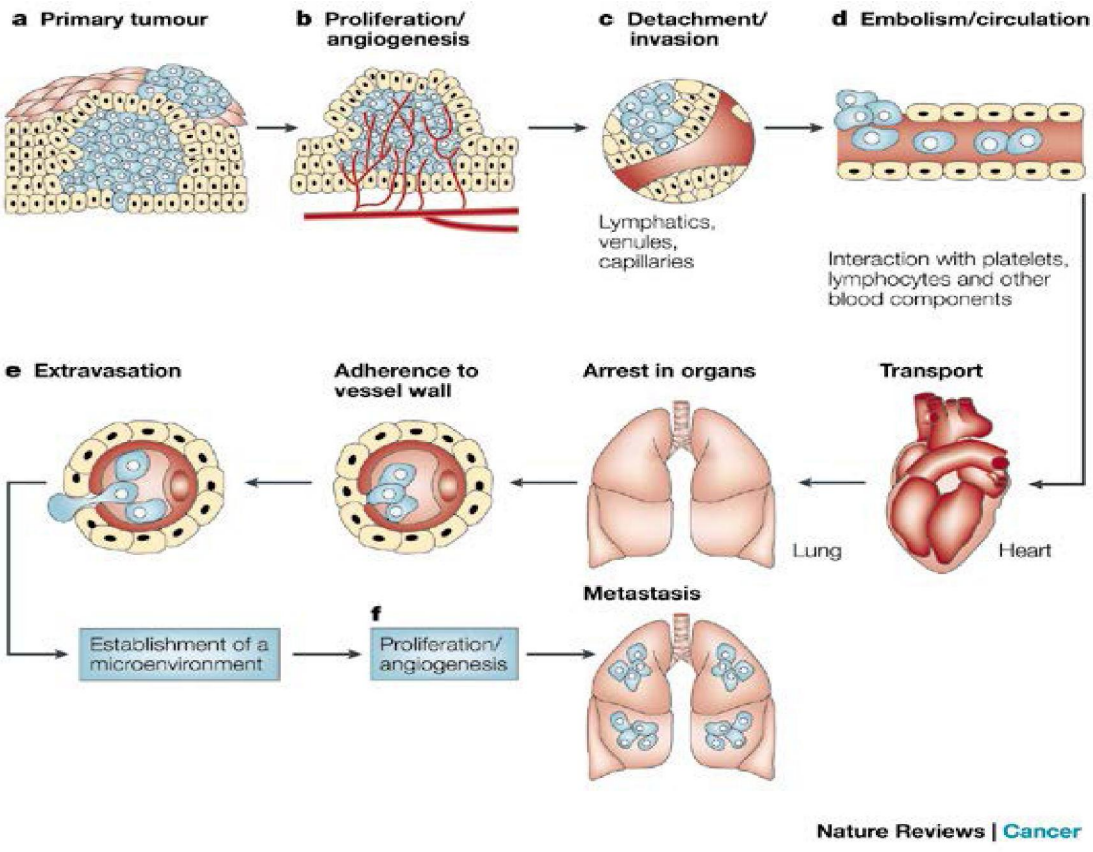

Fig. 4. Main steps in formation of metastasis

Table 2. Side effects of currently available drugs of cancer

Chemotherapy Drug	Possible Side Effects
	(Not all side effects are listed. Some of those listed may be short-term side effects; others are long-term side effects.)
carboplatin (Paraplatin) › usually given intravenously (IV) › used for cancers of the ovary, head and neck, and lung	› decrease in blood cell counts › hair loss (reversible) › confusion › nausea, vomiting, and/or diarrhea (usually a › short-term side effect occurring the first 24 to › 72 hours following treatment)
cisplatin (Platinol, Platinol-AQ) › usually given intravenously (IV) › used for cancers of the bladder, ovary, and testicles	› decrease in blood cell counts › allergic reaction, including a rash and/or labored breathing › nausea and vomiting that usually occurs for 24 hours or longer › ringing in ears and hearing loss › fluctuations in blood electrolytes › kidney damage
cyclophosphamide (Cytoxan, Neosar) › can be given intravenously (IV) or orally › used for lymphoma, breast cancer, and ovarian carcinoma	› decrease in blood cell counts › nausea, vomiting, abdominal pain › decreased appetite › hair loss (reversible) › bladder damage › fertility impairment › lung or heart damage (with high doses) › secondary malignancies (rare)
doxorubicin (Adriamycin) › given intravenously (IV) › used for breast cancer, lymphoma, and multiple myeloma	› decrease in blood cell counts › mouth ulcers › hair loss (reversible) › nausea and vomiting › heart damage
etoposide (VePesid) › can be given intravenously (IV) or orally › used for cancers of the lung, testicles, leukemia, and lymphoma	› decrease in blood cell counts › hair loss (reversible) › nausea and vomiting › allergic reaction › mouth ulcers › low blood pressure (during administration) › decreased appetite › diarrhea and abdominal pain › bronchospasm › flu-like symptoms
fluorouracil (5-FU) › given intravenously (IV) › used for cancers of the colon, breast, stomach, and head and neck	› decrease in blood cell counts › diarrhea › mouth ulcers › photosensitivity › dry skin
gemcitabine (Gemzar) › given intravenously (IV) › used for cancers of the pancreas, breast, ovary, and lung	› decrease in blood cell counts › nausea and vomiting › fever and flu-like symptoms › rash
irinotecan (Camptosar) › given intravenously (IV) › used for cancers of the colon and rectum	› decrease in blood cell counts › diarrhea › hair loss (reversible)
methotrexate (Folex, Mexate, Amethopterin) › may be given intravenously (IV), intrathecally (into the spinal column), or orally › used for cancers of the breast, lung, blood, bone, and lymph system	› decrease in blood cell counts › nausea and vomiting › mouth ulcers › skin rashes and photosensitivity › dizziness, headache, or drowsiness › kidney damage (with a high-dose therapy) › liver damage › hair loss (reversible) › seizures
paclitaxel (Taxol) › given intravenously (IV) › used with cancers of the breast, ovary, and lung	› decrease in blood cell counts › allergic reaction › nausea and vomiting › loss of appetite › change in taste › thin or brittle hair › joint pain (short term) › numbness or tingling in the fingers or toes
topotecan (Hycamtin) › given intravenously (IV) › used for cancers of the ovary and lung	› decrease in blood cell counts › diarrhea › hair loss (reversible) › nausea and vomiting
vincristine (Oncovin, Vincasar PFS) › usually given intravenously (IV) › used for leukemia and lymphoma	› numbness or tingling in the fingers or toes › weakness › loss of reflexes › jaw pain › hair loss (reversible) › constipation or abdominal cramping
vinblastine (Velban) › given intravenously (IV) › used for lymphoma and cancers of the testis and head and neck	› decrease in blood cell counts › hair loss (reversible) › constipation or abdominal cramping › jaw pain › numbness or tingling in the fingers or toes

Doxorubicin is a common chemotherapeutic drug used to treat solid and hematopoietic tumors. Its use is limited by the major side effect of cardiac toxicity (Singal and Iliskovic, 1998), which has not been effectively prevented by pharmacologic intervention with cardioprotective drugs (Gharib and Burnett, 2002; Wojtacki *et al*., 2000). The mechanism by which doxorubicin or its metabolites cause chronic cardiomyopathy is not fully understood. Hypotheses regarding the mechanism of cardiac toxicity include perturbation of calcium homeostasis, formation of iron complexes, generation of radical oxygen species, mitochondrial dysfunction, and damage to cell membranes (Mordente *et al*., 2001). Gemcitabine (2',2'-difluoro-2'deoxixitidine) is a chemotherapatic agent and an antimetabolite (Aapro *et al*., 1998). Alone or inside the combinations, it is used for non small cell lung cancer, pancreas, bladder, over and breast cancer. It has been used since 1989. Generally it has simple side effects. These are; flu-like symptoms, nausea, vomitting and also bone marrow depression may be seen depending on the dosage (Aapro *et al*., 1998; Vander EIs and Miller, 1998; Maniwa *et al*., 2003; Joerger *et al*., 2002). First pulmonary toxicity is mentioned in 1997 (Pavlakis *et al*., 1997).

In this system the most common side effect is mild and temporary dyspnea (Aapro *et al*., 1998; Joerger *et al*., 2002; Sabria-Trias *et al*., 2002; Detterbeck *et al*., 2003). It is recorded in 8-10% of the cases (Sabria-Trias *et al*., 2002; Detterbeck *et al*., 2003). Acute Respiratory Distress Syndrome (ARDS) is also reported. Some of these cases may be fatal (Pavlakis *et al*., 1997). Long term side effects are reported as interstitial covers (Joerger *et al*., 2002). This time period is 3-4 months (Maniwa *et al*., 2003; Joerger *et al*., 2002). As the clinical usage of gemcitabine increased, the side effects become more important. gemcitabine was given to a patient with pancreas cancer and the side effects occured after a year were reported like dyspnea, interstitial infiltration and nonspecific pneumonia which were seen with biopsy (Nuri Tutar *et al*., 2012). The use of increasingly aggressive methods of cancer treatment during the last 20 years has brought clinical attention to the need for more effective management of pain, nausea, and other aversive side effects of state-of-the-art cancer therapy.

Despite improvements in the efficacy of antiemetics, nausea and vomiting associated with chemotherapy continue to be common problems for many cancer patients (Morrow *et al*., 1998; Watson *et al*., 1998) Chemotherapy affects normal as well as cancerous cells. Side effects of chemotherapy depend largely on the specific drugs and the dose (amount of drug given). Common side effects of chemotherapy for lung cancer include nausea and vomiting, hair loss, mouth sores, and fatigue. Radiation therapy, like chemotherapy, affects normal as well as cancerous cells. Side effects of radiation therapy for lung cancer depend mainly on the part of the body that is treated and the treatment dose. Common side effects of radiation therapy are a dry, sore throat; difficulty swallowing; fatigue; skin changes at the site of treatment; and loss of appetite. Patients receiving radiation to the brain may have headaches, skin changes, fatigue, nausea and vomiting, hair loss, or problems with memory and thought processes. Photodynamic therapy makes the skin and eyes sensitive to light for 6 weeks or more after treatment. Patients are advised to avoid direct sunlight and bright indoor light for at least 6 weeks. If patients must go outdoors, they need to wear protective clothing, including sunglasses. Other temporary side effects of PDT may include coughing, trouble swallowing, and painful breathing or shortness of breath.

INABILITY OF MODERN MEDICINE:

Cancer is still a challenging disease for human community mainly because of the inability of the modern medicine. The modern drugs fail to meet the expectations of the novel drug which has a potentiality to kill cancer cells without side effects. We can state several reasons for the inability of modern medicine. One of the most challenging aspects of treating cancer with chemotherapy is the development of resistance to the cytotoxic agents. Drug resistance ultimately leads to the ineffectiveness of the agent where there is nominal clinical benefit compared to the side effects of the treatment. In most of the cases no proper diagnostic is done. This may lead to more side effects and also failure of a particular drug. Global scale proteomics studies undoubtedly revealed specific metastatic markers often related to cell-signaling processes. However they proved to be patient specific rather than type of tumor stage specific, which necessitates a need for individual therapeutic approach towards each patient.

Another main reason is the increasing rate of failure in drug designs over the past few decades is mainly due to the dominant assumption which has historically relied upon particular families of ''druggable''proteins (Paolini *et al*., 2006; Hu and Agarwal, 2009; Scheiber *et al*., 2009; Hopkins, 2008; Yildirim *et al*., 2007).The continuing decline of drug discovery productivity has been documented by many studies. In 2006, only 22 new molecular entities were approved by the Food and Drug Administration (FDA) despite research and development expenditures of $93 billion USD by biotech companies and large pharmaceutical companies, and this low productivity has not improved since (Steven *et al*., 2010). From discovering, developing to bringing one new drug to market, clinical trials are the most expensive step, accounting for 63% of the overall cost (Lawrence, 2006). The cancer cells have peculiar characters such as behaving like stems cells, acquiring mesenchymal characteristics during metastasis, drug resistance property also leads to the inability of modern medicine.

NECESSITY OF NATURAL MEDICINE

To counter the development of the resistance, side effects, metastasis property, mesenchymal characteristics of the cancer cells we are urgently in the need of potential natural drugs which cause no side effects. Marine floras, such as bacteria, actinobacteria, cyanobacteria, fungi, microalgae, seaweeds, mangroves, and other halophytes are extremely important oceanic resources, constituting over 90% of the oceanic biomass. They are taxonomically diverse, largely productive, biologically active, and chemically unique offering a great scope for discovery of new anticancer drugs. The marine floras are rich in medicinally potent chemicals predominantly belonging to polyphenols and sulphated polysaccharides. The chemicals have displayed an array of pharmacological properties especially antioxidant, immune stimulatory, and anti tumour activities. (Boopathy and Kathiresan, 2010). The discovery of the bio-regulatory role of different endogenous

Table 2. Some of the marine floral derivatives and their anticancer activities

Marine flora	Chemical	Biological activity	Reference
	Microbial flora		
Microcystis aeruginosa	MicroviridinToxin BE-4, Siatoxin	Antibiotic, anticancer	[86, 87]
Streptomyces peucetius	Daunorubicin	Anticancer activities on acute myeloid leukemia and acute lymphocytic leukemia	[88]
	Algal flora		
Cyanobacteria *Nostoc linckia* and *Nostoc spongiaeforme* var. *tenue*	Borophycin	Cytotoxicity against human epidermoid carcinoma (LoVo) and human colorectal adenocarcinoma activity	[89]
Cyanobacteria	Apratoxins	Inhibit a variety of cancer cell lines	[90]
Nostoc linckia	Cyptophycin 1	Cytotoxicity against human tumor cell lines and human solid tumors	[91]
Nostoc spongiaeforme	Cryptophycin 8	Greater therapeutic efficiency and lower toxicity than cryptophycin 14 *in vivo*	92]
Stylopodium sp.	Stypoldione	Cytotoxic	[93]
Chondria sp.	Condriamide A	Cytotoxicity	[94]
Caulerpa sp.	Caulerpenyne	Cytotoxicity, anticancer, antitumour, and antiproliferating activity	[95–97]
Cystophora sp.	Meroterpenes and Usneoidone	Antitumour	[98]
Symploca sp.	Largazole	Antiproliferative activity	[99]
Lyngbya boulloni	apratoxin A	Cytotoxicity to adenocarcinoma	[100]
Leptolyngbya sp.	coibamide A	Cytotoxicity against NCIH460 lung and mouse neuro-2a cells	[101]
Stigonema sp.	Scytonemin	Antiproliferative and anti-inflammatory activities	[102]
Acanthophora spicifera	Crude	Tumoricidal activity on Ehrlich's ascites carcinoma cells developed in mice	[103, 104]
Acanthophora spicifera	Crude	Antioxidants and inhibiting cancer cell proliferation	[103, 104]
Palmaria palmata	Phloroglucinol and its polymers, namely, eckol (a trimer), phlorofucofuroeckol A (a pentamer), dieckol, and 8,8′-bieckol (hexamers)	Antioxidant activity of the phlorotannins	[105]
Eisenia bicyclis	Phloroglucinol and its polymers, namely eckol (a trimer), phlorofucofuroeckol A (a pentamer), dieckol, and 8,8′-bieckol (hexamers)	Antioxidant activity of the phlorotannins	[106, 107]
Sargassum thunbergii	Crude	Antitumour activity, inhibition of tumour metastasis in rat mammary adeno carcinoma cell (13762 MAT)	[108,109]
Ascophyllum nodosum	Fucoidan	Antiproliferative antitumour, anticancer, antimetastatic, and fibrinolytic	[110, 111]
	Mangroves and other coastal plants		
Ceriops decandra	Lignins	Antioxidant	[112]
Ceriops decandra	Mangrove tea	Anticancer	[113]
Acanthus ilicifolius	Ribose derivatives of benzoxazoline	Anticancer	[114, 115]
Calophyllum inophyllum	Xanthone, biflavonoids, benzophenones, neoflavanoids, and coumarin derivatives	Anticancer, antitumour, and lipid peroxidation	[116, 117]
Excoecaria agallocha	Diterpenes exhibited remarkable antitumour promoting activity *in vivo* on two-stage carcinogenesis test of tumour	Antitumour activity of methanolic extract based on three assays: (i) DPPH radical scavenging, (ii) linoleic acid oxidation assay, and (iii) oxidative cell death assay	[118]

peptides in the organism as well as the understanding of the molecular mechanisms of action about some new bioactive peptides obtained from natural sources on specific cellular targets, contributed to developing peptides as promising lead drug candidates. Recently, marine peptides have opened a new perspective for pharmaceutical developments (de Vries and Beart, 1995). Marine peptides induce cell death via the following pathways, apoptosis, affecting the tubulin-microtubule equilibrium and angiogenesis pathway. Apoptosis as a form of programmed cell death is one of the major mechanisms of cell death in response to cancer therapies (Reed, 2000). Also, apoptosis is a naturally occurring and evolutionarily conserved process by which cells that are no longer useful are directed to their deaths (Danial and Korsmeyer, 2004). Apoptosis plays an indispensable role and is a fundamental process in development, physiology and homeostasis (Thompson, 1995; Rowinsky, 2005; Call *et al*., 2008; Iannolo *et al*., 2008). Its deregulation, i.e., either loss of pro-apoptotic signals or gain of anti-apoptotic signals, can lead to a variety of pathological conditions such as cancer initiation, promotion and progression or result in treatment failures (Burz *et al*., 2009; Fulda and Pervaiz, 2005). As apoptosis does not usually trigger inflammatory or immune response, it becomes a preferable way of cancer cell death during cancer treatments. As such, modulation of apoptotic pathways and selective induction of apoptosis by chemical agents are likely to be a promising approach for cancer therapy (Call *et al*., 2008; Ghobrial *et al*., 2005; Eberle *et al*., 2007; Ziegler and Kung, 2008; Cheng *et al*., 2009; Lin *et al*., 2010; von Schwarzenberg and Vollmar, 2013). In mammals, there are two major signaling systems that result in the activation of caspases, the extrinsic death receptor pathway (Abe *et al*., 2000; Ozoren and El-Deiry, 2003; Peter and Krammer, 2003; Thorburn, 2004) and the intrinsic mitochondrial pathway (Kroemer, 2003; Gupta *et al*., 2009). These two pathways include many cross talks between them. There is a long list of pro- or anti-apoptotic molecules that can trigger or regulate apoptosis. Therefore, developing anticancer peptides that

target these molecules has become an important strategy for anticancer therapies. Microtubules are intracellular organelles formed from the protein tubulin. These organelles have a number of essential cellular functions including chromosome segregation, the maintenance of cell shape, transport, motility, and organelle distribution. Drugs that affect the tubulin-microtubule equilibrium are effective anticancer drugs (Hadfield *et al*., 2003). Tubulin binding molecules have generated considerable interest after the successful introduction of the taxanes into clinical oncology and the widespread use of the Vinca alkaloids Vincristine and Vinblastine. These compounds inhibit cell mitosis by binding to the protein tubulin in the mitotic spindle and preventing polymerization into the microtubules (MTs). This mode of action is also shared with other natural agents. Therefore, there is a strong need to design and develop new natural analogs as antimitotic agents to interact with tubulin at sites different from those of Vinca alkaloids and taxanes (Islam and Iskander, 2004). Dolastatin 10, a linear pentapeptide containing several unique amino acid subunits, was derived from the marine mollusk Dolabella auricularia; it is the most potent member of a large class of related peptides (Pettit *et al*., 1981; Luesch *et al*., 2001).

Vitilevuamide, a bicyclic 13 amino acid peptide, was isolated from two marine ascidians, Didemnum cuculiferum and Polysyncranton lithostrotum. Vitilevuamide was strongly positive in a cell-based screen for inhibitors of tubulin polymerization, displaying activity in vivo against P388 lymphocytic leukemia. Vitilevuamide exhibits non-competitive inhibition of Vinblastine binding to tubulin. Colchicine binding to tubulin was stabilized in the presence of Vitilevuamide. GTP binding was also found to be weakly affected by the presence of Vitilevuamide, suggesting the possibility that Vitilevuamide inhibits tubulin polymerization via an interaction at a unique site (Edler *et al*., 2002). Angiogenesis, the formation of new blood vessels, is a complex multistep process, including the destabilization of established vessel, endothelial cell proliferation, migration and new tube formation. Angiogenesis plays an important role in the growth, invasion and metastasis of most solid tumors. Both tumor growth and metastasis depend on the expansion of host vasculatures into tumors through angiogenesis (Folkman, 1992; Folkman, 1995; Bouck *et al*., 1996; Folkman, 1997).

Vascular Endothelial Growth Factor (VEGF) and its receptor, VEGFR-2 (Flk-1/KDR), play a key role in tumor angiogenesis (Ferrara, 2000; Ferrara *et al*., 2003). Tumor growth may be inhibited via blocking the VEGF-VEGFR-2 pathway and downstream intracellular signaling. Neovastat (AE-941) is a derivative of shark cartilage extract. Rather than being a specific monomolecular compound, AE-941 is a defined standardized liquid extract comprising the <500 kDa fraction from the cartilage of shark, *Squalus acanthias*, directly inhibits tumor cell growth and angiogenesis (Lee and Langer, 1983; Dupont *et al*., 1999). Lee *et al*. founded that Neovastat was mediated via inhibition of VEGF and HIF2 alpha pathway**.** Mice treated with Neovastat had significantly reduced inflammatory cell count in BAL fluid. Furthermore, Mice treated with Neovastat showed significantly reduced VEGF and HIF2 alpha expression on lung tissue (Lee *et al*., 2007). Although the underling mechanism of source specificity of the marine peptides is unclear, it is conceivable that the special environment of marine offers the diversity of marine natural products. It is also possible that the organisms, which may contain the peptides, have not been found since the study of marine peptides is still in its infancy. Compared with the peptides found from other sources, there is more diversity on the style/classes of marine peptides; more cyclic peptides or depsipeptide were found in marine organism. These marine peptides seem to be very useful and promising for biomedical research. There is no doubt that the diversity of marine peptides in its structure and mode of action provide a rich source for the design of very specific and potent new pharmaceuticals for a wide variety of diseases (Lan-Hong Zheng *et al*., 2011). So search of marine drugs for new therapeutic uses is an efficient approach to drug discovery

Conclusion

This review highlights the importance of cancer as a major healthcare issue in terms of mortality and morbidity. Even though there are several therapies available for cancer still it remains incurable because of its properties, discussed earlier. Agency for research on cancer, International Agency for Research on Cancer (IARC) announced that 1.5 million lives which would be lost due to cancer could be saved if decisive measures would have taken. We need to urge the discovery of a potential drug from marine source to counter the development of resistance of the cancer cells to achieve the world health organization's '25 by 25' target which focus premature death by cancer.

Acknowledgement

We are very thankful to UGC, Govt. of India, New Delhi, India and Srimad Andavan Arts and Science College, Trichy, India for providing the necessary facilities.

REFERANCE

Aapro MS, Martin C, Hatty S. Gemcitabine-a safety review. Anticancer Drugs 1998, pp.191-201.

Abe K, Kurakin A, Mohseni-Maybodi M, Kay B, Khosravi-Fa R. The complexity of TNF-related apoptosis-inducing ligand. Ann. N. Y. Acad. Sci. 2000, 926, 52–63.

Almog N. Molecular mechanisms underlying tumor dormancy. Cancer Lett.2010, pp. 139–146

Boopathy N S and Kathiresan K. Anticancer Drugs from Marine Flora: An Overview. J Oncol. 2010; 2010: 214186.

Bouck, N, Stellmach, V, Hsu, S.C. How tumors become angiogenic. Adv. Cancer Res. 1996, 69, 135–174.

Burz C, Berindan-Neagoe I, Balacescu O, Irimie A. Apoptosis in cancer: Key molecular signaling pathways and therapy targets. Acta Oncol. 2009, 48, 811–821.

Call J.A, Eckhardt S.G, Camidge D.R. Targeted manipulation of apoptosis in cancer treatment. Lancet Oncol. 2008, 9, 1002–1011.

Chambers A. F, Groom A. C, and Mac Donald I. C. Dissemination and growth of cancer cells in metastatic sites. Nature Reviews Cancer, 2002 .vol. 2, no. 8, pp. 563–572,

Chambers A.F, Groom A.C, MacDonald I.C. Dissemination and growth of cancer cells in metastatic sites Nat. Rev. Cancer.2002, pp. 563–572

Cheng L, Wang X, Zhang J, Zhang S.B, Zheng S.Q and Zheng J. Targeting apoptosis signaling pathways in cancer therapy. Zhonghua Bing Li Xue Za Zhi 2009, 38, 639–642.Mar. Drugs 2011, 9 1852

Danial N.N, Korsmeyer S.J. Cell death: Critical control points. Cell. 2004 Jan 23; 116(2):205-19

de Vries D.J, Beart P.M. Fishing for drugs from the sea: Status and strategies. Trends Pharmacol. Sci. 1995, 16, 275–279.

Detterbeck FC, Jones DR, Kernstine KH, Naunheim KS;American College of Physicians. Lung cancer. Special treatment issues. Chest. 2003, pp.244S-58S.

Dupont, E, Brazeau, P, Juneau, C. Extracts of shark cartilage having an anti-angiogenic activity and an effect on tumor regression: Process of making thereof. *U.S. Patents 5,985,839*, 16 November 1999.

Eberle J, Fecker, L.F, Forschner T, Ulrich, C, Rowert-Huber J, Stockfleth E. Apoptosis pathways as promising targets for skin cancer therapy. Br. J. Dermatol. 2007, 156S, 18–24.

Edler, M.C, Fernandez, A.M, Lassota, P, Ireland, C.M, Barrows, L.R. Inhibition of tubulin polymerization by vitilevuamide, a bicyclic marine peptide, at a site distinct from colchicine, the *Vinca* alkaloids, and dolastatin 10. *Biochem. Pharmacol.* 2002, *63*, 707–715.

Eger A, Mikulits W Models of epithelial–mesenchymal transition.Drug Discovery Today.2005, pp. 57–63

Ferlay j, Shin H R, Bray F, Forman D, Mathers D and Maxwell D. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008 nt. J. Cancer: 127, 2893–2917

Ferrara, N, Gerber, H.P, LeCouter, J. The biology of VEGF and its receptors. *Nat. Med.* 2003, *9*, 669–676.

Ferrara, N. VEGF: An update on biological and therapeutic aspects. *Curr. Opin. Biotechnol.* 2000, *11*, 617–624.

Fidler I.J. Metastasis: quantitative analysis of distribution and fate of tumor embolilabeled with 125 I-5-iodo-2′-deoxyuridine J. Natl. Cancer Inst.1970, pp. 773–782

Fidler I.J. Cancer biology is the foundation for therapy. Cancer Biol. Ther.2005, pp. 1036–1039

Fidler I.J. Nature Reviews Cancer 3: 73: 2003

Finger LR, Harvey RC, Moore RCA, Showe LC, Croce CM. A common mechanism of chromosomal translocation in T- and B-cell neoplasia. Science. 1986; 234:982-5.

Folkman, J. Angiogenesis and angiogenesis inhibition: An overview. EXS 1997, 79, 1–8.

Folkman, J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat. Med. 1995,1, 27–31.

Folkman, J. The role of angiogenesis in tumor growth. Semin. Cancer Biol. 1992, 3, 65–71.

Fulda S, Pervaiz S. Apoptosis signaling in cancer stem cells. Int. J. Biochem. Cell Biol. 2009,42, 31–38.

Gharib M. I, and Burnett A. K. Chemotherapy-induced cardiotoxicity: current practice and prospects of prophylaxis. Eur. J. Heart Fail. 2002, pp. 235–242

Ghobrial I.M, Witzig T.E, Adjei A. A. Targeting apoptosis pathways in cancer therapy. CA Cancer J. Clin. 2005, 55, 178–194.

Gupta S, Kass G.E, Szegezdi E, Joseph B. The mitochondrial death pathway: A promising therapeutic target in diseases. J. Cell. Mol. Med. 2009, 13, 1004–1033.

Hadfield J.A, Ducki S, Hirst N, McGown A.T. Tubulin and microtubules as targets for anticancer drugs. Prog. Cell Cycle Res. 2003, 5, 309–325.

Hopkins AL Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol. 2008, 4: 682–690.

Hu G, Agarwal P. Human disease-drug network based on genomic expression profiles. PLoS One. 2009 Aug 6; 4(8):e6536.

Iannolo G, Conticello C, Memeo L, de Maria R. Apoptosis in normal and cancer stem cells.Crit. Rev. Oncol. Hematol. 2008, 66, 42–51.

Islam M.N, Iskander M.N. Microtubulin binding sites as target for developing anticancer agents. Mini Rev. Med. Chem. 2004, 4, 1077–1104.

Joerger M, Gunz A, Speich R, Pestolazzi BC. Gemcitabine related pulmoner toxicity: case series. Swiss Med Wkly. 2002, pp.17-20

Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, and Weinberg RA: Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature* 2007, 449:557-563.

Kitamura H, Okudela K, Yazawa T, Sato H, Shimoyamada H: Cancer stem cell: implications in cancer biology and therapy with special reference to lung cancer. *Lung Cancer.* 2009, 66:275-281.

Konopka JB, Watanabe SM, Singer JW, Collins SJ, Witte ON. Cell lines and clinical isolates derived from Ph1-positive chronic myelogenous leukemia patients express c-abl proteins with a common structural alteration. Proc Natl Acad Sci U S A 1985;82:1810-4

Kroemer G. Mitochondrial control of apoptosis: An introduction. *Biochem. Biophys. Res.Commun.*2003, 304, 433-435.

Kurrey NK, Jalgaonkar SP, Joglekar AV, Ghanate AD, Chaskar PD, Doiphode RY, Bapat SA: Snail and slug mediate radioresistance and chemoresistance by antagonizing p53-mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells. Stem Cells. 2009, 2059-68.

Lan-Hong Zheng, Yue-Jun Wang, Jun Sheng, Fang Wang, Yuan Zheng 1, Xiu-Kun Lin, Mi Sun. Antitumor Peptides from Marine Organisms. Mar. Drugs 2011, pp.1840-1859

Lawrence S .Drug output slows in 2006. Nature Biotechnology .2007, 25, 1073

Lee, A, Langer, R. Shark cartilage contains inhibitors of tumor angiogenesis. Science. 1983, *221*, 1185–1187.

Lee, S.Y, Chung, S.M. Neovastat (AE-941) inhibits the airway inflammation via VEGF and HIF-2 alpha suppression. Vasc. Pharmacol. 2007, *47*, 313–318.

Li Y, Welm B, Podsypanina K, Huang S, Chamorro M, Zhang X, Rowlands T, Egeblad M, Cowin P, Werb Z, Tan LK, Rosen JM, and Varmus HE: Evidence that transgenes encoding components of the Wnt signaling pathway preferentially induce mammary cancers from progenitor cells. Proc Natl Acad Sci USA. 2003, 100:15853-15858.

Lin X, Liu M, Hu C, Liao D.J. Targeting cellular proapoptotic molecules for developing anticancer agents from marine sources. Curr. Drug. 2010, pp. 708-715(8)

Lodish H, Berk A, Zipursky SL, *et al*. New York: W. H. Freeman; 2000. Molecular Cell Biology. 4th edition.

Luesch, H, Moore, R.E,Paul, V.J, Mooberry, S.L, Corbett, T.H. Isolation of Dolastatin 10 from the Marine Cyanobacterium Symploca Species VP642 and Total Stereochemistry and Biological Evaluation of Its Analogue Symplostatin 1. *J. Nat. Prod.* 2001, *64*, 907–910.

Mack G.S, Marshall A. Lost in migration Nat Biotechnol. 2010, pp.214-29

Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M, Campbell LL, Polyak K, Brisken C, Yang J, and Weinberg RA: The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell 2008, 133:704-715.

Maniwa K,Tanaka E, *et al*. An autopsy case of acute pulmonary toxicity associated with Gemcitabine. Intern Med. 2003, pp.1022-5.

Mehlen P, Puisieux A .Metastasis: a question of life or death. Nat. Rev. Cancer, 2006, pp. 449–458.

Mordente A, Meucci E, Martorana G. E, Giardina B, and Minotti G. Human heart cytosolic reductases and anthracycline cardiotoxicity. IUBMB Life. 2001, pp. 83–88.

Morrow GR, Roscoe JA, Hynes HE, Flynn PJ, Pierce HI, Burish T. Progress in reducing anticipatory nausea and vomiting: a study of community practice. Support Care Cancer 1998; 6:46–50.

Nuri Tutar, Hakan Buyukoglan, İnci Gülmez, Fatma Sema Oymak, Ramazan Demir. Gemcitabine Induced Pulmonary Toxicity with Late Onset. Eur J Gen Med. 2012;9(3):208-210

Ozoren, N, El-Deiry, W.S. Cell surface Death Receptor signaling in normal and cancer cells.Semin. Cancer Biol. 2003, 13, 135–147.

Paolini GV, Shapland RH, van Hoorn WP, Mason JS, Hopkins. AL Global mapping of pharmacological space. Nat Biotechnol . 2006, 24: 805–815.

Pavlakis N, Bell DR, Millward MJ, Levi JA. Fatal pulmonary toxicity resulting from treatment with Gemcitabine. Cancer. 1997, pp.286-91.

Peter, M.E, Krammer P.H. The CD95 (APO-1/Fas) DISC and beyond. Cell Death Differ. 2003, 10, 26–35.

Pettit, G.R, Kamano, Y,Fujii, Y, Herald, C.L, Inoue, M, Brown, P, Gust, D,Kitahara, K.;Schmidt, J.M, Doubek, D.L, Michel, C. Marine animal biosynthetic constituents for cancer chemotherapy. *J. Nat. Prod.* 1981, *44*, 482–485.

Reed J.C. Mechanisms of apoptosis. Am. J. Pathol. 2000, 157, 1415–1430.

Reya T, Morrison SJ, Clarke MF, Weissman IL: Stem cells, cancer, and cancer stem cells. Nature 2001, 414:105-111

Rowinsky, E.K. Targeted induction of apoptosis in cancer management: The emerging role of tumor necrosis factor-related apoptosis-inducing ligand receptor activating agents. J. Clin. Oncol.2005, 23, 9394–9407.

Sabria-Trias J, Bonnaud F, Sioniac M. Severe interstitial pneumonitis related to Gemcitabine. Rev Mal Respir. 2002, pp.645-7.

Sandra Kraljevic P, Mirela S, Hrvojka B, Sime S and Kresimir P. *Metastasis: new perspectives on an old problem.* Molecular Cancer 2011, 10:22

Scheiber J, Chen B, Milik M, Sukuru SC, Bender A, Mikhailov D, Whitebread S, Hamon J, Azzaoui K, Urban L, Glick M, Davies JW, Jenkins JL. Gaining insight into off-target mediated effects of drug candidates with a comprehensive systems chemical biology analysis. J Chem Inf Model. 2009 Feb; 49(2):308-17

Schulenburg A, Bramswig K, Herrmann H, Karlic H, Mirkina I, Hubmann R, Laffer S, Marian B, Shehata M, Krepler C, Pehamberger H, Grunt T, Jager U, Zielinski CC, Valent P: Neoplastic stem cells: current concepts and clinical perspectives. *Crit Rev Oncol Hematol*. 2010, 76:79-98.

Singal P. K and Iliskovic N. Doxorubicin-induced cardiomyopathy. N. Engl. J. Med., 1998.pp. 900–905,

Soerjomataram I,Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, Bray F. Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer. Lancet. BMC Med Res Methodol. 2012; 12: 125.

Steven M. P, Daniel S, Christopher T. D, Charles C. P, Bernard H. M, Stacy R. L & Aaron L. S. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery .2010, 203-214.

Thiery JP. Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer 2002, 2:442-454.

Thompson C.B. Apoptosis in the pathogenesis and treatment of disease. Science 1995, 267, 1456–1462.

Thorburn, A. Death receptor-induced cell killing. Cell Signal 2004, 16, 139–144.20.

Vander EIs NJ, Miller V. Succesful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy. Chest. 1998, pp.1779-81.

Varmus H. Retroviruses. Science 1988; 240:1427–35.

von Schwarzenberg K, Vollmar A.M. Targeting apoptosis pathways by natural compounds in cancer: Marine compounds as lead structures and chemical tools for cancer therapy. Cancer Lett. Cancer Lett. 2013. pp.295-303

Watson M, Meyer L, Thomson A, Osofsky S. Psychological factors predicting nausea and vomiting in breast cancer patients on chemotherapy. Eur J Cancer. 1998; 34:831–7

Wicha MS, Liu S, Dontu G: Cancer stem cells: an old idea--a paradigm shift. *Cancer Res.* 2006, 66:1883-1890.

Willis L, Alarcón T, Elia G, Jones JL, Wright NA, Tomlinson IP, Graham TA, Page KM. Breast cancer dormancy can be maintained by small numbers of micrometastases. Cancer Res. 2010 pp.4310-7.

Wojtacki J, Lewicka-Nowak E., and Lesniewski-Kmak K. Anthracycline-induced cardiotoxicity: clinical course, risk factors, pathogenesis, detection and prevention–review of the literature. Med. Sci. Monit. 2000, pp. 411–420,

World Health Organization. The Global Burden of Disease: 2004 Update. Geneva: World Health Organization; 2008.

Yildirim MA, Goh KI, Cusick ME, Barabasi AL, Vidal M Drug-target network. Nat Biotechnol .2007, 25: 1119–1126.

Zhang XH, Wang Q, Gerald W, Hudis CA, Norton L, Smid M, Foekens JA, Massague J: Latent bone metastasis in breast cancer tied to Src-dependent survival signals. *Cancer Cell.* 2009, 16:67-78.

Ziegler D.S, Kung A.L. Therapeutic targeting of apoptosis pathways in cancer. Curr. Opin. Oncol. 2008, 20, 97–103.

****