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Review

Anticancer and cancer preventive compounds from edible marine organisms

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ABSTRACT

A direct impact of food on health, which demonstrates that dietary habit is one of the most important determinants of chronic diseases such as cancers, has led to an increased interest of the consumers toward natural bioactive compounds as functional ingredients or nutraceuticals. Epidemiological studies revealed that the populations of many Asian countries with high consumption of fish and seafood have low prevalence of particular type of cancers such as lung, breast, colorectal and prostate cancers. This observation has led to extensive investigations of the benefits of compounds present in edible marine organisms such as fish, marine invertebrates (mollusks, echinoderms) and marine algae as cancer chemopreventive agents. Interestingly, many of these marine organisms not only constitute as seafood delicacy but also as ingredients used in folk medicine of some East and Southeast Asian countries. The results of the investigations on extracts and compounds from fish (cods, anchovy, eel and also fish protein hydrolysates), mollusks (mussel, oyster, clams and abalone), as well as from sea cucumbers on the *in vivo/in vitro* anticancer/antitumor activities can, in part, support the health benefits of these edible marine organisms.

1. Introduction

A large number of studies have demonstrated that dietary habit is one of the most important determinants of chronic diseases such as cardiovascular disease, diabetes, gallstones, neurodegenerative diseases, cataract and several types of cancer. Such an association between dietary habit and disease shows that food has a direct impact on health. Interestingly, it was reported that the predominant forms of cancer, as determined by population and epidemiological studies, are those of the lung and bronchus, breast, colorectal and prostate which are prevalent in the western parts of the world, while their incidence is much lower in Asian countries [1]. In 2007, the World Cancer Research Fund (WCRF) published a systematic review report on food, nutrition, physical activity and prevention of cancer, concluding that food and nutrition have a highly important role in prevention and causation of colorectal cancer and consumption of fish has also been associated with a reduced risk of colorectal cancer [2]. Recently, a great deal of interest has been paid by the consumers toward natural bioactive compounds as functional ingredients or nutraceuticals, especially bioactive compounds derived from marine organisms, which have served as a rich source of health-promoting components [3]. Therefore, this review will focus on the chemopreventive properties of compounds produced by marine organisms which are used as seafood in different parts of the world. Since there are already several recently extensive reviews on the health benefits and chemopreventive effects of compounds derived from marine macro- and microalgae [4–7], they are not included in this review.

2. Fish and fish products

Fish consumption is associated with health benefits due not only to its rich content in proteins of high biological value but also unsaturated essential fatty acids, minerals and vitamins [8]. Moreover, fish proteins are highly sensitive to proteolytic digestion and this enhanced digestibility is due mainly to the absence of strong collagenous fibers and tendon in fish muscle. Additionally, fish proteins are rich in all the essential amino acids, especially methionine and glycine [9].

2.1. Cod and cod liver oil

Among the marine captures, polar fishes such as cod, receive special attention since they are not only an excellent low-calorie source of

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protein but also contain a variety of very important nutrients which are useful in a number of different health conditions. Northern cods, including Atlantic cod (*Gadus morhua*), Greenland cod (*Gadus ogac*) and Pacific cod (*Gadus macrocephalus*), also express abundant Thomsen-Friedenreich Disaccharide (TFD)-containing antifreeze glycoprotein (AFGP) which protects them from freezing. Fish AFGPs are usually composed of tripeptide of alanine-alanine-threonine whose last triad is glycosidically linked to TFD (Galβ1, 3GalNAc). The fact that galectin-3 (gal3), which is one of the 15 members of a β-galactoside-binding lectin family which promotes tumor-endothelial cell adhesion), expressed by the capillary endothelium, participates in docking of cancer cells by specifically interacting with TFD present on their surface, while the circulating gal3 mediates homotypic adhesion of cancer cells by binding to the surface TFD, has led Guha et al. [10] to explore the potential antitumor properties of a TFD-containing natural product that could use as food supplement. For this, they have isolated a TFD-containing glycopeptide of molecular mass 100 kDa (TFD_{100}) from the Pacific cod by affinity chromatography and gel permeation chromatography, and have set up an experiment to verify if this exogenous TFD could block gal3-mediated homotypic aggregation and tumor cell-endothelial interaction to prevent metastasis. They have found that TFD_{100} inhibited both *in vitro* tube formation of human umbilical vein endothelial cells (HUVECs), by binding to the endogenous gal3, as well as *in vivo* vascular endothelial growth factor (VEGF)-induced formation of blood vessels in C57BL/6 black mice. Investigation of TFD_{100} for its capacity to inhibit tumor-endothelial cell interactions revealed that this compound inhibited the binding of HUVECs and androgen-independent prostate cancer cells PC3. Moreover, since human cancer cells are capable of blocking or evading the host-immune response, TFD_{100} was also investigated for its capacity to protect T-cells from tumor-induced apoptosis. The results showed that TDF_{100} was also able to inhibit gal3-mediated apoptosis of T-cells. Since tumor-endothelial interaction and angiogenesis are considered as key steps before cancer metastasis, TDF_{100} could be considered as a promising antimetastatic agent. Thus, they have suggested that TFD-containing compound from edible fish like cod could be a promising antimetastatic agent for the treatment of various cancers, including prostate adenocarcinoma.

Besides cod, “cod liver oil”, a well-known product of cod industry, which was first used to treat rheumatism and then as a source of vitamins A and D, was considered in recent years as a good source of ω-3 PUFAs. Interestingly, only recently much attention has been paid to the research on the anticancer properties of both ω-3 PUFAs and vitamin D. Although there are several reports on the *in vitro* effects of vitamin D and ω-3 PUFAs on breast, prostate, colorectal and lung cancers, as well as epidemiological studies which suggested an inverse correlation between increasing consumptions of both vitamin D and ω-3 PUFAs and increased cancer risk, there is still no research on the efficacy in cancer prevention and treatment of the combination of these two compounds [11].

2.2. Anchovy

Another important capture as food staple is anchovies. Anchovies are small, salt water fish comprising more than 100 different species and are found in large schools throughout the Pacific, Atlantic, and Indian Oceans. However, the most popular place to catch anchovies is the Mediterranean. Anchovies are rich in protein, vitamins and minerals, and for this reason anchovies are largely present in a large part of European, Middle Eastern, and North African cuisines [12]. On the other hand, anchovy sauce has widely been used as a fermented food in Asia. It is also a rich source of amino acids and peptides [13]. Anchovy sauce has been found to possess some interesting biological activities such as antihypertensive [14] and antioxidant properties [15]. Additionally, Lee et al. [16] have found that the hydrophobic peptide fraction of the anchovy sauce was able to exhibit strong antiproliferative activity against a human lymphoma cell (U937), by induction of apoptosis which was accompanied by an increase of caspase-3 and −8 activities. The active peptide fraction was further purified by silica gel chromatography, TLC and reversed-phase HPLC. Analysis of its molecular weight and amino acid composition by MALDI-MS and Pico-Tag HPLC revealed that the antiproliferative peptide was composed of Ala and Phe, having the estimated molecular weight 440.9 Da [17].

2.3. Eel

Another important food fish in East Asia, especially in Japan and Korea, is *Anguilla japonica* or Japanese eel. They are found in Japan, Korea, China, Taiwan, and Vietnam as well as the northern Philippines, where they are raised in aquaculture ponds. It is well established that the skin of eels is covered with carbohydrate-specific proteins, mucus, and mucopolysaccharides for innate immune reaction [18,19]. It was reported that the lectin AJL-2 and the AJN-10 peptide, isolated from the skin mucus of the Japanese eel, possessed antibacterial activities against *Escherichia coli* K 12 and *Aeromonas hydrophila,* respectively. [20]. Recently, Kwak et al. [21] reported a growth inhibitory activity of the eel skin mucus (ESM), isolated from *A. japonica* from Korea, on human leukemia K562 cells, by causing apoptosis. The results from the immunoblotting analysis suggested that extracellular signal-regulated kinase 1 and 2 (ERK1/2) and p38 signals could be involved in the ESM mediated-apoptosis. Furthermore, they have also found that treatment with lactose rescued the ESM-mediated decrease in cell viability, thus suggesting that lactose binding lectin-like molecules in ESM may be the apoptosis-inducing factors. Therefore, the authors have suggested that the skin mucous of eel could be exploited as a potential new drug candidate for an alternative therapy for human leukemia.

2.4. Fish protein hydrolysate

It is also important to note that more than 70% of the world fish production, which is mainly derived from marine capture fisheries, has been used for processing [22]. Since the majority of fisheries by-products are used to produce low economic-value products such as fish oil, fish meal, fertilizer, pet food and fish silage [23], much attention has been focused on the identification of bioactive compounds from remaining fish muscle proteins, fish oil, fish bone and internal organs, as high-value products for human consumables. These bioactive compounds, particularly bioactive peptides, have been identified as potential nutraceuticals to improve human health and prevent diseases [24]. One of these by-products is fish protein hydrolysates (FPH) which are obtained by controlled enzymatic hydrolysis. FPH are believed to possess an excellent nutritional value since they have a balanced amino acids composition and high digestibility. However, due to their bitter flavor and strong fishy odor, they are still currently used in animal nutrition [25]. Although peptides from various fish protein hydrolysates have been shown to possess antihypertensive [26], anticoagulant [27], and antioxidant activities [28], investigations of their anticancer activity are still scarce. Picot et al. [25] have investigated the *in vitro* antiproliferative activity of eighteen FPH from Atlantic salmon (*Salmo salar*), Atlantic cod (*Gadus morhua*), plaice (*Pleuronectes platessa*), blue whiting (*Micromesistius poutassou*), Atlantic emperor (*Lethrinus atlanticus*), pollack (*Pollachius pollachius*), and Portuguese dogfish (*Centroscymnus coeloepsis*) on two human breast carcinoma cell lines, MCF-7/6 and MDA-MB-231. They have found that the FPH from the three Blue whiting, cod, plaice and one salmon, at 1 g/mL, induced significant inhibition of cancer cell growth. Moreover, FPH from the three Blue whiting, which contained low NaCl concentration and 96% peptide, were found to induce growth inhibition of 24.5, 22.3, and 26.3% of MCF-7, and 13.5, 29.8 and 29.2% of MDA-MB-231. The authors have pointed out that these values were in the range of those measured in the presence of the anticancer agents: etoposide, roscovitine and kenpaullone, at 10^{-6} M concentration. They have found also that the antiproliferative activities of these FPH were dependent on the cell lines