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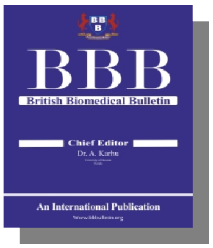

Original

Anticancer Properties of Secondary Metabolites of Medicinal Plants in Carcinoma

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A B S T R A C T

Traditional medicinal plants having the different types of secondary products. The secondary products have great pharmaceutical importance. The secondary metabolites includes the tannins, saponins, catechins, phytoestrogens, mimosins. These products are extracted from the plants by different methods. These are called secondary metabolites. They showed anti-oxidant properties, anti-microbial properties, anti-inflammatory effect and anti cancer properties. Tannis, saponis, mimonins shows the major anticancer properties against breast, prostate and ovarian cancer. The studies proved that the anti cancer properties of secondary metabolites are the alternative medicine to allopathy.

Introduction

Plants produce an amazing variety of metabolites that are gaining importance for their therapeutic and biotechnological applications[1]. He evolution of new genes to synthesize novel secondary products in plants is an ongoing process that might account for most differences in gene function among the plant genomes. Among the thousands of metabolites, only a few are part of the "primary" metabolic pathways and the rest are termed as secondary as they have no specific function in the plants[2]. Levels of secondary metabolites are both environmentally induced as well as genetically controlled. The variety of herbivore deterring phyto metabolites is diverse and, depending on their structure, degree of polymerization, and concentration, may be genotoxic, hepatotoxic, pneumotoxic, neurotoxic, or cytotoxic to the susceptible host[3]. Plant secondary metabolites (PSMs), such as polyphenols, have properties including antioxidant, antimutagenic, anticarcinogenic, anti-inflammatory, and antimicrobial effects that might potentially be beneficial in preventing diseases and protecting the stability of the genome[4]. Herbal medicines along with chemotherapy and radiotherapy have been recommended for patients who become resistant to radiotherapy and chemotherapy or who are not suited for conventional treatment due to old age and marked weakness. The ability of certain PSMs such as polyphenolic compounds to act as scavengers of free radicals, besides their antioxidant and antimicrobial properties, is raising the possibility of their food and pharmaceutical applications. The knowledge gained at the cellular and molecular levels, and biological activities of PSMs including tannin-polyphenols, saponins, mimosine, flavonoids, terpenoids, and phytates, would be useful in planning for future epidemiological studies and human cancer prevention trials, especially when a large pure dosage is not the option to deliver the active compounds to many tissues. It is well observed that alteration of cell cycle regulatory gene expression is frequently found in tumor tissues or cancer cell lines, and studies have suggested that the herbal-based or plant-originated cell cycle regulators might represent a new set of potential targets for anticancer drugs.

Tannins

Tannins are naturally occurring water soluble polyphenols of varying molecular weights and are the most abundant polyphenolic compounds with the ability to precipitate proteins from solutions[5]. Chemically there are two main classes of tannins widely distributed in vascular and woody plants including pteridophytes such as ferns[6]. Hydrolyzable tannins (HTs) are esters of polyol (most often *â*-D-glucose) or hexahydroxydiphenic acid (ellagitannins). In plant cells, the tannins are located separately from the proteins and the enzymes of cytoplasm, but when tissue is damaged, for example, when animals feed, tannins may react with proteins, making them less accessible to the gastric juices of the animals. Tannin-containing plants have been put to use since ancient times. Oak (*Quercus robur*), rich in tannins (gallotannins, ellagitannins, monomeric and dimeric catechins, and leucocyanidins), has long been used for its medicinal properties. Tannins may be either procarcinogenic or anticarcinogenic and either mutagenic or antimutagenic. However, except for extreme cases such betel quid chewing, which enhances accumulation of mitochondrial DNA (mtDNA) deletions in oral cells[7], there appears to be no evidence that tannins are procarcinogenic in humans[8].

Anticarcinogenic attributes of Tannin-polyphenols

There has been a great interest in free radicals and oxygen species generated in vivo, which have been implicated in diseases such as cancer, atherosclerosis, and multiple sclerosis. Agents causing oxidative DNA damage usually increase the risk of cancer development[9]. Ellagitannins have been found to exhibit higher cytotoxicity against human oral squamous cell carcinoma and salivary gland tumor cell lines than against normal gingival fibroblasts[10].

Catechins and their miscellaneous therapeutic uses

Catechins are a group of polyphenolic compounds, (-)-epigallocatechin-3-*O*-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-*O*-gallate (ECG), and (-)-epicatechin (EC), which are abundantly present in vegetables and plant-derived beverages and foods[11]. Chemically, catechins are polyhydroxylated flavonoids, which exhibit water soluble characteristics. Being important microconstituents of the human diet, for instance, with an average intake of 50 mg/ day in The Netherlands, catechins need to be taken into account when the relationship between diet and chronic diseases is investigated[12]. Studies have indicated that EGCG can preferentially induce apoptosis in T lymphocytes of leukemia patients[13] or cultured cancer cell lines[14,15]. Investigating the specific anticancer activity of EGCG, Wang and Bechrach[16] concluded that, compared to normal controls, the transformed NIH-pATMras fibroblasts were sensitive to EGCG at a 5 *i*M concentration. Anticancer activity of the catechins tested was found to be selective and therefore might have a therapeutic value.

Phytoestrogens

Phytoestrogens (PEs) are natural phytometabolites known to possess estrogenic activity[17] and comprise of a number of classes, including isoflavones, lignans, coumestans, and resorcylic acid lactones[18,19]. PEs are structurally or functionally similar to mammalian estradiol[20]. Various plants, specifically those belonging to the Leguminosae and Gramineae families, which include important grain crops, vegetables, oilseeds, and livestock forage[21], are the major sources of various dietary PEs. Two of the major isoflavonoids in soybeans are daidzin and genistin, which are glycoside conjugates of daidzein (7, 4¢-dihydroxyisoflavone) and genistein (5, 7, 4¢-trihydroxyisoflavone), respectively[22].

Phytoestrogens as anticarcinogens

Antioxidant species may act in vivo to prevent oxidative damage to DNA, proteins, and lipids, thus reducing the risk of coronary heart disease and cancers. Both scientific and lay publications on the proposed health-related and clinical benefits of PEs have attracted much attention from the medical scientific community. Consumption of soy products in some Japanese populations, with PE levels in the diet as much as 200 mg/day, has been related to a lower risk of hormone-dependent cancers and other chronic diseases[23]. Approximately 60% of breast cancer patients have hormone dependent breast cancer containing estrogen receptors and therefore require estrogen for proliferation of these cancer cells. In tumors, the expression of aromatase, which converts androgen to estrogen, is up-regulated compared to surrounding noncancerous tissue[24,25]. Aromatase suppression in postmenopausal women could be a potential chemopreventive modality against breast cancer. A high consumption of PEs is

inversely correlated with the incidence and mortality rate of prostate cancer. Studies have shown that genistein inhibits prostate cancer cell growth in vitro and in vivo and decreases secreted and intracellular levels of the androgen-related protein prostate-specific antigen (PSA). Elucidating the mechanism by which genistein modulates PSA protein expression in prostate cancer cells, Davis *et al*[26]. Have reported that expression of PSA is transcriptionally regulated by genistein in prostate cancer cells. Low-dose genistein induces cyclin-dependent kinase inhibitors and cell cycle arrest in human prostate cancer cells.

Saponins

Saponins are glycosidic compounds of steroid (C27)[27] or triterpenoid (C30)[28] sapogenin nucleus with one or more side chains of carbohydrates. Many forage legumes grown in temperate areas contain various saponins and have varieties of biological effects with both positive and negative implications. As a consequence of their amphiphilic nature and surface active properties, saponins are excellent foaming agents, forming very stable foam. Their biological value is closely related to chemical structure, which determines the polarity, hydrophobicity, and acidity of the compounds.

Anticarcinogenic attributes of saponins

Despite the known antinutritional attributes of saponins, the beneficial effects, for instance, hypocholesterolemic[29], anticarcinogenic[30], and immunostimulatory properties[31], are being currently investi-gated. Experimental and epidemiologic carcinogenesis studies showing that >90% of cancer incidents are associated with mutagens and mitogens[32] suggest a search for agents that inhibit or reverse cellular processes derived from mutagenesis and mitogenesis. The active component in several herbal medicines that have been used as chemotherapeutic agents in Eastern countries was shown to be saponins. Ginseng species (e.g., *Panax ginseng*, *P. quiquefolius*, *P. japonocus*, *P. pseudoginseng*, *Eleutheroccus senticosus*, etc.) are widely employed in Chinese medicine, Eastern Asia regions, and Oriental medicine as tonic or adaptogenic and as treatment of cancer, diabetes, and hepatic and cardiovascular diseases[33,34]. These species share many common phytometabolites incuding alkaloids, phytosterols, amino acids, and 0.5-3% of saponins[35]. Ginsenosides, the ginseng saponins constituting 2-4% of its dry weight, are claimed to be responsible for most, if not all, of the pharmacological activities of ginseng. Ginsenoside Rh2 (G-Rh2) isolated from the root of *P. ginseng* inhibited the growth of MCF-7 human breast carcinoma cells through induction of protein expression of p21 and reducing the protein levels of cyclin Cdk, resulting in the down-regulation of cyclin/Cdk complex kinase activity, decreased phosphorylation of pRb, and inhibition of E2F release[36]. Apart from triterpenoid saponins in ginseng, acetylenic alcohols obtained from ginseng, especially panaxytriol, showed anticancer activity against melanoma B16 when intramuscularly administered[37]. 20-*O*-(*â*-D-Glucopyranosyl)-20 (*S*)-protopanaxadiol (IH-901), a novel intestinal metabolite of ginsenosides Rb1, Rb2, and Rc, is of particular interest in cancer chemoprevention and treatment. IH-901 has been reported to exert significant cytotoxic activity against cancer cell lines (HL-60 cells) by inducing internucleosomal DNA fragments. The treatment of HL-60 cells with IH-901 led to activation of caspase-3-protease and subsequent proteolytic cleavage of poly (ADP-ribose) polymerase. These results may provide a pivotal mechanism for the use of IH-901 in the

prevention and treatment of leukemia[38]. Some steroidal saponins showed higher cytotoxic activity against human oral squamous cell carcinoma cell lines (HSC-2) compared to normal human gingival fibroblasts HGF[39]. The tumor specificity of saponins has been reported to exceed that of tannins and flavonoids, suggesting that an oxidation-mediated mechanism was not involved in the cytotoxicity induced by the steroidal saponins.

Mimosin

Mimosine [â-[*N*-(3-hydroxy-4-oxypyridyl)]-R-aminopropionic acid] is found in the plants of Mimosaceae, which include *Leucaena leucocephala*, *L. glauca*, and other legumes including *Mimosa spp*.

Mimosine and cancer therapy

Cell growth and differentiation are the processes intimately associated with carcinogenesis and regulated by tyrosine kinases and other signaling proteins [40]. Natural or synthesized agents that can inhibit cell cycle progression at specific points or the chemicals that affect DNA synthesis are potentially useful for the development of anticancer drugs and effective tools for the investigation of DNA metabolism.

Conclusion

The secondary metabolites from the different plants can show the anticancer properties. Oak (*Quercus robur*), rich in tannins (gallotannins, ellagitannins, monomeric and dimeric catechins, and leucocyanidins), has long been used for its medicinal properties. Tannins may be either procarcinogenic or anticarcinogenic and either mutagenic or antimutagenic. The active component in several herbal medicines that have been used as chemotherapeutic agents in Eastern countries was shown to be saponins. A high consumption of PEs is inversely correlated with the incidence and mortality rate of prostate cancer. Studies have shown that genistein inhibits prostate cancer cell growth in vitro and in vivo and decreases secreted and intracellular levels of the androgen-related protein prostate-specific antigen (PSA). Cell growth and differentiation are the processes intimately associated with carcinogenesis and regulated by tyrosine kinases and other signaling proteins. Most of the herbal medicinal plants secondary products shows the antibacterial activity. So we can use the certain doses of these secondary products as preventive medicine for any type of cancer which may be occur in future.

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