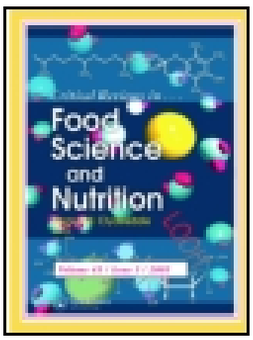

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Chemopreventive role of food-derived proteins and peptides: a review

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Abstract

Cancer is one of the leading causes of mortality and disability worldwide. Although great advances in cancer treatments such as chemotherapy, surgery and radiation are currently being achieved, their application is associated with numerous and expensive adverse side effects. Epidemiological evidence has demonstrated that the consumption of certain foods potentially prevents up to 35% of cancer cases. Bioactive components are ubiquitous in nature, also in dietary food, providing an essential link in health maintenance, promotion and prevention of chronic diseases, such as cancer. Development of bioactive proteins and peptides is a current and innovative strategy for cancer prevention/cure. A growing body of anticancer protein and peptides from natural sources has shown the ability to reduce tumor progression through multiple mechanisms including apoptotic, anti-proliferative, anti-angiogenic and immunomodulatory activities. This review is focused on proteins and peptides from different food sources including

plants, milk, egg, and marine organisms in which chemopreventive properties have been demonstrated. Other aspects such as mechanism of action, bioavailability, and identification and characterization of food-derived peptides by advance separated technologies are also included. This review highlights the potential application of food-derived peptides as functional food ingredients and pharmaceutical candidates in the auxiliary therapy of cancer.

Keywords

Anti-proliferative protein and peptide, apoptosis, cancer, food-derived bioactives

1. Diet and cancer

Cancer is one of the leading causes of mortality and disability worldwide, responsible for approximately 13% of deaths (Ferlay et al., 2010). In the last decades, there have been great advances in cancer treatments such as chemotherapy, surgery, and radiation. However, these therapies are highly expensive and include drugs with numerous adverse side effects. Thus, there is a clear need for cheaper and more effective strategies to maximize cure rates with minimal toxicity. In addition, many researchers have focused on alternatives to prevent tumour, thus reducing the high rates of mortality and the elevated costs of therapies. It has been estimated that only 5-10% of all cancer cases are due to genetic defects whereas the remaining 90-95% are attributed to environmental and lifestyle factors (Anand et al., 2008). Epidemiological evidence has demonstrated that modifications of nutritional factors and food consumption patterns can potentially prevent up to 35% of cancer cases (Marmot et al., 2007), although the actual percentage depends on the dietary component and the specific type of cancer (Davis and Milner, 2007).

Chemoprevention has been defined as “the use of natural and/or synthetic substances to block, reverse, or retard the process of carcinogenesis”. Among chemopreventive agents, those present in foods have been demonstrated to exert anti-proliferative activity, to lower cancer risk, and even to sensitize tumour cells against anti-cancer therapies (Béliveau and Gingras, 2007). Extensive research has revealed that a diet consisting of fruits, vegetables, spices, and grains has the potential to prevent cancer. The bioactive substances contained in these plant species, including essential nutrients, polyunsaturated fatty acids and phytochemicals, are responsible for the demonstrated cancer preventive effects, and thus, they have been extensively studied (Anand

et al., 2008). However, food bioactives are not limited to plants, since animal and fungi food products can also contain compounds with anticancer properties. Recently, the crucial role played by gut microbiota to release compounds with both pro-cancerigen and anti-cancerigen effects has been recently reported (Milner, 2004). Therefore, knowledge on the effect of dietary components on health will bring new opportunities for chemoprevention through intense alterations in dietary regimens.

2. Chemopreventive effects of food proteins and peptides

Currently, the development of proteins and peptides with useful anticancer potential is an innovative strategy for cancer prevention/cure (Bidwell and Raucher, 2009; Raucher et al., 2009). They (mainly peptides) possess certain key advantages over alternative chemotherapy molecules, such as their high affinity, good penetration in tissues, strong specificity for targets, and low toxicity (Bhutia and Maiti, 2008). A number of anticancer protein and peptides from natural sources have been reported. They have shown the ability to reduce tumor progression through multiple mechanisms including apoptotic, function-blocking, anti-angiogenic and immunomodulatory activities (Bhutia and Maiti, 2008). Among them, those proteins and peptides derived from foods have become an interesting alternative because of their low price, non-toxic nature, less adverse side effects, and their high acceptance by consumers (Silva-Sánchez et al., 2008). It has been reported that these food peptides can act preventing the different stages of cancer, including initiation, promotion, and progression (de Mejia and Dia, 2010). This review is focused on proteins and peptides from different food sources for which chemopreventive properties have been demonstrated by *in vitro* and *in vivo* studies. Other

aspects such as mechanism of action, bioavailability and clinical evidence of the effects of these components will also be included.

2.1. Anti-cancer plant proteins and peptides

In the last years, plant proteins and peptides with cytotoxic activity against cancer cells have become promising alternatives for the development of new anti-cancer drugs. The following section focused on those proteins and peptides with demonstrated anti-carcinogenic properties.

2.1.1. Plant lectins

Plant lectins are proteins or glycoproteins of non-immune origin widely distributed in seeds, roots, stems, and leaves (Moreira et al., 1991). They contain at least one non-catalytic domain which enables them to selectively identify and reversibly bind to specific carbohydrates without altering their structure (Van Damme et al., 1998). According to their carbohydrate-binding specificity, lectins are classified into 12 different families, such as (1) *Agaricus bisporus* agglutinin homologs, (2) Amaranthins, (3) Class V chitinase homologs with lectin activity, (4) Cyanovirin family, (5) *Euonymus europaeus* agglutinin family, (6) *Galanthus nivalis* agglutinin family, (7) proteins with hevein domains, (8) Jacalins, (9) proteins with legume lectin domains, (10) Lys motif domain, (11) Nictaba family (formerly *Cucurbitaceae phloem* lectins), and (12) Ricin-B family (Van Damme et al., 2008). Among them, proteins with legume lectin domains have been the most extensively studied for their activities against different pathological diseases including cancer (Liu et al., 2010a). Serial studies have shown that lectins possess mitogenic, antiproliferative, antitumor, antiviral and immune-stimulating potential. The chemopreventive activity reported from plant lectins using cell experiments and animal models as well as the mechanisms of action elucidated to date are summarized in Table 1.

Lectins from mistletoe received more attention for their anti-proliferative activities against multiple cancer cell lines. Firstly, lectins from European mistletoes were identified and studied, although subsequent analyses have demonstrated similar effects for Chinese and Korean mistletoes-derived lectins. Their sugar-binding capacity seems to play a crucial role in determining selective toxicity for cancer cells through interaction with sugar-chain or sugar-containing receptor present on the cell surface (Hoessli and Ahmad, 2008). Accumulating evidence in the anti-proliferative effects of mistletoe lectins towards various types of cancers such as human acute lymphoblastic and monoblastic leukemia (Pae et al., 2001; Fulda and Debatin, 2006; Hoessli and Ahmad, 2008; Seifert et al., 2008), hepatocarcinoma (Lyu et al., 2002), lung cancer A549 (Fulda and Debatin, 2006; Hoessli and Ahmad, 2008), and colon cancer cells (Khil et al., 2007; Monira et al., 2009) are currently available. In addition to mistletoe, lectins are also present in other plant species. Concanavalin A is a lectin belonging to legume lectin family that was originally extracted from *Canavalia ensiformes* (jack-bean). It possesses a wide range of biological functions such as anti-tumor, anti-viral, and anti-fungal activities (Fu et al., 2011). As it has been reported for mistletoe lectins, the functions of concanavalin A have also been linked to its sugar-binding ability. Initially, this lectin was demonstrated to mediate cytotoxicity towards BALB/c 3T3 and gingival fibroblasts through apoptotic induction (Kulkarni and McCulloch, 1995). As shown in table 1, the anti-proliferative effects have also been observed against melanoma A375 and hepatocarcinoma HepG2 (Liu et al., 2009d; 2010b), gliobastoma U87 (Proulx-Bonneau et al., 2010; Sina et al., 2010), ovarian cancer SKOV3, and Li-Fraumeni syndrome MDAH041 cells (Amin et al., 2007).

Although lectins derived from various plant sources have been demonstrated to exert chemopreventive effects against different cancer cell lines, only those derived from mistletoe and *Arbus* spp. have been assayed in animal models. First study showed that administration of Chinese mistletoe lectin delayed colon cancer development in a mice model through regulation of immune responses (Ma et al., 2008). Li and co-workers also demonstrated the anti-neoplastic activity of mistletoe lectins in colorectal bearing mice (Li et al., 2011). Intraperitoneal administration of mistletoe lectin preparations improved survival of mice injected with leukemia cells without any adverse side effects (Seifert et al., 2008), and inhibited melanoma growth and its spread to the lung in a human melanoma cells xenograft mouse model (Thies et al., 2008). In the case of *Arbus*, its derived-agglutinin has been shown to activate tumor-associated macrophages, to increase nitric oxide production, and to induce cytotoxicity against tumor cells in Dalton's lymphoma mouse model (Ghosh and Maiti, 2007). Anti-tumor effects have also been observed in tumor-bearing mice after administration of lectin-derived peptide from *Arbus* through immunomodulatory actions (Bhutia et al., 2009).

Considering the fact that plant lectins were initially described more than 30 years ago, their molecular mechanism of action is yet to be completely elucidated. Several mechanisms have been proposed, including effects on tumour cell membranes, ribosomes-binding ability, inhibitory activity of protein synthesis, cell cycle arresting ability, apoptotic induction through caspases-dependent and independent-pathways, autophagy stimulating effects, angiogenesis and metastasis inhibitory capacities, and immunomodulatory properties through inducting tumour-specific cytotoxicity of macrophages (de Mejia and Prisecaru, 2005; de Mejia and Dia, 2010; Fu

et al., 2011; Liu et al., 2013). Some of these plant proteins are currently being proven as therapeutic agents against cancer in human trials, holding considerable potential.

2.1.2. Protease inhibitors

Proteolysis, a tightly controlled process by enzymes, plays a crucial role in multiple physiological processes such as fertilization, homeostasis, neuronal development, apoptosis, and immunological responses (Safavi and Rostami, 2012). The proteolytic enzymes constitute a protease family, which components are classified in four major subcategories according to the interaction of protease catalytic residue with specific inhibitors. These categories are (1) serine proteases, (2) metalloproteases, (3) aspartic proteases, and (4) cysteine proteases. Proteases have been recognized as essential players in a wide range of physiological processes including cell cycle and signaling, digestion, immune response, blood coagulation, and wound healing. However, their deregulated proteolytic activity is linked to multiple human diseases, ranging from degenerative and inflammatory disorders to cancers (Clemente and Arqués, 2014). Thus, the activity of proteases requires to be tightly controlled through multiple pathways, such as modulation of enzyme expression and/or secretion, activation of inactive pro-enzymes (zymogens), pH regulation, and reversible/irreversible inhibition (Debowski, 2013).

Protease inhibitors are distributed into several families, including Bowman-Birk protease inhibitor (BBI), Kunitz-type protease inhibitor (KTI), serine protease inhibitor (serpin), squash inhibitory, potato I and II inhibitor, barley trypsin inhibitor, cysteine protease inhibitor (cystatin), and barley trypsin inhibitor families (Laskowski and Kato, 1980). This section of the review focuses on the most studied protease inhibitors families, BBI and KTI families, present in

legume seeds, which chemopreventive properties have been evaluated by multiple *in vitro* and *in vivo* models.

The BBI family comprises polypeptides composed of less than 100 amino acids including 14 cysteine residues, and containing two inhibitory domains for trypsin and chymotrypsin-like enzymes. It has been demonstrated that BBI resists the acidic conditions and the action of proteolytic enzymes present in the gastrointestinal tract, allowing this polypeptide reaching the distal intestine in an intact and active form to exert its bioactive properties (Clemente et al., 2011). Although BBI is ubiquitously distributed in the plant kingdom, the soybean BBI and BBI concentrate (BBIC) have received special attention because of their anti-inflammatory and chemopreventive activities against different types of cancer (Losso, 2008). Evidence on the beneficial properties of BBI against cancer demonstrated by cell experiments and animal models as well as its potential modes of action are shown in Table 2. Treatment with BBI has been reported to be effective in preventing chemical carcinogenesis-induced transformation in cultured mouse mammary glands (Du et al., 2001). Moreover, BBI suppresses proliferation of human breast MCF-7 cells through reduction of proteasome function, resulting in up-regulation of MAP kinase phosphatase-1, induction of apoptosis and lysosome membrane permeabilization (Zheng et al., 1999; Chen et al., 2005; Ho and Ng, 2008). BBI also possesses chemopreventive activity associated with induction of Cx43 expression and apoptosis in human prostate cancer LNCaP cells (Tang et al., 2009), and in different prostate cancer animal models (Kennedy & Wan, 2002; McCormick et al., 2007; Tang et al., 2009). The anti-carcinogenic activities of BBI have also been shown in human osteosarcoma U2OS (Saito et al., 2007), ovarian sarcoma M5067 (Sakurai et al, 2008a, b), hepatocarcinoma HepG2 (Ho and Ng, 2008), and promyelocytic

leukemia NB4 cells (Huang et al., 2007). Recent studies have demonstrated a significant dose- and time-dependent decrease of colorectal human adenocarcinoma (HT29, Caco2, LoVo) cells proliferation after treatment with different BBI variants derived from pea (Clemente et al., 2005), lentil (Caccialupi et al., 2010**)**, and soybean (Clemente et al., 2010). However, BBI did not affect the growth of non-malignant colonic fibroblastic CCD18-Co cells. In animal models, both BBI and BBIC have shown suppressive effects on carcinogen-induced transformation in the colon (Clemente and Arqués, 2014), oral cavity (Kennedy et al., 1993), prostate (Wan et al., 1999), lung (Kennedy et al., 2003) and skin (Huang et al., 2004).

In 1992, the Food and Drug Administration (FDA) approved the use of BBIC in clinical trials as a New Investigational Drug. Since then, different human trials have been completed in patients with benign prostatic hyperplasia (Malkowicz et al., 2001), oral leukoplakia (Armstrong et al., 2000, 2003; Meyskens, 2001), and ulcerative colitis (Lichtenstein et al., 2008). Results from these studies indicated that BBI and BBIC are well-tolerated, and no side-effects have been associated with their use for a prolonged time.

KTI is another protease inhibitor originally isolated from soybean with trypsin inhibitory properties. Its ability to suppress invasion and metastasis of cancer cells has been demonstrated in several xenograft animal models after implantation of ovarian cancer HRA and Lewis lung carcinoma cells in C57BL/6 mice (Kobayashi et al., 2004a, b). In addition, cell cultures have been carried out to elucidate the mechanism of action of this protease inhibitor. In lymphoma Nb2 cells, KTI caused decrease of cellular viability, apoptosis, DNA hypodiploidy and fragmentation, without affecting normal lymphocytes (Troncoso et al., 2003). KTI has also been shown to suppress urokinase-type plasminogen activator (uPA) signalling cascade and invasion

in Y529F ovarian cancer cells (Inagaki et al., 2005). Recently, a weak anti-proliferative activity of Korean large black soybean-derived KTI has been revealed in nasopharyngeal cancer CNE-2 and HNE-2, breast cancer MCF-7 and hepatoma HepG2 cells (Fang et al., 2010). Similar results in MCF-7 and HepG2 cells were found after treatment with KTI isolated from seeds of small glossy black soybean (Ye and Ng, 2009). However, little information on the mechanisms of action of KTI is still available, and thus, further pharmacological, proteomic and genetic approaches are required to allow its application in the future.

2.1.3. Lunasin

Lunasin is a 43-amino acid peptide identified in soybean sixteen years ago (Galvez and de Lumen, 1999) and afterwards, in other seeds and legumes. A number of cell culture experiments and animal models have demonstrated the potent anti-carcinogenic effect of this peptide in addition to its antioxidant and anti-inflammatory properties. All these effects have been summarized in Table 3. Early studies demonstrated that lunasin neither affects morphology nor proliferation of non-cancerigen mammalian cells. However, when a transformation event occurs, lunasin gets into action within the cell preventing induced-carcinogenic processes. Lunasin is capable to suppress transformation of chemical, and viral and *ras*-oncogenes-induced carcinogenesis in mammalian cells. Moreover, this peptide also exerts anti-neoplastic effects in established cancer cells, such as breast, colon and prostate, leukemia, and lymphoma cell lines through modulation of multiple cellular pathways implied in the initiation, promotion and progression stages of cancer. Initially, the ability of lunasin to internalize into mammalian cells and sit within the nuclear compartment was highlighted (Galvez et al., 2001; Lam et al., 2003). Beyond its internalization into the cell, biochemical evidence has shown that lunasin, either

synthetic or extracted from natural plants tends to bind to deacetylated core histones, and to inhibit core histones H3 and H4 acetylation. Moreover, this peptide acts in the presence of the histone deacetylase inhibitor sodium butyrate competing with different histone acetyltransferases (HAT) enzymes, such as PCAF, CBP/p300 and yGCN5 (Galvez et al., 2001; Jeong et al., 2002, 2003, 2007). This evidence implied lunasin's role in chromatin remodeling, a process intimately related to the control of cell cycle progress and tumor progression (Esteller and Herman, 2002; Lund and van Lohuizen, 2004), suggesting an epigenetic nature of the mechanisms of action of lunasin (Stefanska et al., 2012). In addition, several studies on the lunasin´s cancer-preventive effects have reported that this peptide is able to modulate expression of different genes and proteins involved in cell cycle, apoptosis, and signaling transduction as well as to act as anti-metastasic agent (Table 3).

Recent animal studies have confirmed the properties of lunasin against different types of cancer, such as skin, breast, colon cancer, and lymphoma. Hsieh and co-workers demonstrated that lunasin acts against breast cancer in both xenograft MDA-MB-231 and chemically-induced breast cancer mice models (Hsieh et al., 2010a; 2010b). Also, it has been reported that lunasin treatment delayed liver metastasis using colon cancer KM12L4 cells directly injected into athymic mice (Dia and de Mejía, 2011a). A recent study has revealed that lunasin reduces tumour volume in the xenograft Raji mice lymphoma model (Chang et al., 2014). The evidence makes lunasin as a promising candidate for a new generation of chemopreventive/chemotherapeutical agents derived from natural seeds. There is still much to learn about the effects of this peptide and its complete mechanisms of action, although this research area holds a huge potential.

2.1.4. Other chemopreventive plant derived proteins and peptides

In the last years, the search of plant-derived proteins and/or peptides with anti-cancer properties has extended to multiple species. Hazelnuts, mainly used as ingredients for confectionary and for the production of hazelnut cream, have been recently found to contain proteins with potent antiproliferative activity against colon cancer CCC221/DLD-1 cells (Aydemir et al., 2014). The protein isolate obtained from the *Amaranthus mantegazzianus* seed has shown antiproliferative effects, cell adhesion inhibitory and apoptosis inducing properties against the osteosarcoma UMR106 cell line, being these effects higher after the hydrolysis of seed proteins (Barrio and Añón, 2010). Hydrolysis of walnut proteins also allows liberating peptides with the antiproliferative action on human breast, colon and cervical cancer cells without affecting the growth of normal epithelial cells (Zhai et al., 2013). Similarly, trypsin has been used to hydrolyze the seed proteins of *Polyalthia longifolia* releasing peptides with cytotoxic activity against A549 and HeLa cells (Rupachandra and Sarada, 2013).

Canola or rapeseed production has increased rapidly over the past 40 years because of the importance of the canola oil that has become the third most produced vegetable oil worldwide (Alashi et al., 2013). The remaining by-product, known as canola seed meal, is used as a high protein animal feed (Aachary and Thiyam, 2012). Also, its adequate balance of amino acids and its functional properties make canola meal an excellent supply of protein for human consumption. In addition, there is accumulated evidence on the relationship between canola proteins and health, which is due as a result of the presence of many peptides within the primary structure of proteins that once released, exert multiple beneficial properties, such as antihypertensive, antidiabetic, antioxidant, and anti-cancer properties (Aachary and Thiyam, 2012). The antiproliferative and

apoptotic inducing properties of rapeseed peptides have been recently demonstrated in human cervical cancer HeLa cells (Xue et al., 2011). Treatment of cells with these peptides provoked morphology changes including cell shrinkage, nuclear fragmentation, and chromatin condensation which are the typical characters of apoptotic cells.

Corn-derived peptides have shown to induce apoptosis and arrest cell cycle in hepatoma HepG2 cells, as well as to inhibit tumour growth and prolong survival of H22-bearing mice (Li et al., 2013). However, the sequence of these peptides has not been elucidated yet. In other studies, some peptides have been characterized as being responsible for the observed effects. As an example, peptide ENPRP was identified in rice bran and characterized by its cell proliferative inhibitory properties against colon carcinoma Caco-2 and HCT-116, breast cancer MCF-7 and MDA-MB-231, and liver cancer HepG2 cells (Kannan et al., 2010). Recently, it has been identified the peptide AWKLFDDGV in the seeds of *Cycasrevoluta revolute* with inhibitory properties of human epidermoid cancer Hep2 and colon carcinoma HCT15 cells proliferation (Mandal et al., 2012).

2.2. Anti-cancer proteins and peptides from milk

Lactoferrin is a whey protein with multiple physiological activities such as anti-microbial and immunomodulatory properties that play a significant role in its chemopreventive effects (Kanwar and Kanwar, 2013). Treatment of lactoferrin inhibited breast cancer MDA-MB-231 cells growth through arresting cell cycle at the G1/S transition (Damiens et al., 1999). Additionally, lactoferrin induced growth arrest via nuclear accumulation of Smad-2 in HeLa cells (Zemann et al., 2010), and suppressed AKT signaling in nasopharyngeal carcinoma cells (Deng et al., 2013). In animal studies, oral administration of recombinant human lactoferrin

significantly reduced head-and-neck squamous cell carcinoma in tumor-bearing mice. The possible mechanisms of action of this protein include the increase of interleukine (IL)-8 and activation of natural killer and CD8+ T-cells (Varadhachary et al., 2004). Similarly, after oral administration of bovine lactoferrin to lung cancer transgenic mice, a significant suppression of tumor formation and reduction of tumor necrosis factor (TNF)-α, IL-4, IL-6, and IL-10 levels were observed (Tung et al., 2013). In addition, bovine lactoferrin improved the chemotherapeutic effects of tamoxifen in the 4T1 breast cancer xenograft Balb/c mice model (Sun et al., 2012).

Lactoferrin-derived peptide lactoferricin is one of the most studied anti-cancer peptides derived from milk. It has demonstrated potent activity against different types of cancer cell lines, including breast, colon, fibrosarcoma, leukemia, oral, and ovarian cancer cells, without harming normal lymphocytes, fibroblasts, endothelial, or epithelial cells (Furlong et al., 2010). The strongly cationic character of this peptide that allows it to interact with negatively charged structures found in cancer cells seems to be responsible for its action (Hoskin and Ramamoorthy, 2008). In addition to this mechanism, lactoferricin has been shown to arrest cell cycle, induce apoptosis, and modulate gene expression and to prevent angiogenesis (de Mejia and Dia, 2010). *In vivo* evidence has revealed that subcutaneous treatment of lactoferrin in Meth A fibrosarcoma mice and neuroblastoma xenografts significantly inhibited tumor growth (Eliassen et al., 2002, 2006). Similarly, administration of lactoferricin resulted in a significant inhibition of spontaneous melanoma cells growth, and suppression of lymphoma metastases in mouse liver and lung (Yoo et al., 1997). Moreover, these authors demonstrated the capacity of this peptide to reduce the number of tumor-induced blood vessels inhibiting tumor angiogenesis.

Chemopreventive properties have also been demonstrated for whey protein α-lactalbumin combined with oleic acid. The complex formed with this protein from bovine origin and oleic acid, and known as Bovine Alpha-lactalbumin Made Lethal to Tumor cells or BAMLET has been reported to induce cancer cell death (Pepe et al., 2013). This complex acts through modulation of lysosomal membrane permeabilization and activation of the pro-apoptotic protein Bax (Fast et al., 2005; Svensson et al., 2003). In addition, BAMLET causes chromatin condensation and cancer cells shrinkage. Human Alpha-lactalbumin Made Lethal to Tumor cells (HAMLET) has also been found to be cytotoxic against cancer cells. Treatment with HAMLET induced caspase activation and caused mitochondrial permeability resulting in a loss of mitochondrial membrane potential and cytochrome c release (Brinkmann et al., 2013).

Recently, a whey-derived peptide mixture has been shown to induce apoptosis of human colon carcinoma HT-29 cells accompanied by induction of nuclear condensation, DNA fragmentation and modulation of carcinogenesis biomarkers (Kreider et al., 2011). However, to date, the responsible peptides for these effects have not been identified.

Casein has also been reported as a source of antiproliferative peptides. Among them, opioid casein-derived peptides, β-Casomorphin 7 and β-Casomorphin 5, have shown antiproliferative and cell cycle arresting activities in breast cancer cells that seem to be mediated through interaction with opioid receptors (Hatzoglou et al., 1996; Maneckjee et al., 1990). Similarly, the interaction with specific opioid and somatostatin receptors present in the intestinal tract of mammals might be responsible for the antiproliferative effects on colon cancer cells treated with β-casomorphins and other milk-derived opioid peptides (Pepe et al., 2013). Caseinophosphopeptides, through their ability to bind calcium and activate voltage-dependent

calcium channels, seem to inhibit cellular proliferation and induce programmed cell death in intestinal tumor HT-29 and AZ-97 cells (Perego et al., 2012).

2.3. Anti-cancer properties of egg proteins and peptides

Lysozyme is a bactericidal protein which anti-cancer properties have been extensively studied. It was demonstrated that oral administration of this protein inhibited formation and growth of multiple tumours (Sava et al., 1991; Das et al., 1992; Pacor et al., 1999). Moreover, this protein, administered to mice bearing B16 melanoma, significantly reduced the formation of spontaneous lung metastases and prolonged the survival after surgical removal of the primary tumour (Sava, 1989). It has also been found as the ability of lysozyme to enhance the efficacy of chemotherapy treatments. Therefore, this protein is becoming a promising co-adjuvant therapy against cancer (Sava et al., 1995).

Some studies have revealed the reduction of colorectal cancer in rats treated with hydrolyzates from egg yolk protein through inhibition of tumour cells proliferation (Azuma et al., 2000). These protective effects might be due to the strong antioxidant properties of protein phosvitin and its derived-phospho-oligopeptides (Ishikawa et al., 2004). Egg ovomucin has also been shown as a precursor of anti-cancer oligopeptides after the action of pronase because of the tumor growth inhibitory activity demonstrated for the hydrolyzate in a murine model (Watanabe et al., 1998).

2.4. Antiproliferative peptides from marine organisms

Marine organisms, which make up approximately one half of the total worldwide biodiversity, contain multiple compounds with potential therapeutic applications (Kim and Wijesekara, 2010). These compounds include phenols, alkaloids, terpenoids, polyesters, and

other secondary metabolites, which are present in sponges, cyanobacteria, mollusks, and ascidians, among others (Jimeno et al., 2004). Among them, an extensive group of peptides and desipeptides with multiple biological activities have been extracted from different marine species. By modulating and improving physiological functions, these bioactive peptides may provide new therapeutic applications for the prevention and/or treatment of chronic diseases, such as cancer (Suarez-Jimenez et al., 2012). Table 4 shows those marine organisms-derived peptides characterized by their anti-cancer activities as well as their mechanisms of action demonstrated by cell culture and animal models. Majority of peptides have been extracted from ascidians, mollusks and sponges. As it is shown in Table 4, sack-like sea squirts are an important source of potent anti-cancer peptides. Didemnins were firstly extracted from tunicate *Tridemnum solidum*, and then from other species of the same genus (Aneiros and Garateix, 2004). Their preclinical evidence made these peptides the first marine natural products to be evaluated in clinical trials. However, phase II trials using Didemnin B at the recommended doses were inefficient, while using higher doses in trials resulted in high levels of toxicity, including cardiotoxicity (Shin et al., 1991). Aplidine is a cyclodepsipeptide isolated from the tunicate *Aplidium albicans*, with potent properties against different cancer cell lines such as breast, melanoma and lung cancer cells (García-Fernández et al., 2002). The mechanism of action of this peptide includes cell proliferation inhibition, apoptosis induction, and cell cycle arrest. Early clinical phase I trials have revealed the efficacy of this peptide in humans, and phase II trials are currently ongoing. Other cyclic peptides with anti-cancer properties contain Tamandarins A and B were extracted from an unidentified Brazilian ascidian (Vervoort et al., 2000), Mollamide from

Didemnum molle (Carroll et al., 1994), and Vitilevuamide from *Didemnum cuculiferum* and *Polysyncranton lithostrotum* (Edler et al., 2002) (Table 4).

Mollusks include species with a wide range of pharmacological applications. Among the bioactive peptides identified in these species, Dolastatins, mainly Dolastatin 10 and 15, isolated from *Dollabella auricularia*, are the most promising reported to date (Pettit et al., 1995; 1998). Keenamide A is a cyclic hexapeptide isolated from the mollusk *Pleurobranchus forskalii*, which exhibits significant activity against the leukemia P388, lung cancer A549, melanoma MEL-20 and colon cancer HT-29 cells (Wesson and Hamann, 1996). Kahalalide F is a dehydroamino-butyric acid- peptide which is known to exhibit interesting specific activity against prostate cancer cells. Also, the efficacy of this peptide demonstrated in phase I trials suggest its potential against other types of tumors, and currently, phase II trials are assaying the activity of Kahalalide F against lung and prostate cancer, and melanoma (Martín-Algarra et al., 2009).

Sponges are other important marine source of bioactive peptides, mostly cyclodepsipeptides, which are secondary metabolites with unusual amino acids and non-amino acid moieties. Jaspamide, a cyclic depsipeptide, was proven to inhibit cell proliferation and induce apoptosis in human promyelocytic leukemia HL-60 and Jurkat T cells (Odaka et al., 2000; Cioca and Kitano, 2002). Arenastatin A is a cyclodepsipeptide isolated from *Dysidia arenaria* that has demonstrated a potent cytotoxicity against epidermal mouth carcinoma KB cells (Aneiros and Garateix, 2004). Phakellistatins is a family of cyclic peptides identified in species from genus *Phalkellia* with proven activity against leukemia and liver cancer (Li et al., 2002). Geodiamolide, Calyxamides A and B, and Milnamides F and G are examples of recently identified marine-

derived peptides with anti-cancer properties mediated through multiple mechanisms (Freitas et al., 2008; Kimura et al., 2012; Tran et al., 2014)

In recent years, there has been a great number of researches focused on the release of bioactive peptides encrypted within marine proteins after the action of proteolytic enzymes (Table 4). Gelatin was obtained from the giant squid *Dosidicus gigas* that once hydrolyzed by Esperase enzyme showed high cytotoxic effect against human breast cancer MCF-7 and glioma U87 cells (Aleman et al., 2011). An oligopeptide-enriched hydrolyzate from oyster (*Crassostrea gigas*) has demonstrated to reduce tumour growth in a sarcoma S180-bearing BALB/C mice model (Wang et al., 2010). These authors also reported that the administration of this hydrolyzate significantly increased the weight of thymus and spleen, activity of natural killer cells, proliferation of splenocyte, and the phagocytic rate of macrophages. Also, recently, the anti-inflammatory properties of the oyster hydrolyzate have been demonstrated (Hwang et al., 2012). This evidence suggests that the chemopreventive properties of this hydrolyzate may be attributed to its immunostimulating and anti-inflammatory activity.

In some studies, the sequences of the peptides responsible for the observed effects have been elucidated. For example, the peptides LPHVLTPEAGAT and PTAEGGVYMVT contained in the hydrolyzate of tuna dark muscle have been recognized by their antiproliferative actions against breast cancer MCF-7 cells (Hsu et al., 2011). Similarly, the cytotoxic activity of the hydrolyzate of shellfish *Mytilus coruscus* has been attributed to the peptide AFNIHNRNLL (Kim et al., 2012).

3. Bioactive peptides in functional foods: future perspectives

With the rise of consumer preferences for natural components, food-derived bioactive substances with potential use as nutraceuticals have attracted the interest of researchers and industries. An extensive number of studies have focused on the identification and characterization of food-derived peptides and their potential application as ingredients of functional food promoting health and reducing the risk of chronic diseases, such as cancer. Nevertheless, most of the studies demonstrating the efficacy of food peptides as anti-cancer agents have been carried out using *in vitro* assays and/or *in vivo* systems. Data obtained from these studies are insufficient to demonstrate the effectiveness of peptides in humans, and to date, a limited number of clinical trials have been performed. The main limitations include obtaining and purifying sufficient quantity of bioactive peptide fractions to perform the human trial, as well as the challenging to identify the sequence responsible for the observed effects.

Application of separation protocols such as membrane processing and chromatographic isolation may also be an area of future interest in the extraction of potent bioactive peptides from natural foods, and their subsequent utilization as functional food ingredients. Additionally, these technologies can be used to fractionate protein hydrolyzates obtaining peptide fractions with higher potency (Barnes and Kim, 2004). Membrane processing offers several advantages over conventional methods for separation, fractionation and recovery of those bioactive components. Combination of membrane separation and supercritical fluid technologies would provide unique advantages resulting in a novel separated technology offering great potential for the nutraceuticals and functional foods industry (Akin et al., 2012). Mass spectrometry-techniques have become the main technology for the characterization of food proteins and peptides, playing

a key role to understand their structure, nature, functional properties, and impact on human health (Mamone et al., 2009).

Discrepancies among different human trials may also be caused by human diversity and phenotypic differences between individuals. In this context, advances in the field of genomics, proteomics, metabolomics and transcriptomics are needed to benefit future clinical trials using food-derived proteins peptides as new anti-cancer agents. Scientific progress must be based on a better understanding of how these food-derived peptides interact with the human body and can prevent the initiation, development or progression of risk factors for cancer and/or other chronic diseases.

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Table 1. Source and chemopreventive activity of plant lectins assayed by cell experiments and animal models

Lectin	Plant source	Cell line	Animal model	Chemopreventive activity	Reference
Lectin	Mistletoe	Multiple tumor cell lines		Cytotoxic activity	Pryme et al., 2006
		Colon cancer COLO cells	NHL cells xenograft mouse models	Induction of apoptosis through activation of caspases and decreased expression of anti-apoptotic proteins	Khil et al., 2007
		Colon carcinoma cells	Colon cancer mouse model	Alteration of cytokine gene expression	Monira et al., 2009
		Epithelial IEC-6 cells	Leukemia mouse model	Alteration of cytokine gene expression	Lyu and Park, 2009
		Lymphoblastic leukemia cells	Xenograft melanoma mouse	Cytotoxic activity through activation of apoptosis	Seifert et al., 2008
		Leukemia PLB-985 and X-CGD cells	HL-29 colorectal xenograft mice model	Induction of apoptosis and degradation of cytoskeletal proteins via caspases activation	Lavastre et al., 2005, 2007

		Lymphoma WSU-1 cells		Cytostatic and apoptosis-inducing activities	Kovacs et al., 2008
		Lymphoblastic leukemia, hepatocarcinoma, lung cancer A549 and myeloleukemic U937 cells		Antiproliferative activity via extrinsic versus intrinsic apoptosis and immunomodulation	Fulda and Debatin, 2006; Hoessli and Ahmad, 2008
		Jurkat leukemic cells		Induction of apoptosis via caspase-8/FLICE	Bantel et al., 1999
		Hepatocarcinoma Hep3B cells		Induction of apoptosis through caspase activation, release of cytochrome C, and increase of reactive oxygen species	Lyu et al., 2002
		Monoblastic leukemia U937 cells		Induction of apoptosis via extracellular signal regulated kinase and p38 mitogen activated protein kinase	Pae et al., 2001

		Molt-4 lymphocyte and melanoma cells		Anti-proliferative and inhibitory activities	De Mejía et al., 2003
				Inhibition of metastasis and decreased tumors weight through inhibition of angiogenesis and induction of apoptosis	Pryme et al., 2006
				Delay of colon cancer development through regulation of immune responses	Ma et al., 2008
				Improvement of mice survival	Seifert et al., 2008
				Decrease of growth and spread of melanoma to lungs	Thies et al., 2008
				Anti-neoplastic activity through modulating gene expression	Li et al., 2011
Ricin	Rice	L540 Hodgkin's lymphoma cells		Induction of apoptosis through modulation of caspases	Polito et al., 2009

Agglutinin	Rice	Promyelocytic leukemia HL-60 cells		Inhibition of proliferation, induction of apoptosis and caspases activation	Miyoshi et al., 2001
		myeloleukemic U937 cells		Effects on chromatin condensation, nuclear fragmentation, DNA release	Kim et al., 2003
Lectin	**Plant source**	**Cell line**	**Animal model**	**Chemopreventive activity**	**Reference**
Abrin	*Arbus*	Jurkat, CCRF-HSB-2, MOLT-4, RPMI8402, and BALL-1 cells		Induction of apoptosis	Moriwaki et al., 2000
		Jurake and MCF-7 cells		Inhibition of proliferation, and induction of DNA fragmentation	Bagaria et al., 2006
		Dalton's Lymphoma ascites cells		Induction of apoptosis through stimulation of caspases expression	Ramnath et al., 2009
		U266B1 cells		Induction of apoptosis through a caspase-independent pathway	Bora et al., 2010

Lectin-derived peptides	*Arbus*		YAC-1 cells xenograft mouse models	Induction of proliferation of thymocytes and splenocytes	Bhutia et al., 2009
				Activation of natural killer cells	
Agglutinin	*Arbus*	Jurake and MCF-7 cells		Inhibition of proliferation, and induction of DNA fragmentation	Bagaria et al., 2006
			Dalton's lymphoma mice	Activation of tumor-associated macrophages, increase of nitric oxide production, and increase of cytotoxicity towards tumor cells	Ghosh and Maiti, 2007
Lectin	*Bauhinia variegate*	Breast MCF-7 and hepatoma HepG2 cells		Inhibition of proliferation	Lin and Ng, 2008
		Mouse splenocytes		Decrease of mitogenic response	Lin and Ng, 2008
Lectin	*Phaseolus vulgaris* cv.	Breast MCF-7 cells		Inhibition of proliferation	Sharma et al., 2009
		Mouse splenocytes		Decrease of mitogenic response	Sharma et al., 2009

Lectin PCL	*Phaseolus coccineus*	Fibrosarcome L929 cells		Inhibition of proliferation through induction of apoptosis and necrosis and caspases activation	Chen et al., 2009c
Concanavalin a A	*Canavalia ensiformes*	Melanoma A375		Inhibition of proliferation through induction of apoptosis, caspases activation and decrease of hemagglutination	Liu et al., 2009c, d
		Balb/c 3T3 and gingival fibroblasts		Induction of apoptosis	Kulkarni and McCulloch, 1995
		Glioblastoma U87 cells		Induction of apoptosis through induction of COX-2 gene expression	Proulx-Bonneau et al., 2010; Sina et al., 2010
		Ovarian cancer SKOV3 and Li-Fraumeni syndrome MDAH041 cells		Induction of apoptosis and regulation of akt-Foxola-Bim signaling	Amin et al., 2007
Lectin	**Plant source**	**Cell line**	**Animal model**	**Chemopreventive activity**	**Reference**

Lectin	*Plygonatum odoratum*	Fibrosarcome L929 cells		Induction of apoptosis through caspase activation and release of cytochrome *c*	Liu et al., 2009f
Lectin	*Clematis montana*	Fibrosarcome L929, breast MCF-7, hepatoma HepG2, and cervix carcinoma HeLa cells		Induction of cytotoxicity	Peng et al., 2009
Lectin	*Sophora flavescens*	Cervix carcinoma HeLa cells		Induction of apoptosis through a caspase-dependent pathway	Liu et al., 2008b
Hemagglutinin PHA-E	Dark red kidney bean	Leukemia L1210 cells		Anti-proliferative activitiy	Xia and Ng, 2006
Lectin	Chinese black soybean	Breast cancer MCF-7 and hepatoma HepG2 cells		Inhibition of proliferation	Lin et al., 2008
Lectin	Del Monte banana	L1210 and HepG2 cells		Inhibition of proliferation	Cheung et al., 2009
Lectin	Extralong autumn purple bean	HepG2 cells		Inhibition of proliferation through induction of apoptosis bodies production	Lam and Ng, 2011

Hemagglutinin	French bean	Breast cancer MCF-7 cells		Induction of apoptosis	Lam and Ng, 2010
Lectin AMML	*Astragalus mongholius*	HeLa, osteoblast-like MG63 and leukemia K562 cells		Induction of apoptosis	Yan et al., 2009
Lectin PCL	*Polygonatum cyrtonema*	HeLa cells		Anti-proliferative activity and induction of apoptosis	Liu et al., 2008a
		Breast cancer MCF-7 cells		Induction of apoptosis through activation of caspases and autophagy	Liu et al., 2009a
		Melanoma A375 cells		Induction of autophagy and apoptosis through activation of caspases, release of cytochrome *c*, and accumulation of reactive oxygen species	Liu et al., 2009a,b
	Ophiopogon japonicus	Fibrosarcoma L929 cells		Induction of apoptosis through activation of caspases	Zhang et al., 2010

Lectin	*Allium sativum* L.	U937 and HL60 cells		Cytotoxic activity, inhibition of DNA synthesis and induction of apoptosis	Karasaki et al., 2001
Lectin LNL	*Liparis noversa*	Breast cancer MCF-7 cells		Inhibition of cell proliferation and induction of apoptosis	Liu et al., 2009e
Lectin OJL	*Ophiopogon japonicus*	Breast cancer MCF-7 cells		Inhibition of cell growth	Liu et al., 2009e

Table 2. Source and chemopreventive activity of Bowman-Birk protease inhibitors assayed by cell experiments and animal models

Type of cancer	Plant source	Cell line	Animal model	Chemopreventive activity	Reference
Colorectal	Soybean	Colon HT-29		Inhibition of proliferation, cell cycle arrest, inhibition of serine proteases	Clemente et al., 2010
	Lentil	Colon HT-29		Inhibition of proliferation	Caccialupi et al., 2010
	Pea	Colon cancer cells		Inhibition of proliferation	Clemente et al., 2005
	Pea (recombinant protein)	Colon cancer cells		Inhibition of proliferation via protease inhibition	Clemente et al., 2012
	Soybean		DMH-induced colon cancer in rat	Inhibition of carcinogenesis	Kennedy et al., 2002
	Soybean		DMH-induced mouse colon and anal gland inflammation	Suppression of adenomatous tumors of the gastrointestinal tract	Billings et al., 1990
	Soybean		DSS-induced mouse colon inflammation	Suppression of histological parameters, decrease of mortality rate	Ware et al., 1999
	Soybean		DMH-induced colorectal cancer in Swiss mice	Protection against inflammation and pre-neoplastic lesions	Carli et al., 2012
	Horsegram		DMH-induced colorectal cancer in Swiss mice	Protection against inflammation and pre-neoplastic lesions	Carli et al., 2012

Breast	Soybean	Breast MCF-7		Inhibition of cell proliferation, cell cycle arrest, inhibition of proteasome chymotrypsin-like activity, up-regulation of p21, p27 expression, inactivation of ERK1/2 phosphorylation	Chen et al., 2005
				Inhibition of proliferation	Ho and Ng, 2008
	Chickpea	Breast MDA-MB-231		Inhibition of proliferation	Magee et al., 2012
	Black-eyed pea	Breast MCF-7		Induction of apoptosis, lysozome membrane permeabilization, and cell cycle arrest	Joanitti et al., 2010
	Brown kidney bean	Breast MCF-7		Inhibition of proliferation	Chan et al., 2013
	Soybean		DMBA-induced breast cancer in mouse	Inhibition of breast carcinogenesis	Du et al., 2001
Prostate	Soybean	Prostate carcinoma LNCaP and PC-3 cells		Inhibition of cell proliferation and induction of apoptosis, invasion, and clonogenic survival	Kennedy and Wan, 2002
	Soybean	Prostate LNCaP cells		Prevention of ROS generation, activation of DNA repair through a p53-dependent mechanism	Sun et al., 2001
		Normal tissue		Improve radiotherapy	Dittmann et al., 2003
	Soybean	Prostate LNCaP		Inhibition of proliferation	Magee et al., 2012
				Inhibition of cell growth, induction of apoptosis, induction of Cx43 and cleaved	Tang et al., 2009

				caspase-3 protein expression	
Prostate	Chickpea	Prostate PC-3 and LNCaP		Inhibition of proliferation	Magee et al., 2012
	Kidney bean	Prostate LNCaP		Inhibition of proliferation	Magee et al., 2012
	Mungbean	Prostate LNCaP		Inhibition of proliferation	Magee et al., 2012
	Soybean		TRAMP mice	Inhibition of tumor development	Tang et al., 2009
	Soybean		NMU-induced prostate cancer in rat	Reduction of incidence of *in situ* and invasive prostate neoplasms	McCormick et al., 2007
	Soybean		LNCaP cells xenograft in mouse	Decrease the final tumor load and increase the tumor doubling time and PSA density	Wan et al., 1999
	Soybean		SV40T antigen transgenic rats	Reduction of multiplicity of adenocarcinomas	Tang et al., 2009
Cervix	*Apios americana*	HeLa cells		Inhibition of proliferation, induction of apoptosis	Zhang et al., 2011

Gastric	Field bean		BP-induced mouse forestomach tumor	Preventive effects as protease inhibitory agent	Fernandes and Banerji, 1995
Hepatic	Hokkaido black soybean	Hepatocarcinoma HepG2		Inhibition of cell proliferation	Ho and Ng, 2008
	Brown kidney bean	Hepatocarcinoma HepG2		Inhibition of cell proliferation	Chan et al., 2013
Leukemia	Soybean	Leukemia L1210		Inhibition of cell proliferation	Wang et al., 2008
	Sweet potato	Promyelocytic leukemia NB4		Inhibition of cell proliferation, cell cycle arrest, induction of apoptosis, activation of caspases-3 and -8 pathways	Huang et al., 2007
	Apios americana	U937 and K562 cells		Inhibition of proliferation and induction of apoptosis	Zhang et al., 2011
Lymphoma	Soybean		CBA mice exposed to space radiation	Reduced risk of developing malignant lymphoma	Kennedy et al., 2008
Lung	Soybean		Tobacco smoke-induced lung tumors in mouse	Suppression of carcinogen-induced transformation	Witschi and Espiritu, 2002

		Alveolar A549 adenocarcinoma		Inhibition of tyrosine kinase and stimulation of DNA repair via epidermal growth factor phosphorylation and nuclear transport	Dittmann et al., 2008
Oral cavity	Soybean		DMBA-induced oral cancer in hamster	Suppression of carcinogen-induced transformation	Kennedy et al., 1993
Mesothelioma	Soybean	Mesothelioma MM28 cells		Inhibition of cell growth, up-regulation of Cx43 (mRNA and protein)	Kashiwagi et al., 2011
Osteosarcoma	Soybean	Osteosarcoma U2OS cells		Inhibition of proliferation, induction of apoptosis, cell cycle arrest, restoration of Cx43 expression	Saito et al., 2007

Ovarian	Soybean		Sarcoma M5067 xenograft mouse model	Inhibition of cell proliferation, decrease of tumor weight and proliferation of cell nuclear antigen, and restoration of Cx43 gene expression	Suzuki et al., 2005; Sakurai et al., 2008a, b

* Abbreviation: DMH, dimethylhydrazine; DSS, dextran sulphate sodium; DMBA, 7,12-dimethylbenz[a]anthracene; NMU, N-Methyl-N-nitrosourea; BP, benzopyrene

Table 3. Chemopreventive effects and mechanisms of action of peptide lunasin demonstrated by cell experiments and animal models

Type of cancer	**Cell line/Animal model**	**Effects/Mechanism of action**	**Reference**
DMBA and MCA-induced cancer	C3H10T1/2;	Inhibition of foci formation	Galvez et al., 2001
	NIH/3T3	Inhibition of proliferation and foci formation, and synergism with aspirin or anacardic acid	Hsieh et al., 2010d, 2011
		Inhibition of colony formation via H3, H4 acetylation suppression	Maldonado-Cervantes et al., 2010
E1A oncogen-induced cell line	C3H10T1/2; NIH/3T3	Induction of apoptosis, inhibition foci formation	Galvez et al., 2001
		inhibition of cell proliferation and foci formation and up-regulation of p21 protein	Lam et al., 2003
Viral *ras* oncogen-induced cell line	NIH/3T3	Inhibition of colony formation and H3 acetylation	Jeong et al., 2002, 2003

Breast cancer	MDA-MB-231	Inhibition of cell proliferation and arrest of cell cycle at S-phase	Hsieh et al., 2010c, d
		Synergism with aspirin and anacardic acid	Hernández-Ledesma et al., 2011
		Inhibition of histones acetylation	
		Up-regulation of retinoblastoma (Rb) gene expression	
		Down-regulation of cell cycle and transduction signaling genes expression	
	MCF-7	Induction of apoptosis via tumor suppressor PTEN via up-regulation of gene and protein levels of PTEN, and improvement of its nuclear localization	Pabona et al., 2013

		Promotion of non-nuclear E-cadherin and β-catenin levels	
	DMBA-induced breast cancer in SENCAR mice	Decrease in tumor incidence and generation	Hsieh et al., 2010b
	MDA-MB-231 cells	Decrease in tumor incidence, generation, time-appearance, weight and volume	Hsieh et al., 2010a
	xenograft nude mice	Inhibition of cell proliferation and induction of apoptosis	
Colon cancer	HT-29	Inhibition of cell proliferation and synergism with cisplatin	Dia and de Mejía, 2010
		Arrest of cell cycle at G2/M phase and up-regulation of cyclin-dependent kinase p21 gene expression	

		Induction of apoptotic mitochondrial pathway and modulating Bcl-2, Bax, nCLU, and caspase -3	
	KM12L4	Induction of cellular cytotoxic effects and synergism with cisplatin	Dia and de Mejía, 2011a, b
		Arrest cell cycle at G2/M phase and up-regulation of p21 and p27 gene expression	
		Induction of the apoptotic mitochondrial pathway by modulating expression of Bcl-2, Bax, nCLU, cytochrome c and caspase-2, -3 and -9	
		Nuclear condensation and DNA fragmentation	

		Inhibition of FAK/ERK and NF-kB signaling pathways	
		Down-regulation of $\alpha_5\beta_1$ integrin gene expression	
		Modulation of angiogenesis and metastasis-related genes expression	
	HCT-116	Induction of cellular cytotoxic effects	Dia and de Mejía, 2011b
		Inhibition of FAK/ERK and NF-kB signaling pathways	
	RKO	Induction of cellular cytotoxic effects	Dia and de Mejía, 2011b
		Inhibition of FAK/ERK and NF-kB signaling pathways	
		Inhibition of cell migration	

	Liver metastasis mice model by intrasplenic injection of KM12L4 cells	Decrease in the liver metastasis recount, tumor burden and tumor weight	Dia and de Mejia, 2011b, 2013
		Increase in the cell death recount, and reduction in the PCNA expression	
		Modulation on Bcl-2/Bax proteins	
		Inhibition of IKK-α and p-p65 signals related to NF-kB pathway	
		Synergism with oxaliplatin	
Prostate cancer	RWPE-2	Up-regulation of genes expression involved in tumor suppression, apoptosis, mitotic checkpoint, protein degradation, and communication pathways	Galvez et al., 2011

		Inhibition of H4K8, and induction of H4K16 acetylation	
Skin cancer	DMBA-induced cancer in SENCAR mice	Reduction in tumor incidence and yield per mouse	Galvez et al., 2001
		Delay in the tumor appearance	
Leukemia	L1210	Inhibition of cell proliferation	de Mejía et al., 2010
		Arrest cell cycle at G2 phase	
		Induction of apoptosis through activation of caspase-8, -9 and -3	
Lymphoma	Human peripheral blood mononuclear	Synergistic effect with IL-12 and IL-2 cytokines restoring IFNγ production by NK cells	Chang et al., 2014

		Synergism with up-regulation of GZMB and IFNG, and down-regulation of TGFB1 and TGFB2 expressions involved in cytotoxicity	
		Inhibition of H3 acetylation	
		Induction of NK cells-mediated anti-tumor activity	
	Raji cell xenograft mice model	Synergistic effect with IL-2 cytokine in reducing tumor volume	Chang et al., 2014

Table 4. Marine-derived bioactive peptides and their biological activity demonstrated by cell culture and animal models

Source	Peptide name or sequence	Type of peptide	Cell culture/Animal model	Evidence/Mechanism of action	Reference
Ascidian (*Didemnum cuculiferum* and *Polysyncranton lithostrotum*)	Vitilevuamide	Bicyclic peptide	Leukaemia P388 cells	Cytotoxic effects Tubulin polymerization inhibition	Edler et al., 2002
Ascidian (*Didemnun molle*)	Mollamide	Cyclic depsipeptide	Leukaemia P388, lung cancer A549, and colon cancer HT-29 cells	Cytotoxic effects	Carroll et al., 1994
Unidentified Brazilian ascidian	Tamandarins A and B	Depsipeptides	Colon cancer HCT 116 cells	Inhibition of cell growth	Vervoort et al., 2000
Ascidian (*Lissoclinum bistratum*)	Cycloxazoline and bistratene A	Cyclic peptide	Leukaemia HL-60 cells	Arrest of cell cycle Inhibition of cytokinesis	Watters et al., 1994
Ascidian (*Diplosoma virens*)	Virenamides A–C	Linear tripeptides	Leukaemia P388, lung cancer A549, and colon cancer HT29 cells	Cytotoxic effects	Carroll et al., 1996
Ascidian (*Diazona angulata*)	Diazonamide	Macrocyclic peptide	Breast cancer MCF7, prostate cancer PC-3, and lung cancer A549	Cytotoxic effects Tubulin polymerization inhibition	Cruz-Monserrate et al., 2003
Tunicate (*Trididemnum solidum*)	Didemnin A and B	Cyclic depsipeptide	Leukemia L1210 and P388,	Inhibition of proliferation Induction of	Crampton et al., 1984;

			melanoma B16 cells	apoptosis	Blunden, 2001
Tunicate (*Aplidium albicans*)	Aplidine	Cyclic depsipeptide	Breast cancer, melanoma and lung cancer cells	Cytotoxic effects via cell cycle arrest, antiangiogenic effects, and apoptosis induction	García-Fernández et al., 2002
Solitary tunicate (*Styela clava*)	n.d.	n.d.	Gastric cancer AGS, colon cancer DLD-1, and cervical cancer HeLa cells	Antiproliferative effects	Jumeri and Kim, 2011
Mollusk (*Pleurobranchus forskalii*)	Keenamide A	Cyclic peptide	Leukaemia P388, lung cancer A549, colon cancer HT-29 and melanoma MEL-20 cells	Cytotoxic effects	Wesson and Hamann 1996
Mollusk (*Elysia rufescens*)	Kahalalide F	Dehydroamino-butyric acid-peptide	Prostate cancer cells	Cytotoxic effects Induction of apoptosis	Faircloth et al., 2001
Mollusk (*Arca subcrenata*)	n.d.	Polypeptide fraction	Cervical cancer HeLa and colon cancer HT-29 cells Hepatoma S-180 and sarcoma H-22 xenograft mice	Cytotoxic effects Decrease of tumor weight	Hu et al., 2012
Mollusk (*Ruditapes*	AVLVDKNCPD	Linear peptide	Prostate cancer PC-	Cytotoxic effects	Kim et al., 2013

philippinarumk)			3, breast cancer MDA-MB-231 and lung cancer A549 cells	Induction of apoptosis	
Mollusk (*Dolabella auricularia*)	Dolastatins 10 and 15	Linear depsipeptide	Lymphocytic leukaemia P388 cells	Inhibition of proliferation Binding to *Vinca* domain of tubulin Microtubule assembly inhibition	Cruz-Monserrate et al., 2003
Sponge (*Homophymia* sp.)	Homophymines	Cyclic depsipeptide	Prostate cancer PC3 and ovarian cancer OV3 cells	Cytotoxic effects	Andavan and Lemmens-Gruber, 2010
Sponge (*Geodia corticostylifera*)	Geodiamolide	Cyclic peptide	Breast cancer cells	Inhibition of proliferation, migration, and invasion	Freitas et al., 2008
Sponge (*Discoderma* sp.)	Discodermins	Cyclic peptide	Lung cancer A549 and leukaemia P388 cells	Cytotoxic effects	Aneiros and Garateix, 2004
Sponge (*Dysidia arenaria*)	Arenastatin A	Cyclic depsipeptide	Epidermal mouth carcinoma KB cells	Cytotoxic effects	Aneiros and Garateix, 2004
Sponge (*Phakellia* sp.)	Phakellistatins	Cyclic peptide	Leukaemia and hepatoma BEL-7404 cells	Inhibition of cell growth	Li et al., 2002
Sponge (*Discodermia calyx*)	Calyxamides A and B	Cyclic peptides	Murine leukemia P388 cells	Cytotoxic effects	Kimura et al., 2012
Sponge (*Callyspongia aerizusa*)	Callyaerins	Cyclic peptides	Mouse lymphoma L5178Y and cervical	Cytotoxic effects	Ibrahim et al., 2010

			cancer HeLa cells		
Sponge (*Jaspis johnstoni*)	Jasplakinolide Jaspamide	Cyclic depsipeptide	Jurkat T cells Promyelocytic leukaemia HL-60 cells	Inhibition of proliferation and induction of apoptosis by DNA ladder formation Induction of apoptosis	Odaka et al., 2000 Cioca and Kitano, 2002
Sponge (*Cymbastela, Auletta, Siphonochalina*)	Milnamide A	Tripeptides	Leukaemia P388, breast cancer MCF-7, glioblastoma U373, ovarían cancer HEY, colon cancer HT-29 and LOVO, lung cancer A549, and melanoma B16-F10 cells	Cytotoxic effects Antimitotic activity Tubulin polymerization inhibition	Coleman et al., 1995; Crews et al., 1994; Gamble et al., 1999
Sponge (*Pipestela candelabra*)	Milnamides F and G	Tripeptides	Prostate cancer PC3 cells	Inhibition of cell proliferation	Tran et al., 2014
Sponge (*Scleritoderma nodosum*)	Scleritodermin A	Cyclic peptide	Multiple cancer cell lines	Cytotoxic effects Inhibition of tubulin polymerization	Schmidt et al., 2004
Sponge (*Theonella* sp.)	Orbiculamide A	Cyclic peptide	Leukaemia P388 and melanoma cells	Cytotoxic effects	Fusetani et al., 1991
Sponge (*Theonella* sp.)	Koshikamide B	Peptide lactone	Leukaemia P388 and colon	Cytotoxic effects	Araki et al., 2008

			cancer HCT-116		
Sponge (*Clathria abietina*)	Microcionamides A and B	Linear peptides	Breast cancer MCF-7 and SKBR-3 cells	Cytotoxic effects	Davis et al., 2004
Tuna dark muscle hydrolyzate (*Thunnus tonggol*)	LPHVLTPEAGATPTAEGGVYMVT	Linear peptide	Breast cancer MCF-7 cells	Antiproliferative activity	Hsu et al., 2011
Anchovy sauce	n.d.	n.d.	Lymphoma U937 cells	Induction of apoptosis Increase of caspase-3 and -8 activity	Lee et al., 2003, 2004
Shellfish (*Mytilus coruscus*)	AFNIHNRNLL	Linear peptide	Prostate cancer PC-3, breast cancer MDA-MB-231 and lung cancer A549 cells	Cytotoxic effects Induction of apoptosis	Kim et al., 2012
Oyster (*Crassostrea gigas*)	n.d.	Oligopeptide-enriched hydrolyzate	Sarcoma S180-bearing BALB/c mice	Reduction of tumor growth Immunostimulating effects	Wang et al., 2010
Squid (*Dosidicus gigas*)	n.d.	Hydrolyzate	Breast cancer MCF-7 and glioma U87 cells	Cytotoxic effects Antioxidant activity	Alemán et al., 2011
Shrimp shell (different sp.)	n.d.	Hydrolyzate	Colon cancer HT-29 and hepatocarcinoma HepG2 cells	Inhibition of cell growth	Kannan et al., 2011
Alga protein waste	VECYGPNRPQF	Linear peptide	Gastric cancer AGS	Cytotoxic effects, cell	Sheih et al., 2010

(*Chlorella vulgaris*)			cells	cycle arrest Antioxidant activity	
Algae (*Chlorella pyrenoidosa*)	Polypeptide CPAP	Polypeptide	Hepatocarcinoma HepG2 cells	Inhibitory effects of cell growth	Wang and Zhang, 2013
Algae (*Spirulina platensis*)	Polypeptide Y2	Polypeptide	Breast cancer MCF-7 and hepatocarcinoma HepG2 cells	Inhibition of cell proliferation	Zhang and Zhang, 2013
Tilapia (*Oreochromis mossambicus*)	Hepcidin TH2-3	Linear peptide	Fibrosarcoma HT1080 cells	Inhibition of cell growth Lethal membrane disruption Down-regulation of c-Jun mRNA expression	Chen et al., 2009a
Fish (*Epinephelus coioides*)	Epinecidin-1	Linear Peptide	Fibrosarcoma HT1080 cells Leukaemia U937 cells	Antitumor activity Inhibition of proliferation and induction of apoptosis Regulation of cytokines production	Lin et al., 2009 Chen et al., 2009b
Flyingfish (*Exocoetus volitans*)	n.d.	n.d.	Hepatocarcinoma HepG2 cells	Antiproliferative effects	Naqash and Nazeer, 2010
Threadfin bream (*Nemipterus japonicus*)	n.d.	n.d.	Hepatocarcinoma HepG2 cells	Antiproliferative effects	Naqash and Nazeer, 2010
Chum salmon (*Oncorhynchus keta*)	Marine oligopeptide	Oligopeptide	Radiation-induced immune	Immunostimulating effects Inhibition of	Yang et al., 2010

			suppression in mice	apoptosis of splenocytes	
Lyngbya majuscula/*Schizothrix* sp. Assembly of cyanobacteria	Somocystinamide A	Lipopeptide	Neuroblastoma neuro-2a cells	Induction of apoptosis via activation of caspase-8	Nogle and Gerwick, 2002
Cyanobacteria (*Agmenellum quadruplicatum*, *Mastigocladus laminosus*, *Spirulina platensis*)	*C*-phycocyanin	Tetrapyrrole-protein complex	Cervical cancer HeLa cells	Induction of apoptosis via activation of pro-apoptotic and down-regulation of anti-apoptotic gene expression	Li et al., 2006
Cyanobacteria (*Lyngbya majuscula*)	Desmethoxymajusculamide C	Cyclic depsipeptide	Colon carcinoma HCT-116	Antitumor activity Disruption of cellular microfilament networks	Simmons et al., 2009
Cyanobacteria (*Symploca* sp.)	Symplocamide A	Cyclic depsipeptide	Lung cancer H460 and neuroblastoma neuro-2A cells	Cytotoxic effects	Linington et al., 2008
Cyanobacteria (*Lyngbya majuscula* and *Lyngbya sordida*)	Apratoxin D	Macrocycle Peptide	Lung cancer H460 cells	Cytotoxic effects	Gutierrez et al., 2008
Cyanobacteria (*Geitlerinema* sp.)	Mitsoamide	Linear Peptide	Lung cancer H460 cells	Cytotoxic effects	Andrianasolo et al., 2007
Marine fungus	Sansalvamide A	Cyclic depsipeptide	Pancreatic cancer AsPC-1 and CD18 cells	Induction of apoptosis Cell cycle arrest	Pan et al., 2009
Marine fungus (*Scopulariopsis brevicaulis*)	Scopularides A and B	Cyclic depsipeptide	Pancreatic cancer Colo357 and Panc89, and colon	Inhibition of cell growth	Yu et al., 2008

			cancer HT29 cells		

n.d.: not determined

