

POTENTIAL NATURAL PRODUCTS WITH ANTICANCER PROPERTIES AND THEIR APPLICATIONS

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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 It has been found that the concept of a single drug for treating single disease may become outdated in the near future and the need of polyherbal formulations, as an alternate remedy is under investigation.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 bryostatin, squalamine exhibit a significant antimitotic, and anti-angiogenic activities. The benefits of various anticancer drugs derived 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.

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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 antitumor 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 antitumor activities. The antitumor 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

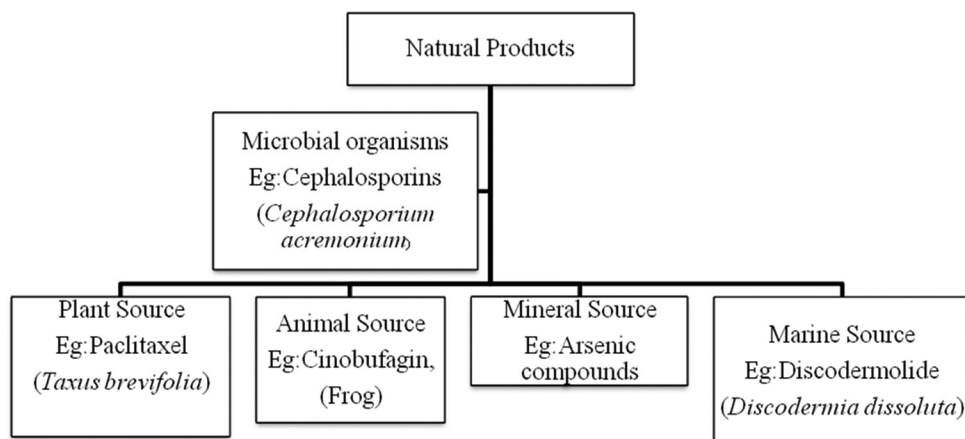


Fig. 1: Sources of natural products

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 RTase and antiproliferative action against numerous cancer cell lines [7].

Taxane and Podophyllotoxin

Taxane and podophyllotoxin have potent antitumor 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 polyploidy 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 flavanones. They are known to possess anticancer effects. Important examples of flavonoids with their anticancer activity are listed below:

Licorice is a traditional medicinal herb. It contains liquiritigenin, the flavonoid that can effectively inhibit the proliferation of human cervical carcinoma cell of tumors xenografts [10]. 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 antitumor 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 ginsenoside 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].

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

Graviola is known by its scientific name, *A. muricata*. Acetogenin is the important component seen in graviola. 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 immuno-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 effects exhibited by *Astragalus membranaceus* *in vitro* and *in vivo* [28].

Bidens pilosa

B. pilosa is found to contain polyacetylenes, 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 Salograviolide A. This was found to be linked to the growth inhibition in the colon. Salograviolide A reduced the growth of colon cancer cell lines at non-cytotoxic concentrations when administered to normal human intestinal cells. Salograviolide A also exhibited potent cytotoxic action against epidermal squamous cell carcinogenesis [31,32].

Camellia sinensis

Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol present in *C. sinensis*. EGCG inhibits the invasion and migration of human colon and oral cancer cells. EGCG 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 called 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 anticancer 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].

Picrorrhiza 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 antimutagenic 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, antidiabetic, renoprotective, hepatoprotective, anticancer, 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 mammary 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 *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 *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]. Olomucine is isolated from *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 *Erythroxylum pervillei* (*Erythroxylaceae*) have resulted in the isolation of Pervilleine-A [57]. In a study conducted on multidrug-resistant oral epidermoid cancer cell lines, Pervilleine-A was found to be cytotoxic when administered with anticancer agent vinblastine and this compound is under preclinical development [58].

Silvesterol was isolated from the fruits of *Meliaceae* family plant, *Aglaiya sylvestre* and it exhibited cytotoxicity against breast and lung cancer cells [59]. Isolation studies on the seeds of *Centaurea schischkinnii* and *Centaurea montana* have resulted in the isolation of two novel alkaloids schischkinnin and montamine. Schischkinnin 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 coral, *Erythropodium caribaeorum* 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 micronuclei and microtubule bundles by arresting at the mitosis stage, depending on concentration, cell line, and length of exposure [62].

(+)-Discodermolide

This promising antitumor agent is a polyketide isolated from the marine sponge, *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 antimetabolic properties [63].

Bryostatin-1

Bryostatin-1 is a macrocyclic lactone isolated from the Bryozoa, *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, phlebitis, and thrombocytopenia. It helps in promoting the immune system, induces apoptosis and enhances hemopoiesis. Bryostatin-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].

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 Indian Russell's viper possess antiproliferative, cytotoxic, and apoptotic activity [66]. L-amino acid oxidase, a flavoprotein obtained from snake venom has been reported to exhibit apoptosis-inducing, platelet aggregation-inducing, or inhibiting effects [65].

Contortrostatin, a dimeric disintegrin, from copperhead snake venom, prevented invasion of human breast cancer cells by blocking $\alpha\text{V}\beta\text{3}$, an important integrin-mediated cell motility and tumor invasion [67].

Colombistatin isolated from *Bothrops colombiensis*, when studied for melanoma skin and human urinary cancer cell line (SK-Mel-28 and T24, respectively) were reported as a potent inhibitor of ADP-induced platelet aggregation [68].

Scorpion venom with anticancer effects

Charybdotoxin, a neurotoxin, obtained from the scorpion venom, *Leiurusquin questriatus*, induced blockage through Ca^{2+} activated channels resulting in the apoptosis of human breast cancer cells at early G1, late G1, and accumulated cells in S phase [69].

Bengalin, isolated from Indian black scorpion *Heterometrus benghalensis*, is a protein with a high molecular weight that showed anticancer activity on human leukemic cells and thus it might elicit anticancer effect through mitochondrial death cascade [70].

Frog/toad venom with anticancer effects

Cinobufagin, from *Bufo siccus* exhibited *in vitro* inhibitory effects against prostate cancer with the constant increase in Ca^{2+} , leading to apoptosis [71]. Onconase, amphinase, the ribonucleases with high

cationic molecules showed a cytotoxic effect on cancer cells. Onconase, clinically known as ranprinasin is under Phase III trial, when studied in human colorectal cancer cell line depicted its ability to overcome the P-glycoprotein 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 NATURALLY 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 antimetabolic effects, and finally cell apoptosis.

Silver

Silver (*Ag*, *Argentum*) is found in nature in its free state. In recent years, oncological 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 mitosis [76].

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 (NeI-H cells). Interestingly, Trisenox, 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]. Sliwinski *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-aging, 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 girinimbine (*Murraya koenigii*) have been studied for liver cancer, kenaf 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 be accomplished.

AUTHORS' CONTRIBUTIONS

R. Balabhaskar, A. Faridha, and Gayathri Gunalan contributed in the conceptualization of the article along with the collection of data and preparation of manuscript. A. Rajendra Kumar and S. Selvarajan provided expertise and feedback.

CONFLICTS OF INTEREST

We declare that we have no conflicts of interest.

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