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Anticancer compounds from medicinal plants

Tatjana Mitrović, Vladimir Ranđelović, Marina Jušković

Department of Biology and Ecology, Faculty of Sciences and Mathematics, University of Niš

Abstract:
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Many pharmaceutical agents have been discovered by screening natural products from plants. Medicinal plants are potent sources for developing strategies against cancer, which is projected to become the major causes of death. This article reviews the most promising plant-derived molecules with various antitumor and anti-invasion mode of action.

Introduction

There are at least 250.000 species of plants out of which more then one thousand plants have been found to possess significant anticancer properties (Mukherjee et al, 2001). This paper summarizes the most notable higher plant-derived compounds employed in cancer treatments. Also, other potential anticancer agents, currently under investigation, are discussed.

The taxanes

One of the most outstanding agents for treatment of refractory ovarian, breast and other cancers is diterpenoid Taxol or Paclitaxel. It was first isolated from the bark of the Pacific yew, *Taxus brevifolia* (Wani et al, 1971). Paclitaxel demonstrates a wide range of anticancer activities. It inhibits tubule disassembly and prevents formation of the mitotic spindle, thereby inhibiting cell division and leading to cell death (Long et al, 1994). Paclitaxel also causes accumulation of cell arrested in the G_2/M phase of the cell cycle and enhances the cytotoxic effects of ionizing radiation (Liebmann et al, 1994; Choy et al, 1993). Other effects of Paclitaxel are: induction of apoptosis, inhibition of P-glycoprotein efflux pump and anti-angiogenic activity (Bhalla et al, 1993; Webster et al, 1994; Klauber et al, 1997).

The projected demand of Paclitaxel for treating patients with ovarian cancer is 25 kg/year (Roja, Rao, 2000). One gram of drug is required for treating one cancer patients and is obtained by cutting three to six trees of *Taxus brevifolia* (Roja, Rao, 2000). Alternative supplies of Paclitaxel are: other *Taxus* species (*Taxus baccata, Taxus cuspidata, Taxus canadiensis, Taxus chinesis, Taxus media and Taxus wallichiana*) and isolation of Paclitaxel precursors from needles and twigs of *Taxus brevifolia* for chemical synthesis (Roja, Rao, 2000). The last one is advantageous for production of paclitaxel without damage to the tree, thus representing a renewable source of the compound. Unfortunately, chemical synthesis of Paclitaxel molecule is very difficult to achieve due to its complex structure and therefore its commercial use is limited. An alternative method is found in production of Plaxitacel in plant tissue culture (Jaziri et al, 1996).

Second-generation taxoid compound is obtained by hemisynthesis, using a precursor from the needles of the European yew, *Taxus baccata*. Its generic name is Taxotere or Docetaxel. Docetaxel

is twice as potent as paclitaxel in promoting polymerisation of tubulin and has additional radiation-sensitising effects (Trudeau, 1995). It is mainly active in breast, ovary, head and neck and non-small cell cell lung cancer.

The vinca alkaloids

The vinca alkaloids (Vincristine, Vinblastine, Vindensine) are derived from the Madagascar periwinkle (*Vinca rosea*). They exert their cytotoxic effect by binding to tubulin and preventing polymerization of the tubulin dimers (Mukherjee et al, 2001). The vinca alkaloids have been approved for clinical use for a number of years. Lately, their synthetic analogue Vinorelbine (Navelbine) is involved in treatment of breast cancer and non-small cell lung cancer (Romero et al, 1994).

Camptothecin and analogues

Camptothecin is a quinoline alkaloid first isolated from Chinese tree *Camptotheca acuminata* and later discovered in the indigenous tree *Nothapodytes foetida* (Wall et al, 1966; Govindachari, Viswanathan, 1972). Its unique mode of action is an inhibition of the enzyme DNA topoisomerase I which results in DNA double-strand breaks, cell cycle arrest in G2 phase and apoptosis (Hsiang et al, 1989; Slichenmyer et al, 1993). Despite promising antitumor activity in a number of solid tumors, clinical trials of Camtothecin were discontinued because of unpredictable side effects.

Intensive research effort has led to development of Camtothecin analogues (Topotecan, Irinotecan or CPT-11) with improved toxicity profiles (Slichenmyer et al, 1993). Topotecan is effective against ovary and small cell lung cancer and Irinotecan is mainly used for colon and non- small cell lung cancer. To improve the production of these drugs plant tissue culture methods have been used (Roja, Rao, 2000).

Podophyllotoxins

Another prominent molecule in cancer therapy is lignan Podophyllotoxin extracted from rhizomes of the Eastern North American may apple (*Podophyllum peltatum*). Synthetic modification of this molecule led to development of Etopside and Teniposide with broad spectrum of antitumor activity (Keller-Juslen et al, 1971). Etopside is included in treatment of patients with lung cancer, testicular cancer, Kaposi's sarcoma, lymphoma and leukemia. Teniposide is known to be effective for acute lymphatic leukemia, non-Hodgkin's lymphoma and neuro-blastoma and brain tumor in children. Their action is against microtubule assembly and they arrest cells in late S or G2 phase (Keller-Juslen et al, 1971).

Natural sources of Podophyllotoxins, *Podophyllum peltatum, Podophyllum emodi* and *Podophyllum hexandrum,* are still collected from the wild. In order to protect these species and to lower the price of Podophylotoxins production, plant tissue cultures are developed (Roja, Rao, 2000).

Another source of Podophyllotoxins is roots of *Linum* species (Broomhead, Dewick, 1990). *Linum flavum* and *Linum album* tissue cultures produce high levels of lignans, comparable to those existing in rhizomes of *Podophyllum* plants (Roja, Rao, 2000).

Other anticancer compounds in medicinal plants

The alkaloid Ellipticine originates from leaves of *Ochrosia elliptica*, which grows on islands in the Indian and Pacific Oceans. It shows antitumoral activity due to its intercalation with the DNA (Hamburger, Hostettmann, 1991). Production of this agent by tissue culture is comparable with the levels in the leaves of the intact plant (Roja, Rao, 2000).

Cephalotaxine esters, Harringtonine and Homoharringtonine are isolated from tree *Cephalotaxus harringtonia* by Powell et al (1969). Harringtonine and Homoharringtonine have both antitumor and anti-invasive activity (Liu et al. 1998). Homoharringtone is proved effective against colon tumors, melanoma and leukemia in mice. The production of these compounds in the nature is low, chemical synthesis inefficient and plant tissue culture under development (Roja, Rao, 2000).

Numerous anticancer agents are present in our everyday's menu. Anticancer actions of citrus flavonoids and garlic allyl sulfur compounds are demonstrated by recent studies (Manthey et al, 2001; Milner, 2001). Similar effects of fruits and vegetables beta-carotenoids (lycopene), grapes and red wine resveratrol, green tea polyphenols, St. John's wort hyperforin are noticed, but still waiting for experimental proofs.

Conclusions

The lack of any real cure for many cancers, particularly solid tumors, means that search for new, more effective ways to fight cancer is of great importance. A number of new chemotherapeutic agents with different modes of action have recently become available. Some of them are already in clinical practice and/or evaluated in clinical trials. Limited sources of these anticancer compounds in the nature and above all, our implicit task to protect endangered plant species, demand development and optimization of large-scale tissue culture systems for their production. Also, there are a huge number of molecules, alternative anticancer drugs, that still remains trapped in the nature and therefore extensive screening of medicinal plants and their bioactive compounds will be continued.

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