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Anticancer and antiproliferative properties of food-derived protein hydrolysates and peptides

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Abstract

Cancers of all types are among the four main non-communicable diseases, a category of diseases responsible for 38 million yearly deaths worldwide. Although various medical procedures including surgery, immunotherapy, radiation therapy, hormone therapy, stem cell transplant and chemotherapy have been used for decades in the treatment and control of cancer, current survival rates suggest that more definitive and effective treatment strategies are warranted. This work provides a succinct summary of the various methods used for producing anticancer peptides and protein hydrolysates from food sources, their modes of action, as well as descriptions of their antitumour properties in cellular and animal models. Although the mechanisms by which protein hydrolysates and peptides exert antitumor and antiproliferative effects are not entirely elucidated, there is evidence pointing to antioxidative function as an important predictor of their anticancer property.

Keywords: Antitumor; Lunasin; Cancer; Apoptosis; Bioactive peptides; Antiproliferative.

1. Introduction

According to data on the global cancer incidence and mortality burden released in 2014 by the WHO, about 8.2 million cancer-related fatalities and 14.1 million new cases of cancer (excluding non-melanoma skin cancer) were diagnosed worldwide in 2012 (WHO, 2014). In spite of the promising advances made over the years in medical sciences in general, and in cancer treatment in particular, current strategies for the treatment of cancer remain inadequate and unsatisfying in terms of treatment outcomes, as well as short and long term health effects (Miller et al., 2016). For instance, apart from aesthetic concerns and post-surgery negative body image, it has been reported that about 25–60% of women develop chronic pain following mastectomy (Miller et al., 2016; Vilholm et al., 2008). In both men and women, radiation therapy, surgery and certain types of chemotherapy have been shown to adversely affect fertility and reproductive organs (Barton et al., 2013; Wasilewski-Masker et al., 2014). Furthermore, irritability, loss of libido, hot flashes and night sweats have been reported in patients undergoing hormone therapy, with certain types of hormone therapy increasing the potential for subsequent diagnosis with diabetes, osteoporosis and obesity (Keating et al., 2010; Saylor and Smith, 2013; Wadhwa et al., 2009). Studies have also shown that cancer survivors who underwent stem cell transplantation are prone to subsequently face the challenge of chronic anemia and recurrent infections (Miller et al., 2016). Given cancer's standing as a major cause of morbidity and mortality, which affects people in every country and region as well as the expectation that the global cancer burden will surpass 20 million new cancer cases by 2025 (WHO, 2014), the development of alternative and/or supplementary strate-

gies for reducing the risk of cancer is critically needed.

The idea that cancer incidence and/or progression can be prevented, delayed, suppressed or reversed by lifestyle modification such as the administration or consumption of natural or biological (including dietary) substances with the capacity to enhance the host organism's defense mechanisms or limit exposure to and/or interaction with carcinogens is not new (Munjal et al., 2012; Steward and Brown, 2013). Studies have reported increased cancer risk in subjects with lower intakes of fruits, vegetables, whole grains and red meat (Hoang et al., 2018; Levi et al., 1999; McCullough et al., 2003). Improved diet and other lifestyle changes like weight management, increased physical activity and minimal or zero alcohol consumption have all been shown to lower the disease risk for cancer (McCullough et al., 2011). However, a considerable proportion (37–87%) of cancer patients are known to take advantage of alternative cancer therapies due to a number of reasons as previously summarized (Rajendran et al., 2017), including increased patient awareness and access to information, the belief that "natural is safer", the side effects of conventional drugs, and increased patient autonomy. Furthermore, apart from the adoption of specific dietary habits and the increased consumption of certain classic nutrients as a strategy for reducing cancer risk (Milner, 2002), there is a growing body of evidence (Chatterjee et al., 2018; Daliri et al., 2017; Hsu et al., 2011; Sheih et al., 2010; Suarez-Jimenez et al., 2012) suggesting that food-derived protein hydrolysates and peptides could be important for reducing cancer risk thus explaining the significant attention this area of research currently enjoys and justifying the need for this work.

2. Food sources of anticancer peptides and potential mechanisms of action

Food-derived bioactive peptides and protein hydrolysates with anticancer properties have been produced from a variety of animal and plant sources including soybean (Mora-Escobedo et al., 2009), half-fin anchovy (Song et al., 2014), chickpea (Xue et al., 2012), common bean (Luna-Vital et al., 2016), sea cucumber (Pérez-Vega et al., 2013), tuna cooking juice (Hung et al., 2014), blood clam muscle (Chi et al., 2015), walnut (Jahanbani et al., 2016), maize (Ortiz-Martinez et al., 2017), mung bean (Gupta et al., 2018), loach (You et al., 2011), fish protein (Picot et al., 2006), tunicate (Kim, 2011), as well as whey and casein (Sah et al., 2018). Table 1 contains additional sources of protein hydrolysates and peptides with anticancer properties. In general, these products are generated from the enzymatic hydrolysis of food proteins to produce a complex matrix of peptides called protein hydrolysate. The hydrolysates are usually composed of active and non-active peptides; therefore, further processing to obtain fractions that are enriched with active fractions may be carried out (Doyen et al., 2011; Perego et al., 2011). In some cases, the active peptide fractions are subjected to additional separation and purification protocols that yield homogenous peptides suitable for amino acid sequence analysis (Hung et al. 2014; Ma et al. 2015; Pan et al., 2016; Wang and Zhang, 2017; Wang et al., 2013; You et al., 2011).

2.1. Anticancer peptides and hydrolysates: mechanisms of action

Food-derived protein hydrolysates and peptides are believed to modulate their anticancer functions through a number of well delineated mechanisms of action including apoptosis induction and cell cycle arrest, inhibition of intracellular signaling systems, regulation of immune system, protease inhibition, and nucleic acid impairment (Ortiz-Martinez et al., 2014; Rajendran et al., 2017). Apoptosis, the carefully controlled and programmed death of cells is widely recognized as one of the most effective means through which the body regulates cell death and division, with homeostatic maintenance of the appropriate number of cells (Indran et al., 2011). Anticancer protein hydrolysates and peptides are known to induce apoptosis in cancer cells by upregulating apoptotic gene expression as was observed with the enhancement of caspase-3, p21 and p53 expressions in MCF-7 human breast cancer cells by soybean-derived peptides (Park et al., 2009), as well as downregulating tumorigenic genes as seen with the suppression of PTTG1 and TOP2A gene expressions by soybean-derived peptide fractions in HeLa cells (Robles-Ramírez et al., 2012). Bioactive peptides and protein hydrolysates are also known to exert their anticancer effects by orchestrating cellular DNA damage as was the case with common bean-derived peptide GLTSK whose impairment of DNA function was observed as the overexpression of the histone γH2AX in HCT116 human colorectal cancer cells (Luna-Vital et al., 2016). The histone variant H2AX is known to be rapidly phosphorylated at the Ser-139 residue as a result of DNA double-strand breakage yielding γH2AX, whose formation is routinely used as a highly specific and sensitive indicator of DNA damage (Luna-Vital et al., 2016; Mah et al., 2010). Additionally, the polypeptide lunasin was reported to reduce KM12L4 human colon carcinoma cells adhesion by disrupting $\alpha_5\beta_1$ integrin and extracellular matrix interaction (Dia and González de Mejia, 2011; Rajendran et al., 2017) and thus impair tumor progression. This is because integrin adhesion to extracellular matrix is critical for intra-tumor endothelial cell proliferation and migration (Conconi et al., 2010). In an earlier study in which lunasin induced apoptosis in HT-29 human colon cancer cells by means of mitochondrial pathway activation and induction of nuclear clusterin expression, Dia and González de Mejia (2010) credited the anticancer property of the polypeptide to its RGD motif, which promotes adhesion and internalization of lunasin into the cell through interaction with the extracellular matrix (Rajendran et al., 2017). Also, using molecular docking studies, Wang et al. (2008) revealed the potential of three soy bean-derived peptides (FEITPEKNPQ, IETWNPNNKP, and VFDGEL) to inhibit topoisomerase II. Other described mechanisms of action include histone deacetylation, protease inhibition, membrane permeation and disruption, and calcium modulation as reviewed by Rajendran et al. (2017) and Sah et al. (2015).

2.2. Food protein anticancer properties—the antioxidant connection

Reactive oxygen species (ROS) such as hydroxyl radicals, hydrogen peroxide, singlet oxygen and superoxide anions are typically produced as a result of endogenous and exogenous stimuli, and are often routinely neutralized by living organisms using well-established endogenous antioxidant defense systems (Nwachukwu and Aluko, 2019). When produced in excess, ROS can overwhelm natural defense systems resulting in a state of oxidative stress. Sustained and cumulative oxidative stress has the potential to cause deleterious oxidative damage to cellular macromolecules such as proteins, lipids and nucleic acids resulting in irreversible alteration of cellular functions (Fuchs-Tarlovsky, 2013; Nwachukwu and Aluko, 2019). In the case of oxidative damage to DNA for instance, ROS can react with cellular components such as phospholipids and proteins to form secondary reactive intermediates, which can irreversibly bind to DNA bases to form DNA adducts (Marnett, 2000). Since DNA adducts can promote miscoding and

Table 1. Sources, methods of production and mechanisms of action of anticancer food-derived protein hydrolysates and peptides*

Source	Protein hydrolysates/Peptide	Production Method	Cellular and/or animal model	IC_{50} value	Mechanism	References
Tuna cooking juice	KPEGMDPPLSEPEDRRDGAAGPK, KLPPLLLAKLLMSGKLLAEPCTGR	Enzymatic hydrolysis with Protease XXIII and ultrafiltration	Human breast cancer MCF-7 cells and MCF-10A mammary epithelial cells	1.39 mg/mL	Apoptosis induction and tumour suppression	Hung et al., 2014
Peptides from *Spirulina platensis*	HVLSRAPR	Enzymatic hydrolysis and fractionation	HT-29 cancer cells	99.88 µg/mL	Tumour suppression	Wang and Zhang, 2017
Mung bean vicilin	Protein hydrolysates and vicilin seed extracts	Ammonium sulfate fractionation of vicilin followed by separate hydrolyses with alcalase and trypsin	MCF-7 and MDA-MB-231 breast cancer cells	0.32, 0.73 and 0.45 mg/mL for MCF-7; 0.26, 0.48 and 0.54 mg/ml for MDA-MB-231 cells	Tumour suppression	Gupta et al., 2018
Chickpea	Protein hydrolysates	Alcalase hydrolysis	Tumour-bearing mice	Not mentioned	Tumour suppression	Xue et al., 2012
Maize	Peptides	Alcalase hydrolysis followed by ion exchange column chromatography fractionation	Hepatocarcinoma human HepG2 cells	1.5–150 µg/mL for peptide fractions and 0.001–1.5 mM for derived peptides.	Apoptosis induction, cell growth inhibition	Ortiz-Martinez et al., 2017
Soybean (germinated)	Peptide fractions	Extraction, precipitation, enzymatic hydrolysis and membrane fractionation	HeLa cells	1.83 mg/mL	Apoptosis induction and down regulation of PTTG1 and TOP2A tumorigenic genes	Robles-Ramírez et al., 2012
Soybean	Lunasin	Simulated GIT digestion with pepsin and pancreatin	L1210 leukemia cells	14 µM	Activation of Caspase-3 and dose-dependent G2 cell cycle arrest	González de Mejia et al, 2010
Soybean	Lunasin	Lunasin obtained by aqueous extraction from soybean followed by ion exchange and size exclusion chromatography, and further purified by HPLC separation	HT-29 colon cancer cells	61.7 µM	Activation of mitochondrial pathways and increased induction of pro-apoptotic nuclear clusterin expression	Dia and Mejia, 2010
Soybean	XMLPSYSPY	Thermoase and ethanol extraction	P388D1	0.16 mg/mL	Not investigated	Kim et al., 2000
Soybean	Isoflavone-derived soy	Sequential hydrolysis with endopeptidase, exopeptidase and amylase in that order	MCF-7	Not stated	Apoptosis via p21, p53, and caspase-3 expression, and inhibition of VEGF and HSP90	Park et al., 2009

Table 1. Sources, methods of production and mechanisms of action of anticancer food-derived protein hydrolysates and peptides* *- (continued)*

Source	Protein hydrolysates/Peptide	Production Method	Cellular and/or animal model	IC_{50} value	Mechanism	References
Soybean	Kunitz trypsin inhibitor		HRA human ovarian cancer cells	2–3 μM	Inhibition of the upregulation of urokinase-type plasminogen activator, uPA, and its specific receptor, uPAR	Kobayashi et al, 2004
Soybean	VFDGEL, IETWNPNNKP and FEITPEKNPQ	Pepsin and pancreatin	L1210	7.9, 4.0 and 2.4 mM in that order	Human topoisomerase II inhibition	Wang et al., 2008
Rapeseed	Rapeseed peptide	Alcalase and flavourzyme	HeLa	Not stated	DNA structural damage and apoptosis induction	Xue et al, 2010
Amaranthus mantegazzianus (seed)	Mantegazzianus peptide isolate	Alcalase	UMR106, Caco-2, TC7, MC3T3E1	1.0, 1.5 and 2.5 and 2.5 mg/mL respectively	Inhibition of cell adhesion, necrosis and apoptosis	Barrio and Añón, 2010
Walnut	Cys-Thr-Leu-Glu-Trp	Alkaline extraction, precipitation by centrifugation and hydrolysis with papain	Human HeLa cervical cancer and MCF-7 breast cancer cells	0.60 and 0.65 mg/mL respectively	Induction of apoptosis and autophagy	Ma et al., 2015
Tilapia	Tilapia hepcidin (TH) 1–5	Chemically synthesized	HeLa, HepG2, HT1080	Not stated	Downregulation of interleukin (IL)-6, IL-8, IL-12, IL-15, interferon-γ, Bcl-2 and caspase-7, as well as upregulation of IL-2 and IL-8	Chang et al, 2011
Estuary cod (*Epinephelus coioides*)	Epinecidin-1	Chemically synthesized	A549, HepG2, HT1080, U937, NIH3T3, RAW264.7 cancer cells	Not stated	Inhibition of cell growth and cell lysis	Lin et al., 2009
Cuttlefish ink (*Sepia esculenta*)	An oligopeptide, N Gln-Pro-Lys	Trypsin	DU-145 prostate cancer cells	Variable	Inhibition of cell viability and growth	Ding et al, 2011
Tuna dark muscle byproduct	LPHVLTPEAGAT PTAEGGVYMVT	Papain and protease XXIII	MCF-7	8.1 μM and 8.8 μM respectively	Inhibition of cell viability and proliferation	Hsu et al., 2011
Loach (*Misgurnus anguillicaudatus*)	Loach peptide fractions	Loach tissue homogenization followed by papain hydrolysis	HepG2, MCF-7 and Caco-2 cells	Not stated	Inhibition of cell proliferation	You et al., 2011
Setipinna taty	Heated products from peptic hydrolysates of marine fish (half-fin anchovy)	Peptic hydrolysates heated for 10 min at 95 °C	DU-145 prostate, 1299 lung, and 109 esophagus cancer cells	13.67, 25.17 and 40.28 mg/mL respectively	Cell proliferation inhibition	Song et al., 2011
Skate (*Raja porosa*) cartilage protein hydrolysate	FIMGPY	Enzymatic hydrolysis with pepsin, trypsin and chymotrypsin	HeLa	4.81 mg/mL	Apoptosis and tumour suppression	Pan et al, 2016

Table 1. Sources, methods of production and mechanisms of action of anticancer food-derived protein hydrolysates and peptides* *- (continued)*

Source	Protein hydrolysates/Peptide	Production Method	Cellular and/or animal model	IC_{50} value	Mechanism	References
Blue whiting cod, Plaice, Atlantic Salmon	Fish protein hydrolysates	pH-shift extraction followed by Protamex and alcalase hydrolysis	MCF-7/6, MDA-MB-231 and breast cancer cells	Not stated	Inhibition of cell growth and proliferation	Picot et al., 2006
Rice bran	Alacalase hydrolysis followed by simulated GIT digestion	Gastrointestinal juice	Caco-2, HepG2, HCT-116, MCF-7, MDA-MB-231	Not mentioned	Not mentioned	Kannan et al., 2010
Snow crab (by-products)	KCl2 cationic peptide	Enzymatic hydrolysis with Protamex, electrodialysis, ultrafiltration	A549, HCT15, BT549, PC3	Not mentioned	Not mentioned	Doyen et al., 2011
Squid gelatin	Squid gelatin protein hydrolysates	Protamex, trypsin, Neutrase, Savinase, NS37005, Esperase, Alcalase	MCF-7, U87	130 and 100 µg/mL for MCF-7 and U87 respectively	Not stated	Alemán et al., 2011
Rough sea squirt/ solitary tunicate	Solitary tunicate (*Styela clava*) enzymatic hydrolysates	Alcalase, Thermoase PC10F, pepsin,	AGS, DLD-1, HeLa	577.1–1,240.0 µg/mL	Not mentioned	Kim, 2011
Japanese threadfin bream	*Nemipterus japonicus* tryptic hydrolysates	4 h hydrolysis with trypsin at 37 °C	HepG2 liver cancer cells	61.1 µg/mL	Inhibition of cell viability	Naqash and Nazeer, 2012
Beef sarcoplasmic protein hydrolysates	Gly-Phe-His-Ile, Asp-Phe-His-Ile-Asn-Gly, Phe-His-Asp, and Gly-Leu-Ser-Asp-Gly-Glu-Trp-Gln	Extraction with phosphate buffer followed by hydrolysis with thermolysin and proteinase A, trypsin, proteinase K, tyrosinase, pepsin, papain, protease (sequentially)	MCF-7, AGS, A549	Not mentioned	Inhibition of cell viability	Jang et al., 2008
Bovine lactoferrin	LfcinB FKCRRWQWRMK KLGAPSITCVRRAF	Synthetic	Human umbilical vein endothelial cells	Not stated	Inhibition of angiogenesis	Mader et al, 2006
Milk	Casein phosphopeptide	Chemically synthesized	HT-29 intestinal tumour cells	Not mentioned	Apoptosis	Perego et al, 2011
Bovine milk	Whey protein isolate and collagen hydrolysate	Membrane ultrafiltration and RP-HPLC fractionation	B1F610	0.19–156.9 mg/mL	Apoptosis (increased caspase-3 expression) and necrosis	Castro et al, 2009
Bovine milk	PGPIPN immunomodulatory peptide		SKOV-3	Not stated	Bcl-2 downregulation, apoptosis and inhibition of cell proliferation	Wang et al., 2013

*Cell lines Key: MCF-6, MCF-7, MDA-MB-231, BT549–breast cancer; HeLa–cervical cancer; Caco-2, HCT-116, TC7, DLD-1–colon cancer; DU-109–esophageal cancer; NIH3T3–mouse fibroblast; HT1080–fibrosarcoma; U87-glioma; L1210- lymphocytic leukemia; HepG-2–liver cancer; A549, DU-1299–lung cancer; U937–histiocytic lymphoma; HT-29, P388D1-mouse monocyte macrophage cell line; RAW264.7 (mouse)–macrophage; MC3T3E1–osteoblastic calvaria-derived cells; DU-145–prostate; UMR106–rat osteosarcoma-derived cells; AGS–stomach adenocarcinoma; HRA–human ovarian cancer; C33–epidermoid cervical carcinoma; B1F610-melanoma cells; SKVO-3–ovarian cancer cell; HUVEC–Human umbilical vein endothelial cells.

even mutations if they evade cellular repair mechanisms, their formation is important in the carcinogenic process (Fuchs-Tarlovsky, 2013). Studies have linked oxidative stress with the pathogenesis of inflammation-related cancers, and agents with the capacity to protect cells against ROS attack by quenching free radicals, are thought to be potent chemopreventive candidates (Chi et al., 2015; Sheih et al., 2010). In fact, the correlation of antioxidative function with anticancer property has traditionally been reported in a range of biological and chemical agents, including dietary kelp and plant phenolics (Cai et al., 2004; Dai and Mumper, 2010; Maruyama et al., 1991). Against this backdrop, peptides with antioxidative functions have been shown to also possess anticancer properties. For example, an antioxidant peptide fraction from algae protein waste was found to induce cell cycle arrest in and dose-dependently inhibit the growth of AGS human gastric cancer cells (Sheih et al., 2010). Additionally, the anticancer activity of protein hydrolysates and peptides with antioxidative properties such as the oyster-derived LANAK (Umayaparvathi et al., 2014), a fresh water fish-derived peptide fraction, LPH-IV (You et al., 2011), and H3 (a polypeptide with 117 amino acid residues) from the marine invertebrate, *Arca subcrenata* (Chen et al., 2013) have also been demonstrated. Due to the proven capacity of antioxidants to protect healthy cells from oxygen-based radicals during cancer therapy and the use of antioxidant compounds in combination with anticancer drugs such as doxorubicin and anthracycline (Fuchs-Tarlovsky, 2013), antioxidant peptides hold great promise for similar chemotherapeutic applications.

3. *Ex-vivo* anticancer protein hydrolysates and peptides

The antitumor and/or antiproliferative capacity of food-derived protein hydrolysates and peptides have been amply demonstrated in various cancer cell models, using hydrolysates and peptides that vary in both their sources and chemical structures. Lunasin, the naturally-occurring 43-amino acid peptide first identified in soybean was found to induce apoptosis and cause cytotoxicity to HT-29 human colon cancer cells (Dia and González de Mejia, 2010). In a recent study, Ortiz-Martinez et al. (2017) reported the antiproliferative effect of peptide fractions from albumin alcalase hydrolysates of a white hybrid maize (Asgrow-773) and a quality protein (CML-502) maize as well as that of their derived peptides on HepG2 cells, an in vitro model of human liver cancer. The peptide fractions from both maize samples were found to inhibit the growth of HepG2 cells in a dose-dependent manner by up to 94% and to increase the rate of apoptosis induction in HepG2 cells by a staggering 400% on the average. Unlike peptide fractions obtained following the alcalase hydrolysis of corn gluten meal, which were shown to block HepG2 DNA replication in the S phase of the cell cycle in a different study (Li et al., 2013), the maize peptide fractions in this study had no modulatory effect on HepG2 cell cycle (Ortiz-Martinez et al., 2017). The study by Li et al. (2013) also found that corn peptides induced apoptosis in HepG2 cells in a dose-dependent manner by significantly inhibiting the expression of antiapoptotic Bcl-2 protein and upregulating the expression of p53 and cleaved caspase-3. It has also been reported that apoptosis induction via the downregulation of Bcl-2, PARP and caspase-9 levels as well as the upregulation of p53, Bax and cleaved caspase-3 expressions was central to the antiproliferative effects of tuna cooking juice protein hydrolysates and ultrafiltration peptide fractions on MCF-7 human breast cancer cells (Hung et al., 2014).

In addition, a study which evaluated the effect of five pure peptide sequences derived from the non-digestible fraction of common bean (*Phaseolus vulgaris* L.) showed that the two most potent peptides (GLTSK and GEGSGA) selectively inhibited the proliferation of HCT116 colon cancer cells but not that of CCD-33Co normal colon cells (Luna-Vital et al., 2016). While the inhibition of HCT116 cells by GLTSK was thought to be through loss of mitochondrial membrane potential, GEGSGA peptide suppressed the proliferation of the cancer cells via DNA damage. Of particular importance was the finding that when combined, either peptide induced apoptosis and synergistically enhanced the effect of the chemotherapy drug oxaliplatin on HCT116 cells—a result that could have wide implications for peptide use in cancer combination therapy. Confocal microscopy data also revealed that when combined with oxaliplatin, GEGSGA promoted PARP cleavage, decreased the levels of antiapoptotic Bcl-2 and caused the activation and nuclear translocation of p53 protein (Luna-Vital et al., 2016). The antioxidant peptide, WPP, from blood clam protein hydrolysates was shown to selectively inhibit the proliferation of PC-3 and DU-145 human prostate cancer cells as well as HeLa and H1299 non–small-cell lung cancer cell lines while showing hardly any cytotoxicity to normal NIH3T3 mouse fibroblast cells (Chi et al., 2015). WPP also induced apoptosis in PC-3 cells with classical apoptotic changes in morphology such as chromatin condensation, cytoplasmic blebbing and nuclear fragmentation being observed in the cells (Chi et al., 2015).

Also, using an MTT-based spectrophotometric assay, a recent study found that alcalase and trypsin protein hydrolysates from mung bean vicilin inhibited the proliferation of human breast cancer cell lines MCF-7 and MDA-MB-231 (Gupta et al., 2018). Additional studies have also demonstrated the anticancer effects of food-derived protein hydrolysates and peptides in cellular models such as the cytotoxic effects of walnut protein hydrolysates on human breast (MDA-MB231) and colon (HT-29) cancer cells (Jahanbani et al., 2016), sea cucumber hydrolysates and peptide fractions on HT-29 colorectal cancer cells (Pérez-Vega et al., 2013), and tuna dark muscle hydrolysates and peptides (LPHVLTPEAGAT and PTAEGGVYMVT) on MCF-7 human breast cancer cell line (Hsu et al., 2011). Other studies include algae protein-derived peptide (VECYGPNRPQF) on AGS human gastric adenocarcinoma cell model (Sheih et al., 2010), germinated soybean protein hydrolysates on HeLa and C-33 cervical cancer cells (Mora-Escobedo et al., 2009), walnut protein hydrolysates on UACC-62 melanoma cells (Carrillo et al., 2017), and rice bran protein hydrolysates on human colon (Caco-2) and liver (HepG2) cancer cells (Kannan et al., 2008). The effect of processing on the anticancer property of food-derived protein hydrolysates has also been studied. Song et al. (2011) showed that the heated products of half-fin anchovy peptic hydrolysates had stronger antiproliferative effects on DU-145, H1299 and ECA-109 human esophageal cancer cells than the unheated samples. Further studies with peptide fractions and a purified peptide (YALPAH) from the heated (121 °C for 30 min) protein hydrolysate products showed potent antiproliferative effects on PC-3 cancer cells and the induction of apoptosis by YALPAH (Song et al., 2014).

4. Animal studies

The anticancer properties of food-derived peptides and protein hydrolysates have been evaluated in animal models and reported by various researchers. In one study where the hepatic carcinoma cell line H-22 was subcutaneously injected into Chinese Kun Ming (KM) mice, the administration of chickpea albumin hydrolysates to the mice by oral gavage was found to significantly increase tumor inhibition rate and decrease tumor volume after a 12-day

treatment (Xue et al., 2012). In addition, chickpea albumin hydrolysate also significantly increased the proliferation of spleen lymphocytes and enlargement of splenic volume thus suggesting that administration of the hydrolysate enhanced the immune system and increased the weight of the immune organ. This is particularly noteworthy given the historical dilemma of administering anti-tumor drugs and contending with the concomitant impairment of the immune system (Xue et al., 2012). In H-22 tumor-bearing BALB/c mice, corn peptide fractions dose-dependently suppressed tumor growth and enhanced spleen volume while upregulating the level of serum cytokines IL-2, IFN-γ and TNF-α in a concentration-dependent manner (Li et al., 2013). Furthermore, the cationic and antimicrobial peptide lactoferricin was found to extend the survival of immune-deficient SCID/beige mice inoculated with Ramos human B-lymphoma cells (Furlong et al., 2010). After B-lymphoma cell inoculation via the tail vein and subsequent intraperitoneal injection of bovine lactoferricin, adult mice were weighed and examined daily for signs of distress while hind limb paralysis as a result of B-lymphoma cell dissemination to the central nervous system was taken as a measure of survival (Furlong et al., 2010). Bovine lactoferricin is an amphipathic, 25-amino acid polypeptide obtained following peptic digestion of the iron-binding protein, lactoferrin in cow milk. It is thought that bovine lactoferricin binds to negatively charged structures on cancer cells and then disrupts the membrane of those cells by inserting its bulky hydrophobic amino acid residues into the phospholipid bilayer of the cell membranes (Furlong et al., 2010; Hoskin and Ramamoorthy, 2008). In an earlier study, the antitumour effect of bovine lactoferricin on mice neuroblastoma xenograft tumors was shown (Eliassen et al., 2006). The results indicated that tumors from rats treated with the polypeptide and weighed at autopsy had significant reductions in weight compared with those from control subjects. Furthermore, in a different study Eliassen et al. (2006) studied the effects of P2, a polypeptide fraction from *Arca subcrenata*, on KM mice subcutaneously inoculated with S-180 sarcoma or H-22 hepatoma tumors and reported significant reductions in tumor weights. P2 reduced tumor weight by up to 60% in S-180 tumor-bearing mice and 46% in H-22 tumor-bearing mice at a dosage of 63 mg/kg/day. Also, using C57BL/6J mice subcutaneously inoculated with B16F10 melanoma cells, the cationic peptide INKKI isolated from bovine β-casein was tested for antitumor activity (Eliassen et al., 2006). Results showed that following peritumoral injection of the peptide, INKKI-treated tumor-bearing mice had significantly reduced tumor volume (up to 72%) and decreased metastasis loci in comparison with the untreated control. Furthermore, the peptide treatment led to a significant delay in tumor growth and doubling time (Eliassen et al., 2006). Lastly, it was reported that female Sprague-Dawley rats with 7,12-dimethylbenz[α]anthracene (DMBA)-induced mammary tumorigenesis, which received 3.3 g soy peptide daily as part of their diet, had significantly reduced (up to 50%) incidence of ductal carcinomas (Eliassen et al., 2006). Additionally, the soy peptide (XMLPSYSPY) also induced apoptosis and the expression of p21, p53, and caspase-3 proteins, significantly reduced the number of tumors per mice, the weight of ductal carcinomas, and also extended the latency period of tumor development when compared to the control (Eliassen et al., 2006). Importantly, the soy peptide used in this study was purified to be isoflavone-free. Questions surrounding the continued efficacy of orally-ingested bioactive peptides in the face of the degradative action of digestive enzymes as well as their absorbability and bioavailability have been duly answered by studies showing the detection of intact peptides in blood circulation following oral gavage (van Platerink et al., 2006; Foltz et al., 2007; Tanaka et al., 2015; Matsui, 2018; Nwachukwu et al., 2019). In one study, up to 17 small angiotensin converting enzyme (ACE)-inhibitory peptides were found in plasma collected from human subjects who had consumed a peptide-enriched drink (van Platerink et al., 2006). In another study, MALDI-MS imaging analysis revealed that Trp-His, an anti-atherosclerotic dipeptide administered by oral gavage to Sprague-Dawley rats, was absorbed intact into the systemic circulation due to its selective transport across the rat intestinal epithelium by the peptide transporter, PepT1 (Tanaka et al., 2015). Recently, our work also reported the detection in blood plasma of certain calmodulin-dependent phosphodiesterase (CaMPDE)-inhibitory peptides administered by oral gavage to adult Wistar rats and absorbed intact across the intestinal epithelium (Nwachukwu et al., 2019).

5. Conclusions

The common practice of grouping cancer types according to the major anatomical sites affected in various reports of global mortality tends to downplay cancer's standing as a leading cause of death (WHO, 2014). It is arguably the top and most widespread cause of death as it affects populations in all countries and all regions of the world. The studies reviewed in this work represent ample proof of the promising potential of food-derived protein hydrolysates and peptides to function as anticancer agents. Given that these bioactive agents are not drugs and are therefore, not designed for use in acute conditions, their consumption as part of the daily diet or as components of nutraceuticals and/or functional foods should be geared towards health promotion and prevention of cancer. Since over 60% of global cancer cases and 70% of cancer deaths occur in the low-income countries of Africa, Asia, and Central and South America (WHO, 2014), which typically have poorly developed healthcare systems, the gains of an early and habitual adoption of bioactive peptides and functional protein hydrolysates as part of a regular diet cannot be overemphasized. In addition, given the use of antioxidants in cancer treatment, future studies should focus on the prospect of utilizing antioxidant bioactive peptides in cancer combination therapy.

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Conflict of interest

The authors declare no conflict of interest.

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