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Lunasin, a Cancer Preventive Seed Peptide

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1. Introduction

Cancer has become one of the most common causes of death in industrialized countries and has been defined as the medical challenge of our times. In 2008, 12.7 million new cancer cases and 7.6 million deaths from cancer worldwide have been reported (Ferlay et al., 2010). These authors also estimate that by 2020, approximately 17 million new cancer cases will be diagnosed, and 10 million cancer patients will die. Evidences have shown that as many as 35% of these cases may be related to dietary factors (Manson, 2003), and thus, cancer can be prevented by modifications of nutritional and lifestyle habits. The rising prevalence of cancer worldwide and the corresponding rise in health care costs is propelling interest among researchers and consumers for multiple health benefits of food compounds, including reduction in cancer risk and modification of tumour behaviour (Béliveau, 2007; Kaefer and Milner, 2008). Epidemiological evidence, cell culture and animal tumour model studies have demonstrated that a large number of natural compounds present in the diet could lower cancer risk and even sensitize tumour cells in anti-cancer therapies (de Kok et al., 2008). Daily intake of food rich in anticancer molecules could be compared to a preventive, non-toxic version of chemotherapy that is harmless to the physiology of normal tissue and stops microtumours (Béliveau, 2007).

Phytochemicals are compounds present in plant foods with capacity to affect and regulate multiple key proteins involved in regulation of cellular proliferation, differentiation, apoptosis, angiogenesis or metastasis, and thus, to affect the different carcinogenesis stages (Fimongnari et al., 2008; Ramos, 2008; van Breda et al., 2008). Chemopreventive and chemotherapeutic properties against human cancers have been revealed for different phytochemicals, such as epigallocatechin gallate [(-)-EGCG] (green tea polyphenol), genistein (soybean), apigenin (celery, parsley), isothiocyanates (broccoli), anthocyanins (berries), quercetin (onions), kaempferol (broccoli, grapefruits), curcumin (turmeric), diallyl trisulfide (garlic), and lycopene (tomatoes) (Chen and Dou, 2008; Yang et al., 2008; Fimongnari et al., 2008; Singh and Goyal, 2008; Ramos, 2008; Seki et al., 2008). These

molecules have become an invaluable treasure in cancer prevention and chemotherapy, and further research is currently under way to explore their properties and mechanisms of action.

2. Soybean and cancer

Soybean (*Glycine max*) is an ancient legume consumed worldwide, but most commonly in Asian countries, such as China, Japan, Korea, Taiwan and Indonesia. Populations from these countries consume an average of 20 to 80 g of traditional soy foods daily in many forms, including soybean, soybean sprouts, toasted soy protein flours, soy milk, tofu, and fermented soy products, such as tempeh, miso, natto, soybean paste and soy sauce (Coward et al., 1993; Wang and Murphy, 1994). This intake equates to a daily intake of between 25 and 100 mg total isoflavones (Messina et al., 2006) and between 8 and 50 g soy protein (Erdman Jr. et al., 2004). Western populations consume much less soy, only about 1 to 3 g daily, and this is mostly in processed forms, such as soy drinks, breakfast cereals, energy bars and soy "burgers" (Fournier et al., 1998).

Epidemiological evidences have demonstrated an association between the consumption of soybean and improved health, particularly as a reduced risk for cardiovascular diseases (Anderson et al., 1999) and cancer, such as breast, prostate, endometrial, lung, and bladder cancer (Swanson et al., 1992; Wu et al., 1996; Goodman et al., 1997; Jacobsen et al., 1998; Zheng et al., 1999; Kolonel et al., 2000; Sun et al., 2002). Moreover, a number of animal models support anticancer properties of soy which constituents have been shown to suppress tumour growth in a variety of tissues including skin, bladder, mammary and prostate (Messina and Flickinger, 2002). In last decades, studies have isolated and identified an array of biologically active compounds or phytochemicals contained in soybean with cancer preventive effects. Genistein, daidzein and glycitein are the three major isoflavonoids found in soybean and soy products which properties have been extensively studied (Park and Surh, 2004). Large bodies of epidemiological studies have shown people consuming high amounts of these soy isoflavonoids in their diets have lower rates of several cancers, including breast, prostate and endometrial cancer (Lof and Weiderpass, 2006). In animal models, these compounds have been reported to inhibit the development of different types of tumors (Barnes et al., 1990; Li et al., 1999), but the results are not completely conclusive. Isoflavones exert both hormonal and non-hormonal action in the prevention of cancer, but the mechanism by which these compounds exert these chemopreventive properties is not yet clear and is currently a hot topic for research. The hormonal action of isoflavones has been postulated to be through a number of pathways, which include the ability to inhibit many tyrosine kinases involved in regulation of cell growth, to augment transformation growth factor- β which inhibits the cell cycle progression, as well as to influence the transcription factors that are involved in the expression of stress response-related genes involved in programmed cell death (Akiyama et al., 1987; Zhou and Lee, 1998). Other non-hormonal mechanisms by which isoflavones are believed to exert their anticarcinogenic effects are via their anti-oxidant, anti-proliferative, anti-angiogenic and anti-inflammatory properties (Gilani and Anderson, 2002).

During last years, soybean proteins and peptides have attracted attention as drug candidates owing to their possession of certain key advantages over alternative chemotherapy molecules. Soy protein itself, which is lower in sulfur amino acid content than animal protein, has been shown to inhibit the development of carcinogen-induced

tumors in animals (Koski, 2006). Soybean proteins also can be a source of bioactive peptides with diverse and unique health benefits that can be used in the prevention of age-related chronic disorders, such as cardiovascular disease, obesity, decrease immune function and cancer. In contrast to most small-molecule drugs, peptides have high affinity, strong specificity for targets, low toxicity and good penetration of tissues (Bhutia and Maiti, 2008). Soy proteins and peptides have become one group of nutraceuticals that shows potential results in preventing the different stages of cancer including initiation, promotion, and progression (Table 1) (de Mejia and Dia, 2010a). Bowman-Birk protease inhibitor (BBI) is a polypeptide with 71 amino acids which chemopreventive properties have been demonstrated in both *in vitro* and *in vivo* bioassay systems (Losso, 2008). As a result of this evidence, BBI acquired the status of "investigational new drug" from the FDA in 1992, and large-scale human trials are currently undergoing to evaluate its use as an anticarcinogenic agent in the form of BBI concentrate (BBIC) (Armstrong et al., 2000, 2003; Meyskens, 2001). These studies have shown that BBIC is well-tolerated by the patients and led to promising results for prostate and oral carcinomas. BBIC is also being used to investigate its efficacy in the treatment of benign prostatic hyperplasia and ulcerative colitis (Kennedy, 2006). Kunitz trypsin inhibitor (KTI) is another protease inhibitor originally isolated from soybean. The biological significance of KTI in carcinogenesis is mainly attributed to its ability to suppress invasion and metastasis of cancer cells (de Mejia and Dia, 2010a). Recently, there has been increased interest in the potential health benefits of other bioactive polypeptides and proteins from soybean, including lectins and lunasin. Soy lectins are a significant group of biologically active glycoproteins that have been shown to possess cancer chemopreventive activity *in vitro*, *in vivo* and in human case studies (de Mejia et al., 2003). The suggested mechanisms of action for lectins include their effect on tumoral cell membranes, the reduction in cell proliferation, the induction of tumor-specific cytotoxicity of macrophages and the induction of apoptosis. Another suggestion is that lectins could have a strong effect on the immune system by altering the production of various interleukins (de Mejia and Prisecaru, 2005). There is still much to learn about the effects of soybean lectins on cancer risk. However, they are currently being used as therapeutics agents in cancer treatment studies and this area of research holds considerable potential. Lunasin is a novel peptide, identified in soybean, which chemopreventive activity has been recently reported. The purpose of this work is to summarize the possible benefits of lunasin as a chemopreventive agent as well as its demonstrated mechanisms of action.

Soybean component	Cell line/Mouse model/Human model	Chemopreventive activity	Reference
Bowman-Birk protease inhibitor	Human osteosarcoma U2OS cells	↓ cell proliferation, arrest cell cycle, apoptosis induction, ↑ expression of C×43 mRNA	Saito et al., (2007)
	Human ovarian sarcoma M5067 cells in mice	↓ cell proliferation, ↑ expression of C×43 mRNA	Sakurai et al., (2008)
	Human breast cancer MCF-7 cells	Arrest cell cycle, ↓ proteasome chymotrypsin-like activity, ↑ expression of p27 and p21, inactivation of ERK1/2	Chen et al., (2005)

Soybean component	Cell line/Mouse model/Human model	Chemopreventive activity	Reference
		phosphorylation ↓ cell proliferation	Ho and Ng, (2008)
	DMBA-induced carcinogenesis in cultured mouse mammary gland	Inhibition of breast carcinogenesis	Du et al., (2001)
	Human prostate cancer cells	↓ cell proliferation, invasion, and clonogenic survival Induction of apoptosis, ↑ expression of C×43, cleavage of caspase-3	Kennedy et al., (2002) Tang et al., (2009)
	Prostate TRAMP mice model	Inhibition of tumour development	Tang et al., (2009)
	Dimethylhydrazine-induced rat colon cancer	Inhibition of colon carcinogenesis	Kennedy et al., (2002)
	Induced rat prostate carcinogenesis	Reduction of incidence of invasive and in situ prostate neoplasms	McCormick et al., (2007)
	Hepatocellular carcinoma HepG2 cells	↓ cell proliferation	Ho and Ng, (2008)
	Radiation-induced skin fibroblasts	Blocking activation of tyrosine kinase and ↓ epidermal growth factor	Dittmann et al., (1998)
	NB4 promyelocytic leukemia cells	↓ cell proliferation, arrest cell cycle, apoptosis induction, activation of the pathway of caspase-3 and -8 cascades	Huang et al., (2004)
	Human colon HT-29 cells	↓ cell proliferation, inhibition of serine proteases	Clemente et al., (2010)
Kunitz trypsin inhibitor	Oral leukoplakia in human trials	Inhibition of oral carcinogenesis	Armstrong et al., (2000, 2003); Meyskens et al., (2001)
	Ovarian cancer cells	Suppression of cell invasion	Kobayashi et al., (2004b)
	Ovarian HRA cells implanted in C57BL/6 mice	↓ total tumour burden in peritoneal metastasis	Kobayashi et al., (2004b)
	Lewis lung carcinoma cells in C57BL/6 mice	Inhibition of spontaneous metastasis	Kobayashi et al., (2004a)
	Nasopharyngeal CNE-1 and CNE-2 cells	↓ cell growth, apoptosis induction	Fang et al., (2010)

Soybean component	Cell line/Mouse model/Human model	Chemopreventive activity	Reference
Lectins	Hepatocellular carcinoma HepG2 cells	↓ cell growth, apoptosis induction	Fang et al., (2010)
	Different tumour cell lines	↑ sensitivity to be attacked by macrophages	Ganguly and Das (1994)
	Human colon cancer SW1222 and HT29 cells	↓ cell proliferation, blocked aggregation	Jordinson et al., (1999)
	T-cell and B-cell leukemia	Interaction with tumour cells	Reysner (1983)
	Human gastric carcinomas	Direct adhesion to cell membranes and receptors	Terashima et al., (1997)
	Human melanoma A375 cells	Induction of apoptosis by a caspase-dependent pathway	Liu et al., (2009)

Table 1. Effects of soybean Bowman-Birk protease inhibitor (BBI), Kunitz trypsin inhibitor (KTI) and lectins against cancer.

2.1 Lunasin: discovery and beyond

A novel peptide, which sequence is **SKWQHQQDSCRKQKQGVNLTPCEKHIMEKIQGRGDDDDDDDDDD**, was originally isolated from soybean cotyledon (Galvez et al., 1997). Because of the properties initially discovered, this peptide was termed lunasin from the Tagalog word “lunas” for cure. Lunasin is composed of 43 amino acid residues with a unique sequence including the presence of a cell adhesion motif composed of RGD and a carboxylic acid tail composed of nine aspartic acid residues. Galvez and de Lumen (1999) reported the biological property of lunasin, formerly known as a soybean cDNA encoding small subunit peptide of 2S soy albumin. They showed that transfection of lunasin plasmid into different mammalian cells caused cell division arrest, abnormal elongation of spindle fiber, chromosomal fragmentation, and cell death or apoptosis. Moreover, treatment of synthetic lunasin showed preferential adherence of this peptide to chromatin, leading to disruption of kinetochore and inhibition of mitosis. This activity seems to be due to the binding of its negatively charged poly-D carboxyl end to the highly basic histones found within the nucleosomes of condensed chromosomes, probably to regions that contain more positively charged, such as the hypoacetylated chromatin found in telomeres and centromeres. Lunasin’s sequence also contains the motif RGD known to allow tumour cell attachment to the extracellular matrix (Ruoslahti and Pierschbacher, 1986). Peptides containing this motif have been reported to prevent metastasis of tumour cells by competitive adhesion to extracellular matrices (Akiyama et al., 1995). In the case of lunasin, this motif has been found to be essential for lunasin’s internalization into the nucleus of C3H10T1/2 cells, but it is completely unnecessary for internalization into the nucleus of NIH3T3 cells, suggesting that the role of RGD motif might be cell-line specific (Galvez et al., 2001). These initial observations suggested a potential and promising chemopreventive role of lunasin in cancer prevention and led to successive studies designed and conducted to verify this hypothesis.

Lunasin concentration in soybean depends mainly on cultivar and environmental factors including temperature and soil moisture. Analysis of five soybean cultivars grown at three

different temperatures and two soil moisture conditions showed that cultivar and temperature but not soil moisture significantly affected lunasin concentration in soy (Wang et al., 2008b). These authors reported that lunasin concentration of the five cultivars ranged from 7.5 to 10.4 mg/g flour, in which US cultivars Loda, Jack and Dwight showed higher values than French cultivars Queen and Imari. Cultivars grown at higher temperature of 28 °C showed lowest lunasin concentration (8.1 mg/g flour) than those grown at intermediate temperature of 23 °C (9.2 mg/g flour) and low temperature condition (8.8 mg/g flour). A significant interaction was found between cultivar and temperature as well as soil moisture and cultivar in affecting lunasin concentration in soybean. Determination of lunasin concentration in 144 selected, diverse soybean accessions from the U.S. Department of Agriculture by enzyme linked immunosorbent assay showed that lunasin concentration ranged from 0.1 g to 1.3 g/100 g flour (de Mejia et al., 2004). Soybean seeds devoid of BBI also showed varying concentrations of lunasin ranging from 3.3 to 16.7 ng lunasin/mg seed indicating that lunasin is still produced on soybean seed even in the absence of BBI (de Mejia and Dia, 2010b). Analysis of lunasin in Korean soybean cultivar Taekwongkong showed that lunasin appears at 6 weeks after flowering (0.01 µg/g seed) with its highest level found at maturity with concentration of 0.12 µg/g seed (Park et al., 2005). Processing also affects lunasin concentration in soybean and soybean products. For instance, sprouting of soybean seed by soaking showed that lunasin starts decreasing 2 days after soaking and completely disappears after 7 days under both light and dark conditions (Park et al., 2005). de Mejia and co-workers (2004) showed that lunasin concentration of commercially available soy protein is in the range of 13 to 44 mg lunasin/g flour. Lunasin-enriched soy flour showed a concentration of 27.3 mg lunasin/g flour while isoflavone-enriched soybean products extracted with ethanol showed almost no lunasin which might be attributed to poor solubility of lunasin in ethanol. Another study conducted by Jeong et al. (2003) reported that defatted soybean flour had the lowest concentration of lunasin (5.5 mg lunasin/g protein) when compared with soy isolate (6.9 mg/lunasin/g protein) and soy concentrate (8.7 to 16.5 mg lunasin/g protein). They also showed that water-washed soy concentrate had higher lunasin concentration than alcohol-washed soy concentrate. These reports indicate that lunasin concentration in soybean products is affected by processing conditions. Recently, it has been found that environmental factors, such as germination time and temperature have a significant influence on the composition and concentration of bioactive compounds in germinated soybean flour from the Brazilian soybean cultivars BRS 133 and BRS 258 (Pauca-Menacho et al., 2010b, c). These authors reported that protein concentration also affects the final distribution of nutrients and bioactive components in soybean, including lunasin (Pauca-Menacho et al., 2010a).

The first study has demonstrated lunasin's presence in US commercially available soy foods, including soy milk, infant formulas, tofu, bean curd, soybean cake, tempeh, and su-jae (Hernández-Ledesma et al., 2009a). As an example, Table 2 shows type, composition, origin and lunasin and BBI concentrations of different soy milk samples analyzed by these authors. Concentrations of two peptides in soy milk and other soybean products seem to be determined by the soybean variety and the process used during manufacturing, indicating that these two parameters can be used to control contents of these two peptides. Previously it had been demonstrated that large-scale processing of soy to produce different protein fractions influences lunasin concentration. This content varied from 12 to 44 mg lunasin/g of flour when different commercially available soy proteins were analyzed (de Mejia et al., 2004; Jeong et al., 2003).

Sample No.	Type of sample	Composition-main ingredients	Country	Lunasin (mg/100 g product)	BBI (mg/100 g product)
Soy milk-1	Enriched soymilk	Soybeans	USA	15.7 ± 1.3	33.1 ± 4.2
Soy milk-2	Organic original soymilk	Soybeans, malted wheat and barley extract	USA	18.9 ± 2.6	27.1 ± 3.4
Soy milk-3	Organic fortified soymilk	Soybeans, malted wheat and barley extract	USA	14.2 ± 1.1	24.7 ± 4.3
Soy milk-4	Organic plain soymilk	Soybeans	USA	13.8 ± 2.6	45.7 ± 7.2
Soy milk-5	Organic unsweetened soymilk	Soybeans	USA	14.4 ± 2.4	55.9 ± 5.0
Soy milk-6	Organic plain soymilk	Soybeans	USA	14.7 ± 0.8	40.0 ± 5.5
Soy milk-7	Organic original soymilk	Soybeans, rice syrup	USA	13.7 ± 0.9	30.3 ± 3.7
Soy milk-8	Organic plain soymilk	Soybeans, soy protein isolate	USA	13.9 ± 1.0	25.9 ± 4.2
Soy milk-9	Organic original soymilk	Soybeans, malt syrup	USA	18.3 ± 2.4	23.1 ± 3.0
Soy milk-10	Organic original soy drink	Soybeans, barley extract	USA	10.7 ± 0.8	7.2 ± 1.5
Soy milk-11	Fortified soymilk	Soybeans	USA	12.3 ± 0.8	18.8 ± 2.7
Soy milk-12	Unsweetened soymilk	Soybeans	Singapore	11.8 ± 1.3	n.d.
Soy formula-1	Soy-based formula	Corn syrup, soy protein isolate	USA	4.1 ± 0.4	n.d.
Soy formula-2	Organic soy formula	Corn syrup, soy protein	USA	2.8 ± 0.2	n.d.
Soy formula-3	Organic soy formula	Rice syrup, soy protein concentrate	USA	1.5 ± 0.1	n.d.
Tofu-1	Soft Tofu	Soybeans	USA	9.62 ± 0.87	4.63 ± 1.76
Tofu-2	Soft Tofu	Soybeans	USA	7.34 ± 1.04	3.72 ± 0.21
Tofu-3	Silken Tofu Kinugoshi	Soybeans	USA	9.60 ± 0.74	12.41 ± 2.11
Tofu-4	Silken Tofu	Soybeans	USA	4.41 ± 0.49	11.87 ± 1.53
Tofu-5	Silken Tofu	Soybeans	USA	3.69 ± 0.49	5.92 ± 1.15
Tofu-6	Medium firm Tofu	Soybeans	USA	14.30 ± 1.80	4.91 ± 0.53
Tofu-7	Organic Medium firm Tofu	Soybeans	USA	6.66 ± 1.29	4.19 ± 0.54
Tofu-8	Firm Tofu	Soybeans	USA	3.50 ± 0.23	8.23 ± 0.58

Sample No.	Type of sample	Composition-main ingredients	Country	Lunasin (mg/100 g product)	BBI (mg/100 g product)
Tofu-9	Extra firm tofu Chinese style	Soybeans	USA	3.66 ± 0.12	4.57 ± 0.55
Tofu-10	Baked tofu	Soybeans, soy sauce (wheat)	USA	5.47 ± 0.34	2.94 ± 0.48
Tofu-11	Fried tofu	Soybean, soybean oil, soy sauce	USA	0.37 ± 0.05	n.d.
Tofu-12	Dry tofu	Soybeans	Taiwan	2.50 ± 0.27	n.d.
Natto-1	Natto	Fermented soybeans (<i>Bacillus subtilis</i> natto)	Japan	n.d.	n.d.
Miso-1	Organic Miso	Soybeans, rice, <i>Aspergillus oryzae</i>	Japan	n.d.	n.d.
Tempeh-1	Organic soy tempeh	Soybeans, <i>Rhizopus oligosporus</i>	USA	n.d.	n.d.
Tempeh-2	Organic soy tempeh	Soybeans, brown rice, <i>R. oligosporus</i>	USA	8.19 ± 0.42	n.d.
Tempeh-3	Organic soy tempeh-flax	Soybeans, flaxseed, brown rice, <i>R. oligosporus</i>	USA	6.12 ± 0.40	n.d.
Tempeh-4	Organic soy tempeh-rice	Soybeans, brown rice, <i>R. oligosporus</i>	USA	n.d.	n.d.
Bean curd-1	Marinated bean curd	Soybeans, soy sauce	Taiwan	9.53 ± 1.01	14.65 ± 0.60
Bean curd-2	Soybean curd noodle	Soybeans	Taiwan	n.d.	n.d.
Soybean cake-1	Deep fried soybean cake	Soybeans, soybean oil	USA	1.91 ± 0.25	6.57 ± 0.41
Soybean cake-2	Baked soybean cake	Soybeans, soy sauce, sesame oil	USA	1.14 ± 0.15	0.73 ± 0.05

Table 2. Type, composition, country of origin and lunasin and BBI concentrations of commercial soy food products

2.1.1 Lunasin’s bioavailability

An important property of an ideal cancer preventive agent is its ability, after being orally administrated, to escape gastrointestinal digestion and to be absorbed through the bloodstream reaching the target tissues and organs in an intact and active form. To date, different lunasin’s bioavailability studies conducted in both animals and humans have shown promising results. First studies carried out in mice and rats fed lunasin-enriched soy protein found that 35% of ingested lunasin reaches the target tissues and organs in an intact and active form (Jeong et al., 2007a). It has also been reported that BBI and KTI contained in soybean protect lunasin against gastrointestinal digestion, making this peptide bioavailable to exert its chemopreventive properties (Park et al., 2007). Hsieh and co-workers reported that synthetic ³H-labeled lunasin was bioavailable after its oral administration to CD-1 mice, reaching different tissues, including lung, mammary gland, prostate, and brain (Hsieh et al., 2010a). These authors also found that lunasin extracted from the blood and liver of lunasin-

enriched soy flour-fed rats was bioactive and able to suppress foci formation in the same concentration as synthetic lunasin. Lunasin from other seeds have also shown stability towards pepsin and pancreatin *in vitro* digestion (Jeong et al., 2009; Jeong et al., 2010a). These authors demonstrated lunasin's presence in different organs, such as liver, kidney, and blood of rats fed with lunasin-enriched rye. First bioavailability study conducted in humans has demonstrated that 4.5% of lunasin ingested in the form of soy protein reaches plasma of healthy volunteer men (Dia et al., 2009a). Results from this study are relevant in supporting future clinical trials to demonstrate lunasin's cancer preventive properties.

2.1.2 Lunasin against cancer: *in vitro* and *in vivo* evidence

Cell culture experiments have demonstrated that lunasin prevent mammalian cells transformation induced by chemical carcinogens without affecting morphology and proliferation of normal cells. Galvez and co-workers (2001) found that lunasin suppresses foci formation in 7,12-dimethylbenz[a]anthracene (DMBA) and 3-methylcholanthrene (MCA)-induced C3H10T1/2 cells. Similar results have been found by Hsieh and co-workers (2011) in DMBA-induced NIH3T3 cells. This suppressive effect is significantly higher than that exerted by the well-known cancer preventive BBI on an equimolar basis. Lunasin's inhibitory effects have been also found in C3H10T1/2 and NIH3T3 cells transformed by oncogenes and genes that inactivate tumor suppressor proteins (Galvez et al., 2001; Jeong et al., 2003; Lam et al., 2003). Ras-oncogenes are frequently activated in human cancers, playing a central role in the ras/mitogen activated protein kinase (MAPK) signalling cascade, which has a pivotal role in cell proliferation, differentiation, survival and cell death (Barbacid, 1987; Malumbres and Barbacid, 2003). Lunasin has been shown to prevent transformation of NIH3T3 cells transfected with an inducible form of ras-oncogene (Jeong et al., 2003). Moreover, addition of lunasin to mouse fibroblasts NIH3T3 stably transfected with the viral oncogene E1A has been reported to suppress foci formation and to increase protein p21 level (Lam et al., 2003). Oncogene E1A has been associated with human tumours because of its ability to inactivate the tumour suppressor retinoblastoma protein (RB) causing cell cycle arrest and cells transformation (Helt and Galloway, 2003).

These first results made lunasin to be considered as a "watchdog" agent that sits in the nucleus of the cells and effectively does nothing when there is no transformation event. When a transformation event occurs, lunasin is triggered into action (de Lumen, 2005). However, recent studies carried out in our laboratories have revealed that lunasin also acts on established cancer cell lines. Lunasin purified from defatted soybean flour by combination of ion-exchange chromatography and size exclusion chromatography (Dia et al., 2009b) showed potent activity against different human colon cancer cells. Lunasin caused cytotoxicity in four different human colon cancer cell lines with IC₅₀ values of 13.0 µM for KM12L4 cells, 21.6 µM for RKO cells, 26.3 µM for HCT-116 cells and 61.7 µM for HT-29 cells (Dia and de Mejia, 2011). These values showed that lunasin is most potent in killing the highly metastatic KM12L4 colon cancer cells than any other colon cell lines used in this study. Crystal violet staining of HT-29 colon cancer cells showed that starting at 10 µM, lunasin caused changes in the morphology and number of viable cancer cells (Dia and de Mejia, 2010). Also, treatment of the oxaliplatin-resistant variants (OxR) of these colon cancer cells showed IC₅₀ values of 34.7 µM for KM12L4OxR, 38.9 µM for RKOOxR and 31.6 µM for HCT-116OxR while HT-29OxR was not affected by lunasin treatment. It has been also demonstrated that lunasin causes a dose-dependent inhibition of the growth of estrogen-independent breast cancer MDA-MB-231 cells, with an IC₅₀ value of 181 µM (Hsieh et al.,

2010b). Studies carried out to establish a structure/activity relationship showed an IC_{50} value of 138 μM for the 21 amino acid sequence localized at the C-terminus of lunasin, thus being the main responsible for lunasin's inhibitory effect on breast cancer cells proliferation (Hernández-Ledesma et al., 2011). Lunasin's suppressive effect on cell growth has been also found in L1210 leukemia cells, with an IC_{50} value of 14 μM (Wang et al., 2008a).

Chemopreventive properties of lunasin have been also demonstrated *in vivo*. First animal model used to demonstrate these properties was a chemical carcinogen induced SENCAR skin cancer mouse model (Galvez et al., 2001). These authors demonstrated that 250 μg lunasin/week, topically administered to SENCAR mice treated with DMBA and tetradecanoylphorbol-13-acetate (TPA), suppresses skin tumor incidence, decreases tumor yield/mouse and increases the tumor latency period by 70% compared with the untreated control. Moreover, lunasin was found to delay the appearance of papilloma by slowing down epidermal cell proliferation in mouse skin in the presence of DMBA (Hsieh et al., 2004). Promising results have been also found when lunasin acts *in vivo* against breast cancer. Our first findings show a relevant inhibitory effect on mammary tumours development when a lunasin-enriched diet is administered to DMBA-induced mice (Hsieh et al., 2010c). Moreover, lunasin reduces tumour incidence and generation, as well as tumour weight in a xenograft mouse model using human breast cancer cells. Tumour incidence was reduced by 49% and 33%, in nude mice transplanted with MDA-MB-231 cells and administered i.p. injections of lunasin, at 20 mg/kg and 4 mg/kg body weight, respectively, compared with the vehicle-treated group, while no effects were observed when mice were treated with BBI (Hsieh et al., 2010a). In the breast tumour histological sections, lunasin was found to inhibit cell proliferation and to induce cell apoptosis. These studies make lunasin a promising alternative to prevent and/or treat skin and breast cancer. Further research should be needed to demonstrate chemopreventive role of this peptide against other types of cancer, as well as to elucidate its *in vivo* mechanism of action.

2.1.3 Mechanism of lunasin's action

Initially, lunasin was found to act through an epigenetic mechanism of action. This peptide has been demonstrated to compete with different histone acetyltransferase enzymes (HATs), such as yGCN5 and PCAF, inhibiting the histones acetylation and repressing the cell cycle progression (Jeong et al., 2002, 2007b, c). Acetylation has been linked to chromatin disruption and the transcriptional activation of genes, being thus considered one of the most important epigenetic modifications acting on signal transduction pathways including those involved in cancer development (Dwarakanath et al., 2008; Dalvai & Bystricky, 2010). Mistargeted and deregulated HATs activities, as well as their over-expression have been reported to play an important role in several human cancers (Gayther et al., 2000). Lunasin has been reported to inhibit histone acetylation in mammalian cells induced by chemical carcinogens and/or viral oncogenes that provoke inactivation of tumor suppressor proteins, such as RB, p52 and pp32. When lunasin is present in the cell nucleus, it acts as a surrogate tumor suppressor and tightly binding to deacetylated core histones and disrupting the balance between acetylation-deacetylation, which is perceived by the cell as abnormal and leads to cell death (de Lumen, 2005). Recently, studies carried out with human breast cancer MDA-MB-231 cells have demonstrated that lunasin inhibits histones H3 and H4 acetylation in these cells (Hernández-Ledesma et al., 2011), being more potent than other compounds which HATs inhibitory activity has been associated with their chemopreventive role (Balasubramanyam et al., 2003, 2004a, b). Structure/activity relationship have demonstrated,

in one hand, that the percentage of inhibition caused by lunasin is specific of lysine position sensitive to be acetylated, and in another hand, that lunasin's sequence is essential for inhibiting H4 acetylation whereas poly-D sequence is the main active sequence responsible for H3 acetylation inhibition (Hernández-Ledesma et al., 2011). Figure 1 shows the activity of each lunasin-related fragment on histone binding and/or acetylation at different Lys positions.

Studies conducted with different tumour cell lines have demonstrated new mechanisms for lunasin's chemopreventive action. Studies with colon cancer HT-29 and KM12L4 cells have shown that lunasin caused a G2/M phase arrest in the cell cycle and induction of the mitochondrial pathway of apoptosis (Dia and de Mejia, 2010). The G2/M phase cell cycle arrest was attributed with concomitant increase in the expression of the p21 protein in HT-29 colon cancer cells while both p21 and p27 protein expressions were up-regulated by lunasin treatment in KM12L4 colon cancer cells. Measurement of protein expressions associated with mitochondrial pathway of apoptosis showed that lunasin treatment affected the ratio of Bax to Bcl-2 by up-regulating the pro-apoptotic Bax and down-regulating the expression of the anti-apoptotic Bcl-2. This might be attributed to increase in the expression of the pro-apoptotic form of clusterin known as nuclear clusterin which is positively affected by increase in p21 expression. Translocation of Bax into the mitochondrial membrane resulted in the release of cytochrome c as shown by increase in the expression of cytosolic cytochrome c in KM12L4 colon cancer cells treated with lunasin. This resulted in an increase in the activity of caspase-9 and the activity of the executioner of apoptosis caspase-3 in both HT-29 and KM12L4 colon cancer cells treated with lunasin when compared to untreated cells. We proposed the mechanism by which lunasin can induce apoptosis in human colon cancer cells as shown in Figure 2.

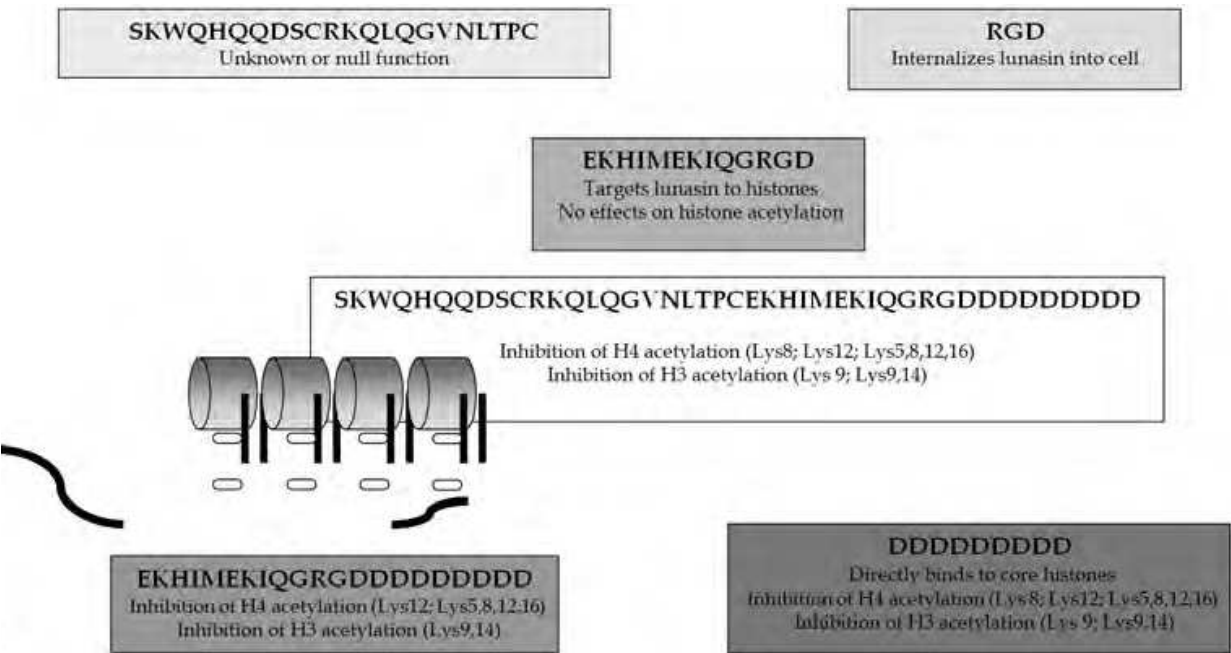


Fig. 1. Amino acids sequence of lunasin peptide and demonstrated histones H3 and H4 acetylation inhibitory activity of the different fragments of its sequence

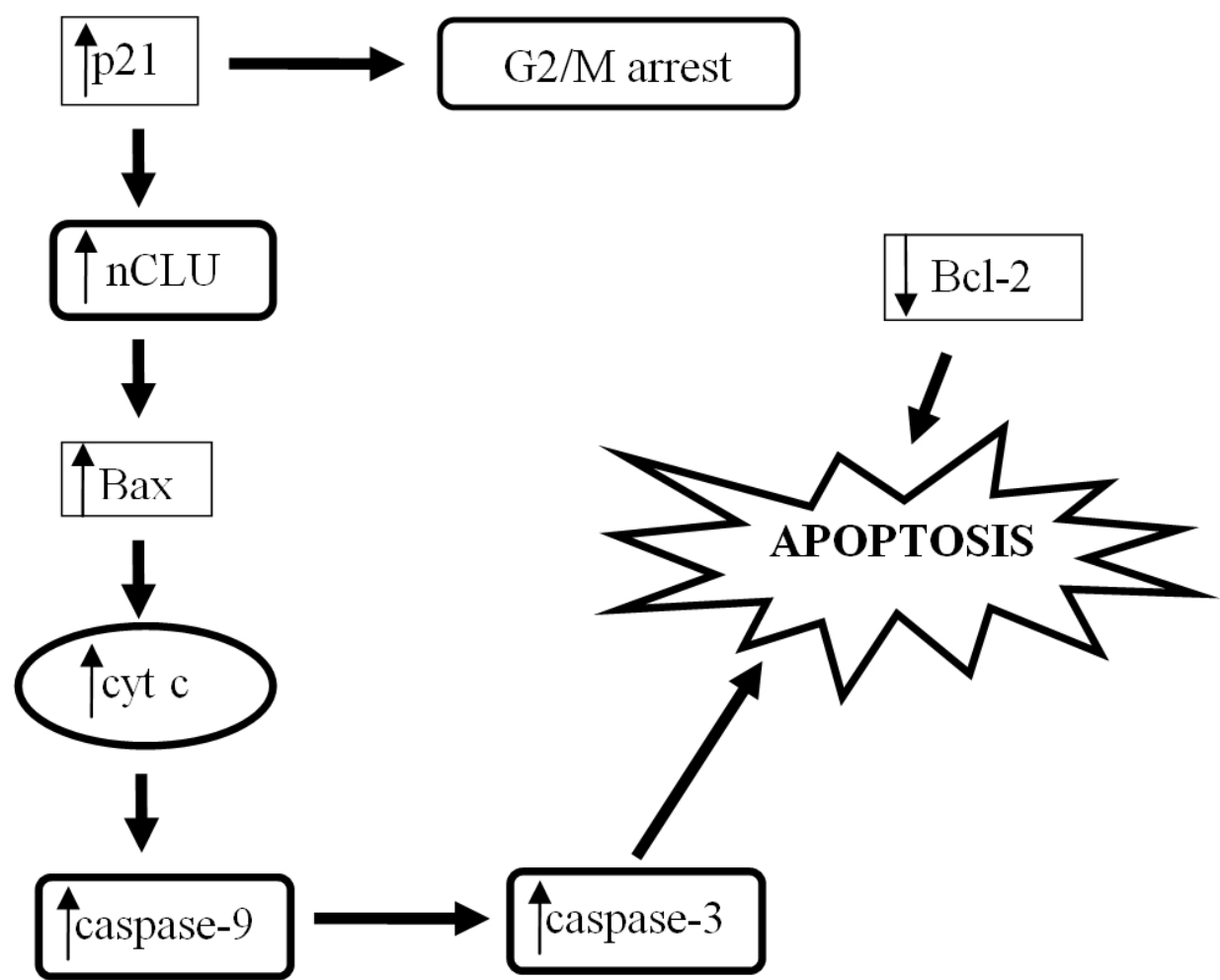


Fig. 2. Proposed mechanism by which lunasin induces apoptosis in human colon cancer cells.

The RGD motif present in the lunasin structure is a recognition site for integrin receptors present in the extracellular matrix (ECM). Integrins are heterodimeric receptors associated with cell adhesion, ECM and cancer metastasis. Treatment of KM12L4 colon cancer cells with lunasin resulted in the modification on the expression of 62 genes associated with ECM and cell adhesion, of which 48 genes were up-regulated and 14 genes were down-regulated (Dia and de Mejia, 2011a). Lunasin down-regulated the gene expression of collagen type VII α 1, integrin β 2, matrix metalloproteinase 10, selectin E and integrin α 5 by 10.1-, 8.2-, 7.7-, 6.5- and 5.0-fold, respectively compared to the untreated KM12L4 colon cancer cells. On the other hand, the expression of collagen type XIV α 1 was up-regulated upon lunasin treatment by 11.6-fold (Dia and de Mejia, 2011). These results suggest a potential role of peptide lunasin in cancer metastasis.

Lunasin has been also demonstrated to arrest cell cycle and to induce apoptosis in breast cancer MDA-MB-231 cells (Hsieh et al., 2010b). These authors demonstrated that lunasin modulates expression of different genes and proteins involved in cell cycle, apoptosis and signalling transduction. Inhibition of deregulated cell cycle progress in cancer cells is being considered an effective strategy to delay or halt tumour growth. It is well established that cyclins play a positive role in promoting cell cycle transitions via their ability to associate

with their cognate cyclin-dependent kinases (CDKs) and to activate them (Kato et al., 1993). Over-expression of cyclins D1 and D3 is one of the most frequent alterations present in breast tumours (Sutherland and Musgrove, 2004). Cyclins D interacts with CDK4 or CDK6 to form a catalytically active complex, which phosphorylates RB to free active E2F (Qu et al., 2003). Up-regulation of RB gene expression (Hsieh et al., 2010b), as well as inhibition of RB phosphorylation (Jeong et al., 2007b) have been linked to lunasin's arresting effect on breast cancer cells cycle progress. Down-regulation of cyclins D1 and D3, and CDK4 and CDK6 protein expression as well as modulation of expression of CDC25A, Caspase 8, and Ets2, Myc, Erbb2, PIK3R1 and Jun signaling genes in breast cancer cells might also contribute on this lunasin's suppressive effect (Hernández-Ledesma et al., 2011; Hsieh et al., 2010b).

Lunasin also showed cytotoxic effect in L1210 leukemia cells with an IC_{50} value of 14 μ M. The mechanism involved was through arrest of cell cycle at G2/M phase with concomitant pro-apoptotic inducing property. The expressions of caspases-3, -8 and -9 were up-regulated by 12-, 6- and 6-fold respectively which resulted in the increase of percentage of L1210 leukemia cells undergoing apoptosis from 2 to 40% (de Mejia et al., 2010).

Lunasin has been found to exert anti-inflammatory and antioxidant activities that might contribute to its chemopreventive properties. First studies demonstrated that lunasin potently inhibits lipopolysaccharide (LPS)-induced production of pro-inflammatory mediators interleukine (IL-6), tumor necrosis factor (TNF- α), and prostaglandin E2 (PGE2) in RAW 264.7 cells through suppression of nuclear factor (NF)- κ B pathways (Hernández-Ledesma et al., 2009b; de Mejia and Dia, 2009). It has been also reported that this peptide exert its anti-inflammatory activity through modulation of cyclooxygenase-2 (COX-2)/PGE2 and inducible nitric oxide synthase (iNOS)/nitric oxide pathways (Dia et al., 2009b). Moreover, lunasin has been found to exert potent antioxidant properties, reducing LPS-induced production of ROS by macrophage cells, and acting as a potent free radical scavenger (Hernández-Ledesma et al., 2009b). Recently, lunasin purified from *Solanum nigrum* L. has been found to protect DNA from oxidative damage by suppressing the generation of hydroxyl radical via blocking fenton reaction (Jeong et al., 2010).

Silva-Sánchez and co-workers, (2008) reported for the first time the presence of a lunasin-like peptide in amaranth protein fractions. Glutelin fraction in amaranth seeds had the highest lunasin concentration (3.0 g/g). Lunasin was also identified in albumin, prolamin and globulin amaranth protein fractions.

Maldonado-Cervantes and co-workers, (2010) found that the amaranth lunasin-like peptide inhibited the transformation of NIH-3T3 cells to cancerous foci. The open reading frame of amaranth lunasin corresponds to a bifunctional inhibitor/lipid-transfer protein (LTP). There are many new intriguing questions about the function of lunasin in plants and its health-promoting benefits that need further investigations.

3. Conclusion

Epidemiological evidence has demonstrated an association between the consumption of soybean and improved health, particularly reduced risk for cardiovascular diseases and cancer. *In vitro* as well as *in vivo* studies support the cancer preventive properties of soy and soy compounds responsible of these properties. This review has summarized the chemopreventive activity of proteins and peptides that contribute to reported cancer preventive effects of soybean. Among them, peptide lunasin holds a considerable potential.

This peptide, administered in soy proteins, has been demonstrated to be bioavailable after resisting gastrointestinal and serum degradation, and reaching blood and target organs in an intact and active form. Lunasin's efficacy against leukemia, breast and colon cancer using cell culture models has been recently revealed. Animal experiments are being conducted to verify these *in vitro* properties, and to date, a promising role of lunasin against skin and breast cancer has been reported. Moreover, genomics, proteomics and biochemical tools are being applied to complete elucidate its molecular mechanism of action. Obtained results from all these studies make lunasin a good candidate for new generation of cancer preventive agents derived from foods. However, there is still much to be learned about lunasin's effects on cancer prevention. The major challenge on the use of lunasin in treating cancer would be the conversion of *in vitro* and *in vivo* results into clinical outcomes. Therefore, it should be needed to design clinical trials that confirm lunasin's chemopreventive properties against different types of cancer. Other aspects, such as searching for lunasin in other seeds, optimization of techniques to enrich products with this peptide and studying lunasin's interactions with other food constituents affecting its activity should also be conducted.

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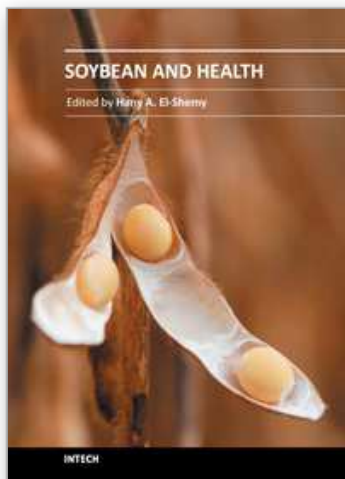
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Worldwide, soybean seed proteins represent a major source of amino acids for human and animal nutrition. Soybean seeds are an important and economical source of protein in the diet of many developed and developing countries. Soy is a complete protein, and soy-foods are rich in vitamins and minerals. Soybean protein provides all the essential amino acids in the amounts needed for human health. Recent research suggests that soy may also lower risk of prostate, colon and breast cancers as well as osteoporosis and other bone health problems, and alleviate hot flashes associated with menopause. This volume is expected to be useful for student, researchers and public who are interested in soybean.

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