Role of fruit and vegetable in the treatment of cancer

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A R T I C L E  I N F O

Article type: Review article
Article history:
Received 03 October 2014
Accepted 25 December 2014
Published 06 January 2015
January 2015 issue

Keywords:
Cancer
Natural products
Fruit
Vegetables

A B S T R A C T

Natural products are important source of new drugs with chemical entities. The plant based drug discovery resulted mainly in the development of anticancer agents including plants, marine organisms and micro-organisms. Beside this there is numerous agents identified from fruits and vegetables can used in anticancer therapy including diallyl sulfide (allium), curcumin (turmeric), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), resveratrol (red grapes, peanuts and berries), genistein (soybean), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), eugenol (cloves), catechins (green tea), indole-3-carbinol (cruciferous vegetables), β-carotene (carrots), limonene (citrus fruits), and dietary fiber. The active compounds derive from natural products are contributing a great opportunity to evaluate the new chemical classes of anticancer agents with novel lead compound and potentially applicable mechanisms of action.

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Capsule Summary: Fruits and vegetable were reviewed and it was found that natural products exhibit anticancer activities and active compounds derive from natural products are contributing a great opportunity to evaluate the new chemical classes of anticancer agents.


INTRODUCTION

Natural Products, especially plants, have been used for the treatment of various diseases for thousands of years. Terrestrial plants have been used as medicines in Egypt, China, India and Greece from ancient time and an impressive number of modern drugs have been developed from them (Samuelsson, 1999; Cragg et al., 1997). Ayurvedic system recorded in Susruta and Charaka dates from about 1000 BC (Kappor, 1990). The Greeks also contributed substantially to the rational development of the herbal drugs (Samuelsson, 1999). Cancer is a major public health burden in both developed and developing countries. It was estimated that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons living with cancer around the world in 2002 (Parkin et al., 2005; Hoyert et al., 2005). Plants have long been used in the treatment of cancer. The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity (Shoeb, 2005). In this instance, natural origin is defined as natural products, derivatives of natural products or synthetic pharmaceuticals based on natural product models (Jaspars and Lawton, 1998). Cancer persists to be one of the main causes of death globally and only modest improvement has been made in reducing the morbidity and mortality of cancer disease (Hail Jr. 2005). Cancers may be caused in one of three ways, incorrect diet, genetic predisposition, and via the environment. Approximately 95% of all cancers are caused by life style and may take as long as 20-30 years to grow. About 12 million cases of cancer were diagnosed in a year, with 7 million deaths worldwide; these numbers may be double by 2030 (Aggarwal et al., 2009). According to a report of World Health
Plants as source of anti-cancer agents: The plant as source of anti-cancer agents started in earnest in the 1950s with the discovery and development of the vinca alkaloids (vinblastine and vincristine) and the isolation of the cytotoxic podophyllotoxins. Vinca alkaloid was responsible for an increase in the cure rates for Hodgkin’s disease and some forms of leukemia. Vincristine inhibits microtubule assembly, inducing tubulin self-association into coiled spiral aggregates (Noble. 1990). Etoposide is a epipodophyllotoxin, derived from the mandrake plant Podophyllum peltatum and the wild chervil Podophyllum emodi. It has also significant activity against small-cell lung carcinoma (Harvey. 1999). Etoposide is a topoisomerase-II inhibitor, stabilizing enzyme–DNA cleavable complexes leading to DNA breaks. The taxanes paclitaxel and docetaxel has been shown to antitumor activity against breast, ovarian and other tumor types in the clinic trial. Paclitaxel stabilizes microtubules and leading to mitotic arrest. In addition, the camptothecin derivatives irinotecan and topotecan, have shown significant antitumor activity against colorectal and ovarian cancer respectively (Creemers et al., 1996; Bertino. 1997). These compounds were initially obtained from the bark and wood of Nyssacea Camptotheca acuminate and act by inhibiting topoisomerase I (Liu et al., 2000). The taxanes and the camptothecins are presently approved for human use in various countries (Table 1).

Rohitukine the plant alkaloid, isolated from the leaves and stems of Dysoxylum binectariferum (Malaiaceae). Synthetic flavone derived from rohitukine, Flavopiridol representing the first cyclin-dependent kinase inhibitor to enter the clinical trial (Losiewicz et al., 1994). The mechanism of action involves interfering with the phosphorylation of cyclin-dependent kinases and arrest cell-cycle progression at growth phase G1 or G2 (Worland et al., 1993; Kelland. 2000). Homoharringtonine an alkaloid isolated from the Chinese tree Cephalotaxus harringtonia (Cephalotaxaceae). The mechanism of action is the inhibition of protein synthesis and blocking cell-cycle progression (Zhou et al., 1995). It has shown efficacy against various leukemias (Kantarjian et al., 1996). A lung-cancer-specific antineoplastic agent 4-Ipomeanol is isolated from the sweet potato Ipomoea batata (Convolvulaceae) (Rowinsky et al., 1993). The mechanism of action is converted into DNA-binding metabolites upon metabolic activation by cytochrome P450 enzymes that are present in cells of the lung (Rehm et al., 1993). DNA topoisomerase I inhibitor β-lapachone, that induces cell-cycle delay at G1 or S (synthesis) phase before inducing either apoptotic or necrotic cell death in a variety of human carcinoma cells, including ovary, colon, lung, prostate and breast (Li et al., 1999). Beside this there are so many plants which are used in cancer; following enlist the plant which prevent and target for future studies as potential anticancer agent (Table 2):

Dietary source of anti cancer agents: Natural dietary agents including fruits, vegetables, and spices have drawn a great deal of attention from both the scientific community and the general public owing to their demonstrated ability to suppress cancers. Recent studies suggest that the consumption of food rich in fruits, vegetables and spices have a lower incidence of cancers (stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas and colon) (Block et al., 1992; Steinmetz and Potter. 1996; Reddy et al., 2003). Dietary agents consist of a wide variety of biologically active components that are responsible for the anti-cancer effects like curcumin, genistein, resveratrol, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, isoeugenol, diethylthiones, isothiocyanates, indole-3-carbinol, isoflavones, saponins, phytoestrogens, inositol hexaphosphate, Vitamin C, D-limonene, lutein, folic acid, beta carotene, selenium, Vitamin E and flavonoids (Table 2). Many of which have been used in traditional medicines for thousands of years. These dietary agents are believed to suppress the inflammatory processes that lead to transformation, hyperproliferation, and initiation of carcinogenesis. Their inhibitory influences may ultimately suppress the final steps of carcinogenesis i.e angiogenesis and metastasis (Aggarwal and Shishodia. 2006; Cheng et al., 1999; Geng et al., 1997).
Marines as source of anti-cancer agents: Marine organisms are a rich source for natural products (Pomponi, 1999). In recent time, advancement in deep-sea collection and aquaculture technology gives significant number of compounds derived from marine organisms entering preclinical and early clinical evaluation as potential anticancer agent (Schwartsmann, 2000; Schwartsmann et al., 2001). Overall, more than 3000 new substances have been identified from marine organisms that demonstrate the great potential as a source of novel chemical classes (Schweitzer et al., 1991). Marine belongs to very diverse structural classes including polyketides, terpenes, steroids and peptides. The organisms yielding these bioactive marine compounds include invertebrate animals, algae, fungi and bacteria (Rinehart, 2000). The first anticancer product didemnin B, a cyclic depsipeptide isolated from the tunicate Trididemnum solidum from marine source enter in clinical trials. Preliminary results showed a partial activity against non-Hodgkin’s lymphoma. It can inhibit protein synthesis and arrest G1 phase of cell-cycle. Another depsipeptide Aplidine appear to be more active as comparison with didemninB in preclinical trial and does not produce life-threatening neuromuscular toxicity. Preclinical data indicate that aplidine is active against several tumors through blockade of cell-cycle progression at G1 phase (Geldof et al., 1999). There are number of eteineasclidins have been isolated from the marine source tunicate Ecteinascidia turbinata. One of these eteineasclidins (ET-743) was selected for clinical trials and antitumor effects have been observed in studies (Demetri et al., 2000). ET-743 is a tetrahydroisoquinoline alkaloid and they acts by selective alkylation of guanine residues in the DNA minor groove (Erba et al., 2001) and also interacts with nuclear proteins (Damia et al., 2001). In Europe and the United States ET-743 is currently in clinical trials (Demetri et al., 2000). The dolastatins are a class of peptides obtained from the Indian Ocean, Dolabella auricularia. These peptides have cytotoxic activity, dolastatins have received the greatest clinical interest. Dolastatins have entered in clinical trials, after showing significant antitumor activity in preclinical models (Poncet, 1999). Its mechanism of action involves inhibition of microtubule assembly ultimately result in cell-cycle arrest in metaphase (Bai et al., 1990; Pathak et al., 1998). The bryostatins, 20 macrocyclic lactones isolated from Bugula neritina and other marine bryozoa. These macrocyclic compounds have shown significant activity against lymphocytic leukemia cell line (Pettit, 1991). Bryostatin has entered clinical trials for the treatment of melanoma, non-Hodgkin’s lymphoma, renal cancer and colorectal cancer (Pagliaro et al., 2000; Varterasian et al., 2000; Zonder et al., 2001) and continues to be evaluated in clinical trials. Bryostatin has been found to promote the normal growth of bone marrow progenitor cells, to provide in vivo protection against normally lethal doses of ionizing radiation and to serve as an immune stimulant, enhancing the normal production of interleukin and interferons (Ahmad et al., 2000). Beside this there are the number of compounds isolated from marine as potential anti-cancer agents (Mayer and Gustafson, 2006; Mayer and Gustafson, 2008).

Microorganisms as source of anti-cancer agents: Antitumor antibiotics are among the most important cancer chemotherapeutic agents, and include members of the anthracycline, bleomycin, actinomycin, mitomycin and aureolic acid families (Cragg et al., 1997). Clinically useful agents from these above families are the daunomycin and related agents like doxorubicin, idarubicin and epirubicin; the peptolides (exemplified by dactinomycin), the mitosans (such as mitomycin C) and the glycosylated anthracenone mithramycin. The anthracyclines are among the most used antitumor antibiotics in the clinic and exert antitumor activity mainly by inhibiting topoisomerase II (Binaschi et al., 2000; Patrick, 1997). Many pharmaceutical agents have been discovered by screening natural products from a wide range of microorganisms. Rapamycin and its analogs are products of Streptomyces hygroscopicus have potent immunosuppressive activity. They inhibit signaling pathways required for T-cell activation and proliferation. Rapamycin blocks progression of the cell cycle at middle-to-late G1 phase in T cells and B cells, and osteosarcoma and rhabdomyosarcoma cell lines, among others (Alberts et al., 1993). Geldanamycin is a benzoquinone ansamycin natural fermentation product and inhibits heat-shock protein HSP 90 (Schulte and Neckers, 1998). Wortmannin is a product of the fungus Talaromyces.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Uses</th>
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<tbody>
<tr>
<td>Vincristine</td>
<td>Leukemia, lymphoma, breast, lung, pediatric solid cancers and others</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Breast, lymphoma, germ-cell and renal cancer</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Ovary, breast, lung, bladder and head and neck cancer</td>
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<tr>
<td>Docetaxel</td>
<td>Breast and lung cancer</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Ovarian, lung and pediatric cancer</td>
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<tr>
<td>Irinotecan</td>
<td>Colorectal and lung cancer</td>
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wortmanni and inhibits signal transduction pathways by forming a covalent complex with an active-site residue of phosphoinositide 3 kinase (PI3K), inhibiting PI3K activity (Cadenas et al., 1998). Thus, toxins that originally evolved to kill competing microorganisms can have a variety of physiological effects in animals. In many cases, the targets of these compounds are components of signal transduction cascades that are conserved in many species, and that have been considered novel targets for anticancer drug discovery (Adjei, 2000).

### DISCUSSION

Natural products discovered from medicinal plants have played an important role in the treatment of cancer. The plant-based drug discovery resulted mainly in the development of anticancer agents including plants (vincristine, vinblastine,
etoposide, paclitaxel, camptothecin, topotecan and irinotecan), marine organisms (citabrine, apliedine and dolastatin) and micro-organisms (dactinomycin, bleomycin and doxorubicin). Beside this there is numerous agents identified from fruits and vegetables can used in anticancer therapy. The agents include curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistin (soybean), diallyl sulfide (allium), lycopene (tomato), indole-3-carbinol (cruciferous vegetables), limonene (citrus fruits), capsacin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), S-allyl cysteine (allium), alllicin (garlic), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), beta carotene (carrots), and dietary fiber. The active principle derive from natural products are offering a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel lead compound and potentially relevant mechanisms of action (Bhanot et al., 2011; Shoeb. 2006; Balunas and Kinghorn. 2005; Cragg and Newman. 2005; Harvey. 1999; Wall and Wani. 1996). Natural products or natural product derivatives, two plant derived natural products, paclitaxel and camptothecin were estimated to account for nearly one-third of the global anticancer market (Oberlines and Kroll, 2004; Butlet, 2004). There are various plants, herbs and sherbs are exist on this planet. But only a small portion has been explored phytochemically, so it is anticipated that plants can provide potential bioactive compounds for the development of new ‘leads’ to combat cancer diseases. Cancer is a major public health burden in both developed and developing countries. Plant derived agents are being used for the treatment of cancer. Several anticancer agents such as taxol, vinblastine, vincristine, camptothecins, topotecan, irinotecan, epipodophyllotoxin are in clinical use all over the world. A number of promising agents flavopiridol, roscovitine, combretastatinA-4, betulinic acid and silvestrol are in clinical development.

CONCLUSION

Natural products have been a prime source for the treatment of many forms of cancer, many of which are consumed daily with the diet. They provide significant protection against various cancers and many other diseases. The antioxidant medicinal plants and their products prevent from the cancer and other diseases by protecting cells from damage. Thus, consuming a diet rich in antioxidant fruits, vegetables, herbs etc. will provide health-protective effects. Microbes and marine organisms also have been offering the great role in the prevention and treatment of cancer. All the natural products discussed in this review exhibit anticancer activities. Natural products offer a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action.

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