POTENTIAL NATURAL PRODUCTS WITH ANTICANCER PROPERTIES AND THEIR APPLICATIONS

BALABHASKAR R¹*, RAJENDRA KUMAR A², SELVARAJAN S³, FARIDHA A², GAYATHRI GUNALAN²

¹Department of Biochemistry, SRM Arts and Science College, Kattankulathur, Kanchipuram, Tamil Nadu, India. ²Siddha Regional Research Institute (CCRS), Kuyavarpalayam, Puducherry, India. ³Central Council for Research in Siddha, Arumbakkam, Chennai, Tamil Nadu, India.

ABSTRACT

Natural products continue to be a source for the discovery of drugs and drug leads even from ancient period. 80% of drug molecules have been obtained from either natural products or derivatives of the natural product. It has been found that the concept of a single drug for treating single disease may become outdated in the near future and the need of polyherbal formulations, as an alternate remedy is under investigation. Medicinal and aromatic plants contain biologically important phytochemicals, which have known curative properties. They are found as secondary metabolites in plants. Plants also contain certain other compounds that moderate the effects of the active ingredients. Medicinal and aromatic plants have their own contribution toward the treatment of both noncommunicable and communicable diseases. A survey done by the WHO indicates that a majority of the world population tends to use plants for treating diseases. Cancer, the second largest cause of death after cardiovascular disease accounts for about 3500 million people globally. Due to the serious side effects of synthetic chemopreventive agents, research is going onto investigate the nature derived chemopreventive agents. In addition to the plant-derived compounds, marine, and animal resources also play an important role as clinically beneficial anticancer agents with minimal or no toxicity. The best examples for plant-derived compounds include vincristine, vinblastine, irinotecan, etoposide, and paclitaxel; they have a different mode of action against cancer such as interaction with microtubules, inhibition of topoisomerases I or II, alkylation of DNA, and interference with tumor signal transduction. The natural products from marine sources such as breostatin, squalamine exhibit a significant antimitic and anti-angiogenic activities. The benefits of various anticancer drugs obtained from natural products are the fact that it can have its effect on cancer cells alone without harming healthy cells, which is unlikely to be the case with other conventional chemotherapeutics. In this review, various natural products and their anticancer properties have been discussed briefly.

Keywords: Natural products, Flavonoids, Cancer, Anticancer agents, Marine products.

INTRODUCTION

Cancer is a major disease that affects the majority of the population. During cancer, abnormal growth of cells occurs in a body that can cause even death. These cells usually invade and tend to spread cancer (metastasis) throughout the body. The treatment of cancer can be done by correcting the abnormal growth. Annually, cancer results in the death of >3500 million people all over the world. There are many chemopreventive agents used for the treatment of cancer, but they cause toxicity and hence cannot be used for a longer time. Cancer starts with mutations in DNA which instructs the cells about their growth and division. The normal cells usually repair most of the mutations in their DNA. The mutation that is not corrected leads the cell to become a cancer cell. The major factor that causes cancer is an environmental factor. This includes smoking chemicals, radiation, infectious diseases, trace levels of pollutants in food, drinking water, and air. The secondary factors include tobacco use, unhealthy diet, and sedentary life. The effect of pollutants depends on concentration, intensity, and exposure. The risk for cancer is high when exposed to ionizing radiation, carcinogenic chemicals, certain metals, and some other specific substances even exposed at low levels. Passive tobacco smoke increases the risk in large populations who do not smoke but exposed to the smoke from smokers [1].

DRUG DISCOVERY FROM NATURAL PRODUCTS

Natural products are useful for treating several ailments. The bioactive compounds obtained from plants, animals, and microbes are very useful in the treatment of many diseases. Majority of the anticancer drugs have been developed from natural products [2]. These include plants, animals, marine organisms, and microbes. >3000 species of plants are found to be useful for the treatment of cancer.

Sources of natural products

Natural products are the secondary metabolites in various plants, animals, and other sources. They are divided into four types based on their biosynthetic origin as depicted in Fig. 1. Source of such products may be of terrestrial plants, animals, minerals, and marine organisms.

Natural products for cancer therapy

The natural products obtained from fruits, vegetables, herbs, and marine products are very useful to fight against cancer. The compounds derived from the natural products exhibit a wide variety of antioxidant properties such as induction of apoptosis, autophagy, and inhibition of cell proliferation. The natural products contain active ingredients such as alkaloids, flavonoids, terpenoids, polysaccharides, and saponins that have potent biological properties such as antitumor, analgesic, anti-inflammatory, immunomodulatory, and antiviral activities.

Animals and marine organisms offer rich sources of anticancer agents with structurally diverse bioactive compounds and bioactive secondary metabolites that possess various antioxidant activities. The antioxidant activity of most natural antineoplastic drugs regulates the human immune function to destroy the tumor cells. Division and duplication are sequential events in the cell cycle, and deregulation of the cell cycle will have an effect on the onset of cancer [3].

The inhibition of Topo I is an important anticancer pathway. Many anticancer drugs fight cancer by arresting the cell cycle, inducing
apoptosis and differentiation as well as by inhibiting the cell growth and proliferation, or a combination of two or more of these mechanisms [4].

**TYPES OF ACTIVE COMPOUNDS FOUND IN NATURAL PRODUCTS**

The important active compounds that can be derived from the natural products and their modes of action are discussed below.

**Alkaloid**

Alkaloids are organic compounds that contain nitrogen. They are responsible for the biological activity and are mostly seen in plants. Camptothecin is an effective broad-spectrum anticancer agent that acts through inhibition of Topo I. Matrine, a major component extracted from *Sophora flavescens*, has shown to exert anticancer effects in a number of cancer cells including breast, gastric, lung, etc. It can inhibit tumor cell line MNK45, inducing apoptosis and autophagy of gastric cancer cells in a dose- and time-dependent manner [5,6]. Indole alkaloid, a kind of marine alkaloid, is marine-derived secondary metabolite that widely occurs amongst a variety of marine sources such as sponges, algae, and microbes. It has been found that a sponge-derived bis-indole alkaloid has the anti-HIV-1 R Tase and antiproliferative action against numerous cancer cell lines [7].

**Taxane and Podophyllotoxin**

Taxane and podophyllotoxin have potent anticancer activities. The main disadvantage of considering them in anticancer therapy is due to their weak cytotoxic selectivity, deleterious side effects, and limited effectiveness [8]. Paclitaxel and docetaxel are very important anticancer drugs that exhibit anticancer activity against several malignancies including lung cancer, breast cancer, ovarian cancer, and prostate cancer. Paclitaxel possess microtubule function that leads to the blocking of mitosis and formation of polyplody giant cancer cells [9]. Podophyllotoxin inhibits the polymerization of tubulin and develops diverse variants of podophyllotoxin, such as, etoposide, etopophos, and teniposide that are used in the treatment of a variety of malignancies and also in combination with other drugs. Deoxypodophyllotoxin and lignans podophyllotoxin from *Podophyllum hexandrum* are secondary metabolites with potential cancer therapy.

**Flavonoids**

Flavonoids include isoflavones, flavonols, flavones, anthocyanidins, catechins, and flavanons. They are known to possess anticancer effects. Important examples of flavonoids with their anticancer activity are listed below:

Licochalcone A has been found to be effective against gastric cancer. It is found to inhibit cell cycle and induce cell apoptosis in cancerous cells [11]. The flavonoid glabridin has an inhibitory effect in human breast cancer. It inhibits cell metastasis, decrease tumor angiogenesis and inhibits invasion of MDA-MB-231 cells [12].

Baicalin possesses anti-inflammatory, antioxidant, and antitumor properties. Isoflavones have been shown to induce apoptosis in vitro and in vivo, even in chemoresistant cancer cells [13]. Quercetin is a plant-derived flavonoid that can inhibit growth and induce apoptosis in several types of tumor cells, such as human cervical cancer, prostate cancer, epidermal growth factor receptor-overexpressing oral cancer, and osteosarcoma.

Propolis contains a variety of compounds. Caffeic acid phenethyl ester (CAPE) is a strong bioactive component extracted from propolis. Researchers have proved that CAPE can suppress human pancreatic cancer cell proliferation and hence it can be used as an adjuvant in the treatment of human oral squamous cell carcinoma. Besides, it also inhibits the growth of cancer cells and Akt signaling in human prostate cancer cells, and also in cervical cancer cells [12,14-16].

**Saponins**

Saponins are distributed widely in plants. They possess a complex structure and are found to exhibit several biological properties such as anticancer and anti-inflammatory activity. The most widely studied saponin is ginsenoside. Ginsenoside is a kind of triterpenoid saponin and it is the main active ingredient in ginseng. Ginsenoside has higher antitumor activity, non-toxic side effects on normal cells and has a synergistic effect with other chemotherapy drugs such as cisplatin. Ginsenoside also regulates the proliferation of tumor cells, inducing differentiation and apoptosis of cells to exert antitumor effects.

Ginsenoside Rg3 and Rh2 are the most studied and the most relevant anticancer components. Rg3 promotes TRAIL (tumor necrosis factor [TNF]-related apoptosis-inducing ligand) by inducing apoptosis of hepatocellular carcinoma cell line. Ginsenoside Rh2 can treat leukemia by blocking the cell cycle. It is used to treat pancreatic cancer by inhibiting proliferation, migration, invasion, and inducing apoptosis of cancer cells [17]. Ginsenoside Rk1 has antitumor activity in HepG2 cells (human hepatocellular carcinoma cells) in vitro. Rk1 markedly inhibits telomerase activity and cell growth along with significant morphological changes and induces apoptosis [18].

The derivatives of ginsenosides are also very strong and have significant anticancer activity. Protopanaxadiol, the metabolites of Rg3, inhibits prostate cancer cell growth and proliferation, and induces apoptosis which leads to arrest in the G1 phase of the cell cycle. Hence, it can function as a potential therapeutic agent in the treatment of prostate cancer and it also has a significant effect on colon cancer [19,20].

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**Fig. 1: Sources of natural products**
**PLANTS HAVING POTENTIAL ANTICANCER ACTIVITY**

**Achyranthes aspera**
A. aspera Linn. is a common herb. It is seen as a weed on roadside throughout India. The methanol extract of A. aspera, its alkaloid, non-alkaloid, and saponin fractions have shown to exhibit potential inhibitory effects on the Epstein-Barr virus early antigen activation induced by the carcinogen 12-O-tetradecanoylphorbol-13-acetate in Raji cells [21,22].

**Allium sativum**
A. sativum is used in the treatment of many diseases in India. Allicin is the primary component of raw garlic. Ajoene is formed as a result of the rearrangement of allicin. Its cytotoxic effect has been studied against human primary fibroblasts, a permanent non-tumorigenic cell line derived from baby hamster kidney cells, and a tumorigenic lymphoid cell line derived from a Burkitt lymphoma [23]. Garlic contains at least 33 sulfur compounds, several enzymes, 17 amino acids, and minerals such as selenium. It contains a higher concentration of sulfur compounds than any other Allium species. The sulfur compounds are responsible both for garlic’s pungent odor and many of its medicinal effects [24]. Thus, the consumption of garlic has shown to provide protection from cancer.

**Andrographis paniculata**
The aerial part of A. paniculata has been found to contain 14 compounds; most of them being flavonoids and labdane diterpenoids. The cytotoxic activities of these compounds are shown to have tumor inhibitory activity against studied cell lines [25].

**Annona muricata**
Gaviola is known by its scientific name, A. muricata. Acetogenin is the important component seen in gaviola. It is found in the fruits, seeds, leaves, and bark of the plant. Preliminary studies showed that acetogenin inhibits the production of adenosine triphosphate, which blocks the pump that removes cancer drugs from the cell. This property allows the drug to be used in chemotherapy. Research studies also suggest that acetogenin may have chemotherapeutic potential, especially against cancer that is resistant to multiple drugs [26].

**Astragalus hedysarum**
A polysaccharide from A. hedysarum contains antitumor activity. A. hedysarum displays immune-potentiating action that can be used in cancer chemotherapy [27]. It has been revealed that there is an association between the activation of the antitumor immune mechanism of the host and the antitumor or effects exhibited by Astragalus membranaceus in vitro and in vivo [28].

**Bidens pilosa**
B. pilosa is found to contain polycyclicenes, flavonoids, terpenoids, and others. Significant antitumor activity was observed in the hexane extract [29].

**Cannabis sativa**
The cannabinoids are the most important active component of C. sativa. Cannabinoids and their derivatives have a palliative effect on cancer patients. It does so by preventing nausea, vomiting, and pain and also stimulates the appetite. These compounds also exhibit antitumor activity in cell culture and animal models by modulating key cell signaling pathways [30].

**Centaurea ainetensis**
The cytotoxic activity of the plant extract has been observed in human colon carcinoma cells. The crude extract is found to inhibit the proliferation of a host of colon-derived cancer cells. Fractionation studies helped in the isolation and characterization of bioactive sesquiterpene lactone molecule called Salogradiolide A. This was found to be linked to the growth inhibition in the colon. Salogradiolide A reduced the growth of colon cancer cell lines at non-cytotoxic concentrations when administered to normal human intestinal cells. Salogradiolide A also exhibited potent cytotoxic action against epidermal squamous cell carcinogenesis [31,32].

**Camellia sinensis**
Epigallocatechin-3-gallate (EGGC) is the most abundant polyphenol present in C. sinensis. EGGC inhibits the invasion and migration of human colon and oral cancer cells. EGGC inhibits the growth of cancer cell lines such as hepatocellular carcinoma cell lines, (ovarian carcinoma cell lines) OVCA, HT-29 (Human colon carcinoma cells), and HCA-7 (rectal cancer cell lines) [33-36].

**Daphne mezereum**
This is used in the treatment of cancer like symptoms. A hydro-alcohol extract of D. mezereum displayed potent antileukemic activity against lymphocytic leukemia in mice. Fractionation studies of the extract resulted in the isolation and characterization of mezerein as a potent antileukemic compound [37].

**Gossypium hirsutum**
It is commonly known as Mexican cotton. It is used as a male contraceptive. It also finds use in the treatment of metastatic carcinoma of endometrium or ovary and also used in HIV. It is found to exhibit antitumor activity on important cytosolic and mitochondrial enzyme systems that are fundamental for tumor cell growth [38-40].

**Centella asiatica**
It is commonly known as brahmi. It has cytotoxic and antitumor properties. It acts directly on DNA synthesis [41]. C. asiatica alters nitric oxide and TNF-alpha in mouse macrophages [42]. When given in combination with vincristine, it induces apoptosis and enhances antitumor activity. This is found to be valuable in cancer chemotherapy [43]. The antitumor effect of the extract on skin cancer has also been observed [44].

**Oroxylum indicum**
O. indicum (Sonapatha) is found to contain baicalein, a flavonoid. It is used in various polyherbal formulations in Indian system of medicine. The flavonoid has been reported for its antitumor effect on human cancer cell lines. The methanolic extract has greater cytotoxic potential and moderate effect against oxidative stress of the DNA [45].

**Picrorhiza kurroa**
It is used as a hepatoprotective agent in Indian system of medicine. It has been found to inhibit liver cancer growth formed due to exposure of chemicals in in vivo studies. The active ingredient, Kutkin possesses free radical scavenging activity and also restores SOD that protects the liver from oxidative damage [46].

**Silybum marianum**
This is found to contain a flavonoid, silymarin. It carries out its action by suppressing the proliferation of tumor cells. It is achieved by arresting the cell cycle at G1/S-phase; inducing the cyclin-dependent kinase inhibitors; downregulating the anti-apoptotic gene products; inhibiting the cell-survival kinases, and inflammatory transcription factors. Studies indicate that silymarin also downregulates the gene products associated with the proliferation of tumor cells, invasion, angiogenesis, and metastasis [47]. Silibinin, a major constituent (flavanolignan) of the fruits of Silybum marianum, was also found to be useful against human breast cancer [48].

**Terminalia chebula**
Tannins are found as chief constituents of T. chebula. Its antiutagenic activity has been studied and proved against Salmonella typhimurium [49]. The fruits contain phenols such as chebulinic acid, tannic acid, and ellagic acid that are considered as cancer growth inhibitors [50]. Various pleiotropic effects such as antioxidant, antiobiotic, renoprotective, hepatoprotective, antianaphylactic, immunomodulatory, and prokinetic have been found to be associated with the plant [51].

**Withania somnifera**
Withaferin-A isolated from the roots of W. somnifera has significant antitumor activity against the carcinoma of the nasopharynx, Sarcoma 180, Sarcoma Black, and E 0771 mammmary adenocarcinoma. It
is commonly used in the treatment of cancer patients in Indian System of Medicine. It is also used to treat cancer like symptoms and also to lead a long life [52-54]. The withanolides from \textit{W. somnifera} have shown to reduce the growth of cancer cells in human breast, central nervous system, lung, and colon cancer cell lines. The study was performed using doxorubicin as a standard drug.

**Zingiber officinale**
The ginger extract and 6-gingerol have been studied for the \textit{in vitro} inhibition of two key aspects of colon cancer biology, cancer cell proliferation, and angiogenic potential of endothelial cell tubule formation. They have a direct effect on cancer cells.

**PROMISING PLANT-DERIVED ANTICANCER LEADS**
Plants have been considered as a source of medicine for many centuries. Many bioactive substances have been isolated and identified as therapeutic agents. Most of the molecules are under investigation for their use.

A synthetic flavone flavopiridol, derived from the plant alkaloid rohitukine, is currently under Phase I and Phase II clinical trials. It is found to be active against tumors, leukemia, lymphomas, and solid tumors [55]. Olo mucine is isolated from \textit{Raphanus sativus} (Brassicaceae) and is converted into a synthetic agent roscovitine [56].

The efforts of the National Cancer Institute to develop systemic and topical formulations for potential clinical trials are ongoing. Phytochemical studies on roots of \textit{Erythroxyllum perville} (Erythroxylaceae) have resulted in the isolation of Pervilvine-A [57]. In a study conducted on multidrug-resistant oral epidermoid cancer cell lines, Pervilvine-A was found to be cytotoxic when administered with anticancer agent vinblastine and this compound is under preclinical development [58].

Silvestrol was isolated from the fruits of \textit{Meliaceae} family plant, \textit{Aglaia sylvestre} and it exhibited cytotoxicity against breast and lung cancer cells [59]. Isolation studies on the seeds of \textit{Centaurea schischkini} and \textit{Centaurea montana} have resulted in the isolation of two novel alkaloids schischkinn and montamine. Schischkinn and montamine both exhibited anticancer activity against human cancer cells. The molecular skeleton of these novel alkaloids can be exploited for synthesizing compound to enhance cytotoxic activity [60].

**NATURAL PRODUCTS FROM MARINE ORIGIN HAVING ANTICANCER PROPERTIES**
The marine environment provides a vast source for compounds with promising therapeutic activity for the treatment of cancer. The marine organisms such as tunicates, sponges, microorganisms, corals provide enormous secondary metabolites with potent anticancer activities and they are mentioned below.

**Eleutherobin**
A novel natural product produced by the coni, \textit{Erythropodium caribaecorum} is a potent inducer for tubulin polymerization. This diterpene glycoside exhibits cytotoxicity similar to that of paclitaxel [61]. It is found to be effective against human breast carcinoma. Eleutherobin has its action in human colon carcinoma cells containing multiple microtubuli and microtubule bundles by arresting at the mitosis stage, depending on concentration, cell line, and length of exposure [62].

**(-)-Discodermolide**
The promising antitumor agent is a polyketide isolated from the marine sponge, \textit{Discodermia dissoluta}. Although structurally distinct from taxol, discodermolide shares a common mechanism of action as a potent tubulin polymerizer. It is one of the tubulin interactive agents and also a cytotoxin. It leads to mitotic arrest at the G2/M phase and results in the suppression of microtubule function, which changes dynamically and finally results in cell death. It also possesses neuroprotective, antiproliferative, and antimitic properties [63].

**Bryostatin-1**
Bryostatin-1 is a macrocyclic lactone isolated from the Bryozoa, \textit{Bugula neritina}, and works as a PKC isozyme modulator. In clinical trials of Phase I and II, it exhibited antitumor activity against various solid tumors along with toxic effects such as myalgia, plethelitis, and thrombocytopenia. It helps in promoting the immune system, induces apoptosis and enhances hemopoiesis. Bryostatine-1 is in use for ovarian carcinoma, lymphoma, and melanoma. It was also reported that, when Bryostatin-1 is given in combination with other anticancer agents, it exhibited better synergistic anticancer activity [63].

**Squalamine**
This is an aminosterol compound obtained from the natural source, the livers of dogfish shark and other species of squaliform sharks. Squalamine exhibits systemic anti-angiogenic activity against rapidly proliferating blood vessels that arise in pathological settings. As a consequence, it is under evaluation in various clinical trials. Squalamine has been evaluated for the treatment of non-small cell lung cancer in Stages I and IIA, ovarian cancer (Stage IV), and prostate cancer as well as several Phase I pharmacokinetic studies. Squalamine revealed significant effect against tumor growth and angiogenesis when studied in laboratory models for brain, lung, and ovarian cancer. Squalamine plays a role in increasing the vascular endothelial growth factor and thus inhibits the endothelial cell proliferation. Furthermore, squalamine, when combined with cisplatin, enhances better prognosis in the treatment of ovarian cancer [64].

**SQUALAMINE**

**NATURAL PRODUCTS FROM ANIMAL ORIGIN HAVING ANTICANCER PROPERTIES**
Venoms and toxins
The existence of various animal venoms and toxins has made it a remarkable source of leads for the treatment of cancer in recent days. The active molecules such as protein and non-protein toxins, peptides, enzymes, extracted from the venom of snake, scorpion, and toad have been reported with therapeutic potential against cancer [65]. The applications of venoms and toxins as therapeutics have been mentioned in traditional medical literature.

**Snake venom with anticancer effects**
drCT-I, a protein toxin extracted from \textit{Erythroxyllum perville} (Erythroxylaceae) have resulted in the isolation of Pervilvine-A [57]. In a study conducted on multidrug-resistant oral epidermoid cancer cell lines, Pervilvine-A was found to be cytotoxic when administered with anticancer agent vinblastine and this compound is under preclinical development [58].

**Contortrostatin**
A dimeric disintegrin, from copperhead snake venom, prevented invasion of human breast cancer cells by blocking \textit{αVβ3}, an important integrin-mediated cell motility and tumor invasion [66].

**Colombistatin**
Isolated from the venom of the Colombian 	extit{Bothrops colombiensis}, it induces apoptosis in human breast cancer cells by blocking \textit{αVβ3}, an important integrin-mediated cell motility and tumor invasion [67].

**Scorpion venom with anticancer effects**
Charybotoxin, a neurotoxin, obtained from the scorpion venom, \textit{Leiurus quinquestriatus}, induced blockage through \textit{Ca}^{2+} activated channels resulting in the apoptosis of human breast cancer cells at early G1, late G1, and accumulated cells in S phase [68].

**Bengalin**
Isolated from the venom of \textit{Bufo siccus} exhibited \textit{in vitro} inhibitory effects against prostate cancer with the constant increase in \textit{Ca}^{2+}, leading to apoptosis [71].

**Frog/toad venom with anticancer effects**
Cinobufagin, from \textit{Bufo bufo} exhibited \textit{in vitro} inhibitory effects against prostate cancer with the constant increase in \textit{Ca}^{2+}, leading to apoptosis [71].
cationic molecules showed a cytotoxic effect on cancer cells. Onconase, clinically known as nanoprisinase is under Phase III trial, when studied in human colorectal cancer cell line depicted its ability to overcome the Pglycoprotein mediated multidrug resistance [72].

Cow urine
Cow urine, one of the constituents of panchagavya, contains necessary minerals, salts, enzymes, urea, and water mainly. Distilled cow urine protects DNA and repairs it rapidly. It protects chromosomal aberrations by mitocycin in human leukocytes. Cow urine helps the lymphocytes to survive and not to commit suicide (apoptosis) [73]. Cow urine therapy also prevents the pathogenic effect of free radicals. These radicals cause damage to various tissues which destroys the normal cell activities, leading to the aging process of a person through the fat, protein, and enzymatic depletion. Thus, the treatment with cow urine can delay this process. It is reported with properties such as antimicrobial, apoptosis inhibitor, DNA repairing potential, and bio-enhancer, and immune-modulator activity [74].

ANTICANCER PROPERTIES OF NATURELLY OCCURRING METALS AND MINERALS
Metals and minerals have been in use for the treatment of various ailments since ancient time. In the treatment of cancer, naturally occurring metals and its complexes and nanoparticles play a key role in recent days. The interaction which takes place between the metals with a positive charge and the phosphate backbone of DNA with negative charge enhances the antitumor property. Other anticancer drugs also act synergistically with some metals by interacting with amino acids having high reduction potential.

• Platinum-based compounds are effective in head and neck tumors. The coordination complexes are thought to act to crosslink DNA in tumor cells.

• In the treatment of rheumatoid arthritis, leukemia, and thrombocytopenia, gold salt complexes have been used immensely. It is believed that they interact with albumin and are taken up eventually by immune cells, triggering antimitochondrial effects, and finally cell apoptosis.

Silver
Silver (Ag, Argentum) is found in nature in its free state. In recent years, oncolgical research is being dominated by nanoparticles. The therapy using nanoparticles can be used as an alternative to conventional chemotherapy. Silver nanoparticles (AgNPs) reacted positively for MCF-7 breast cancer cell line, and hence the predominant cytotoxic effect of AgNPs was proven. Vasanth et al. studied the effectiveness of silver nanoparticles in a cervical cancer cell line (HeLa) and reported about the apoptosis induction and cessation of cell replication [75]. Silver nanoparticles also exhibit a cytotoxic effect against acute myeloid leukemia cell lines such as SHI-1 and THP-1. Li et al. investigated the anti-proliferative effect of silver complexes in a hepatocellular carcinoma cell line (HepG2) at G1 and S phase thereby arresting the anti-proliferative effect of silver complexes in a hepatocellular carcinoma cell line (HepG2) thereby arresting the proliferation of cancer cells.

Arsenic
Arsenic is one of the naturally occurring metal compounds that have been used for various ailments in earlier days. The medicines indicated for complex diseases are prepared with purified or processed arsenic compounds, which are mentioned in traditional literature. He et al. reported the use of arsenic trioxide in patients with acute promyelocytic leukemia (APL) [77]. It is safe and effective with many other malignancies too. It induces a p53-dependent G1 or G2/M cell cycle arrest, through activation of caspase 8 or caspase 9. Arsenic trioxide leads to apoptosis when administered in a high concentration and produces cell proliferation at low concentrations.

Several cell lines are sensitive to arsenic trioxides such as esophageal carcinoma cells, OVCAR-3, renal cell carcinoma cells, and small cell lung cancer (Nel-H cells). Interestingly, Trisonox, the injectable formulation of arsenic trioxide, has no known cross-resistance with all-trans-retinoic acid or other anticancer agents. In addition, Trisenox does not cause hair loss and is not myelosuppressive in patients with APL [78]. The activity of arsenic trioxide with ascorbic acid is effective in refractory or relapsed myeloma.

Zinc
Zinc, although a trace mineral, is required eventually for all the life forms and is found abundantly in nature. It plays an important role in the stabilization of DNA and RNA. Mulhern studied that zinc decreases the incidence of the tumor and about 300 ppm of zinc increases the latent period of PYB6 induced neoplasms in mice [79]. A decrease in zinc leads to the early development of malignancies especially prostate cancer. Zinc may exert a prophylactic anti-cancer effect by preventing the elevation of HDL [80]. Balakrishnan et al. evaluated the anti-hyperlipidemic effect of Naga Parpam, a zinc-based Siddha medicinal preparation, and its stimulating effect was studied by Braverman and Pfeiffer [81]. Siwiński et al. reported the effect of zinc sulfate in normal human lymphocytes and myelogenous leukemia cells for its cytotoxicity and genotoxicity [82]. The results indicated that zinc showed a protective action against H2O2 by preventing normal cell damage by enhancing the DNA repair caused by H2O2 [83]. Zinc delivery agent or mechanism such as an ionophore approach can improve the efficacy for the uptake and accumulation of zinc into the malignant cells.

Bismuth
Bismuth results in regression of the disease, gastric lymphoma caused by Helicobacter pylori or even a cure. Bismuth complexes of 6-mercaptopurine were the first antitumor compounds to be tested. The emission of α-particle by bismuth compounds shows potential in the form of radiotherapeutic agents. Efficacy is increased when the compounds are attached to a monoclonal antibody which can specifically target tumor cells [84].

CONCLUSION
The application of natural products in cancer therapy is a boon to the emerging field of medicine. The plant products are of predominance in the treatment of cancer, superior to other natural products of various sources due to the presence of numerous antioxidants, flavonoids, with easy availability, and higher potency. The promising effects of many natural products have been discussed in this review for various solid tumors and hematological malignancies. The anticancer activities of marine products are being evolved through various phases of pre-clinical and clinical trials for better efficacy and minimal adverse effects. Natural products demonstrate anticancer properties in association with antioxidant, anti-inflammatory, anti-agging, and anti-proliferative activities. Among the known potent anticancer drugs, Vinca rosea alkaloids, vinblastine and vincristine are of greater use in recent days. Taxol isolated from Taxus brevifolia has gained much attention in the treatment of cancer. Several active principles isolated from plants such as girmnibe (Murraya koenigii) have been studied for liver cancer; kenal seed oil (Hibiscus cannabinus) for leukemia is under research. In addition to the plant products, natural metals and minerals are being extensively studied for the treatment of cancer. Nanoparticles of some metals and metal complexes have been used for fighting cancer and its complications. The metallic preparations for the treatment of cancer have also been mentioned in traditional literature. Cancer is associated with high mortality rates, people are turning to the use of contemporary and alternative medicine to overcome the adverse effects of chemotherapy and other synthetic drugs, and hence a better survival can been accomplished.

AUTHORS’ CONTRIBUTIONS
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exhibits anti-neoplastic activity. Int J Oncol 2012; 42(4):1417-26.

2. Bhoomika R, Dey SM, Chatterjee A, Doss AG, Rajappan M, Natarajan S, et al. Screening of natural products for anticancer and antitumor activities. Asian J Pharm Clin Res 2007; 1:745-55.

3. Al-Najjar N, Dakhous S, Darweiche WA, El-Sabbagh M, Saliba NA, Gali-Muhtasib HS, et al. Anti-colon cancer effects of salrangolide A isolated from Centaurea arienicae. Oncol Rep 2008; 21(4):897-904.

4. Kaur S, Grover IS, Singh M, Kaur S. Antimutagenicity of hydrolyzable tannins from the leaves of Emblica officinalis. Pharmacogn Rev 2007; 1:143-50.

5. Wang LM, Ren DM. Flavopiridol, the first cyclin-dependent kinase inhibitor: Recent advances in combination chemotherapy. Mini Rev Med Chem 2010; 10:1058-70.

6. Liu Y, Xie S, Wang Y, Luo K, Wang Y, Cai Y, et al. Liquidiginton inhibits tumor growth and vascularization in a mouse model of bkn cancer cells. Molecules 2013; 18:7206-16.

7. Xiao YY, Hao M, Yang XY, Bu Q, Li M, Ni SJ, et al. Licoricealone A inhibits growth of gastric cancer cells by inducing mitotic arrest and pro-apoptotic ER stress in lung cancer cells. PLoS One 2013;8:e62082.

8. Tang XP, Tang GD, Fang CY, Liang ZH, Zhang LY. Effects of green tea polyphenol epigallocatechin-3-gallate on N-nitrosodiethylamine induced tumor growth. Phytomedicine 2009;16:573-80.

9. Peng G, Dixon DA, Muga SJ, Smith TJ, Wargovich MJ. Green tea polyphenol (-)-epigallocatechin-3-gallate inhibits cyclooxygenase-2 expression in colon cancer cells. Mol Carcinog 2006;45:309-19.

10. Wang J, Ito H, Shimura K. Enhancing effect of antitumor polysaccharide from Astragalus or radix hedysarum on C3 cleavage production of macrophages in mice. Jpn J Pharmacol 1989;51:432-4.

11. Cho WC, Leung KN. In vitro and in vivo anti-tumor effects of Astragalus membranaceus. Cancer Lett 2007;252:43-54.

12. Hsu YL, Wu LY, Hou MF, Tsai EM, Lee JN, Liang HL, et al. Effect of licorice extract on the invasion and metastasis of gastric cancer cells. Asia-pacific J Clin Oncol 2007;4:475-82.

13. Wang J, Ito H, Shimura K. Enhancing effect of antitumor polysaccharide from Astragalus or radix hedysarum on C3 cleavage production of macrophages in mice. Jpn J Pharmacol 1989;51:432-4.

14. Gilbert NE, O’Reilly JE, Chang CJ, Lin YC, Brueggemeier RW. Anti-proliferative activity of gossypol against central nervous system tumor cells. J Neurooncol 1994;19:25-35.

15. Kaur S, Grover IS, Singh M, Kaur S. Antimutagenicity of hydrolyzable tannins from the leaves of Emblica officinalis. Pharmacogn Rev 2007; 1:143-50.

16. Wang LM, Ren DM. Flavopiridol, the first cyclin-dependent kinase inhibitor: Recent advances in combination chemotherapy. Mini Rev Med Chem 2010; 10:1058-70.

17. Wang LM, Ren DM. Flavopiridol, the first cyclin-dependent kinase inhibitor: Recent advances in combination chemotherapy. Mini Rev Med Chem 2010; 10:1058-70.

18. Wang LM, Ren DM. Flavopiridol, the first cyclin-dependent kinase inhibitor: Recent advances in combination chemotherapy. Mini Rev Med Chem 2010; 10:1058-70.

19. Wang LM, Ren DM. Flavopiridol, the first cyclin-dependent kinase inhibitor: Recent advances in combination chemotherapy. Mini Rev Med Chem 2010; 10:1058-70.

20. Wang LM, Ren DM. Flavopiridol, the first cyclin-dependent kinase inhibitor: Recent advances in combination chemotherapy. Mini Rev Med Chem 2010; 10:1058-70.
tannins from *Terminalia chebula* in *Salmonella typhimurium*. Mutat Res 1998;419:169-79.
49. Arora S, Kaur K, Kaur S. Indian medicinal plants as a reservoir of protective phytochemicals. Teratog Carcinog Mutagen 2003;Suppl 1:295-300.
50. Ali M, Shuaib M, Ansari SH. Withanolides from the stem bark of *Withania somnifera*. Phytochemistry 1997;44:1163-8.
51. Khan MU, Khalillullah H, Akhtar J, Elhasan GO. *Terminalia chebula*: An ephemeral glance. Int J Pharm Phar Inf 2015;7:40-3.
52. Chakraborti SK, De BK, Bandyopadhyay T. Variations in the antitumour constituents of *Withania somnifera* Dunal. Experientia 1974;30:852-3.
53. Devi PU, Akagi K, Oستепенков V, Tanaka Y, Sugahara T. Withaferin A: A new radiosensitizer from the Indian medicinal plant *Withania somnifera*. Int J Radiat Biol 1996;69:193-7.
54. Chen Y, Xu X, Zhu Y, Li X. Anti-cancer effects of ginsenoside compound k on pediatric acute myeloid leukemia cells. Cancer Cell Int 2013;13:24.
55. Christian MC, Plada JM, Ho PT, Abruuck SG, Murgio AJ, Saussville EA, et al. Promising new agents under development by the division of cancer treatment, diagnosis, and centers of the national cancer institute. Semin Oncol 1997;24:219-40.
56. Meijer L, Raymond E. Roscovitine and other purines as kinase inhibitors. From starfish oocytes to clinical trials. Acc Chem Res 2003;36:417-25.
57. Silva GL, Cui B, Chávez D, You M, Chai HB, Rasoanaivo P, et al. Eleutherobin, a novel cytotoxic agent that induces tubulin polymerization, is similar to paclitaxel (Taxol). Cancer Res 1998;58:1111-5.
58. Mi Q, Cui B, Silva GL, Lantvit D, Lim E, Chai H, et al. Pervinene A, a novel tropane alkaloid that reverses the multidrug-resistance phenotype. Cancer Res 2001;61:4030-7.
59. Mi Q, Cui B, Lantvit D, Reyes-Lim E, Chai H, Pezzuto JM, et al. Pervinene A, a novel tropane alkaloid aromatic ester that reverses multidrug resistance. Anticancer Res 2003;23:3607-15.
60. Shoeb M, Celik S, Jaspars M, Kumarasamy Y, MacManus SM, Nahar L, et al. Modulation of the multidrug-resistance phenotype by new tropane alkaloid aromatic esters from erythroxylum pervillei. J Nat Prod 2001;64:1514-20.
61. Balabhaskar et al. 2010;48:93-103.
62. Chen Y, Xiang J, Gu W, Xu M. Chemical constituents of *Bufo siccus*. Zhongguo Zhong Yao Za Zhi 1998;23:620-1, 640.
63. Costanzi J, Sidranovsky D, Navon A, Goldsweig H. Ribonucleases as a novel pro-apoptotic anticancer strategy: Review of the preclinical and clinical data for rpinrns. Cancer Invest 2005;23:643-50.
64. Krishnamurthi K, Dutta D, Sivanesan SD, Chakraborti T. Protective effect of distillate and redistillate of cow’s urine in human polymorphonuclear leukocytes challenged with established genotoxic chemicals. Biomed Environ Sci 2004;17:247-56.
65. Randhawa GK, Sharma R. Chemotherapeutic potential of cow urine: A review. J Intercult Ethnopharmacol 2015;4:180-6.
66. Vasanth K, Ilango K, MohanKumar R, Agrawal A, Dubey GP. Anticancer activity of *Moringa oleifera* mediated silver nanoparticles on human cervical carcinoma cells by apoptosis induction. Colloids Surf B Biointerfaces 2014;117:354-9.
67. He X, Yang K, Chen P, Liu B, Zhang Y, Wang F, et al. Arsenic trioxide-based therapy in relapsed/refractory multiple myeloma patients: A meta-analysis and systematic review. Onco Targets Ther 2014;7:1593-9.
68. Mayorga J, Richardson-Hardin C, Dickey KA. Arsenic trioxide as effective therapy for relapsed acute promyelocytic leukemia. Clin J Oncol Nurs 2002;6:341-6.
69. Balakrishnan I, Sultan DS, Krishnamurthy VK, Raman R, Subramanian V, Ethirajan S. Effect of *Naga parbam*, a zinc-based siddha medicine, on hyperlipidemia in rats. J Complement Integr Med 2009;6:112-7.
70. Li YL, Qin NP, An YF, Liu YC, Huang GB, Luo XJ, et al. Study on potential antitumor mechanism of quinoline-based silver (I) complexes: Synthesis, structural characterization, cytotoxicity, cell cycle and caspase-initiated apoptosis. Inorg Chem Commun 2014;40:73-7.
71. He X, Yang K, Chen P, Liu B, Zhang Y, Wang F, et al. Zinc salts differentially modulate DNA damage in normal and cancer cells. Cell Biol Int 2009;33:542-7.
72. Ouadid-Ahidouch H, Roudbaraki M, Ahidouch A, Delcourt P, Prevarskaya N. Cell-cycle-dependent expression of the large ca2+-activated K+ channels in breast cancer cells. Biochem Biophys Res Commun 2004;316:244-51.
73. Gupta SD, Gomes A, Debnath A, Saha A, Gomes A. Apoptosis induction in human leukemia cells by a novel protein bengalins, isolated from Indian black scorpion venom: Through mitochondrial pathway and inhibition of heat shock proteins. Chem Biol Interact 2010;183:293-303.
74. Chen Y, Xiang J, Gu W, Xu M. Chemical constituents of *Bufo siccus*. Zhongguo Zhong Yao Za Zhi 1998;23:620-1, 640.
75. Costanzi J, Sidranovsky D, Navon A, Goldsweig H. Ribonucleases as a novel pro-apoptotic anticancer strategy: Review of the preclinical and clinical data for rpinrns. Cancer Invest 2005;23:643-50.
76. Krishnamurthi K, Dutta D, Sivanesan SD, Chakraborti T. Protective effect of distillate and redistillate of cow’s urine in human polymorphonuclear leukocytes challenged with established genotoxic chemicals. Biomed Environ Sci 2004;17:247-56.
77. Randhawa GK, Sharma R. Chemotherapeutic potential of cow urine: A review. J Intercult Ethnopharmacol 2015;4:180-6.
78. Vasanth K, Ilango K, MohanKumar R, Agrawal A, Dubey GP. Anticancer activity of *Moringa oleifera* mediated silver nanoparticles on human cervical carcinoma cells by apoptosis induction. Colloids Surf B Biointerfaces 2014;117:354-9.
79. He X, Yang K, Chen P, Liu B, Zhang Y, Wang F, et al. Arsenic trioxide-based therapy in relapsed/refractory multiple myeloma patients: A meta-analysis and systematic review. Onco Targets Ther 2014;7:1593-9.
80. Mayorga J, Richardson-Hardin C, Dickey KA. Arsenic trioxide as effective therapy for relapsed acute promyelocytic leukemia. Clin J Oncol Nurs 2002;6:341-6.
81. Mulhern SA, Stroube WB Jr., Jacobs RM. Alopecia induced in young mice by exposure to excess dietary zinc. Experientia 1986;42:551-3.
82. Braverman BA, Pfeiffer CC. Essential trace elements and cancer. Orthomol Psychiatry 1982:11:32-41.
83. Singh M, Kumar D, Singh G, Sharma D, Swami G. Natural minerals and inhibition of heat shock proteins. Experientia 1986;42:551-3.
84. Desoize B. Metals and metal compounds in cancer treatment. Anticancer Res 2004;24:1529-44.