# A REVIEW ON CHEMOPREVENTIVE FOOD BIOACTIVE PEPTIDE: LUNASIN

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**Abstract**

Cancer is one of the leading causes of death. Approximately, one-third of these deaths are preventable through lifestyle changes, such as dietary changes. According to research, adequate nutrition with certain types of foods containing bioactive compounds may provide significant protection against carcinogenesis. However, the relationship between nutritious food consumption and cancer risk remains controversial. Bioactive peptides are isolated small protein fragments that provide physiological health benefits. They act as potential modifiers reducing the risk of many chronic diseases. This review focuses on the current data on Lunasin, a novel food bioactive peptide found primarily in soybean and wheat that has antioxidant, anticarcinogenic, and hypocholesterolemia effects in in vivo and in vitro models. Lunasin is the most studied bioactive soy-peptide, with 43 amino acid residues, some of which form an RGD motif, and the most recent evidence on the lunasin's potential benefits for cancer prevention.

**Keyword:** Cancer, Hypocholesteremia, Lunasin, Peptide, Soybean

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## 1. Introduction

Cancer has become one of the leading causes of death in developed countries, and it is widely regarded as the most pressing medical challenge today[1]. The increasing prevalence of cancer worldwide, as well as the corresponding increase in medical costs and the adverse effects of chemotherapeutic agents, is encouraging researchers and consumers to evaluate the many beneficial health benefits of food compounds, which may reduce the risk of cancer and alter tumor behavior. When compared to a toxic form of chemotherapy, daily consumption of foods rich in bioactive anti-cancer compounds may be preventative. Dietary anti-cancer compounds are non-toxic to healthy tissue physiology and suppress microtumors, implying that substituting functional meals containing bioactive components for pharmaceuticals may provide significant protection against carcinogenesis[2,3].

In the last few years, food proteins and peptides have become one ground of nutraceuticals with demonstrated effects preventing the different stages of cancer, including initiation, promotion, and progression [4]. Certain advantages over alternative chemotherapy molecules, such as their high affinity, strong specificity for targets, low toxicity, and good penetration of tissues, have made food proteins and peptides a new and promising anticancer strategy [5].

Bioactive peptides are the proteins derived fragments which when consumed by humans provide positive influence on health by acting as source of nutrition and demonstrates numerous potential physiological functions in the body [6]. These peptides are released as such by enzymatic proteolysis during gastrointestinal digestion. Peptides can be released by hydrolysis of proteins with the use of food grade proteolytic enzymes and during the processing of foods (cooking, ripening and fermentation), small fragments of bioactive peptides can be obtained in hydrolysates [7]. The bioavailability of isolated peptides majorly depends on the degree of hydrolysis during the isolation which is to be determined in in vitro and in vivo models for their commercialization.

To assess the biological efficacy of the functional foods, bioactive compounds (BAC) are more important. The biological effects of these food BAC's are ultimately determined by their bioavailability and their temporal and spatial distribution in the body.

One such natural bioactive compound with proven anti-cancer activity is lunasin, a peptide containing 43 amino acids residues (sequence SKWQHQQDSCRKQLQGVNL TPCEKHIMEKIQGRGDDDDDDDDD) with a molecular weight of 5.5 k Da [8]. Lunasin peptide is present in *Glycine max* (Soybean), Barley, Wheat, *Solanum nigrum* L., *Solanum lyratum*. Studies performed on Lunasin had revealed its potential strategy for cancer prevention and/or therapy both in cell culture and animal models. The intent of this study is to outline the information on lunasin's potential benefits as a chemopreventive drug, as well as its demonstrated mechanisms of action since its discovery in 1977. Beyond its anti-cancer actions, lunasin has been demonstrated to have a wide range of possible health advantages, including anti-inflammatory and cholesterol-lowering effects as well as potential advantages for bone and heart health.

## 2. Discovery of Lunasin

Lunasin is discovered in an attempt to improve the nutritional quality of soy protein via bioengineering by cloning a gene that codes for a soy albumin protein (GM2S-1) and two other proteins: a signal peptide, and a linker peptide [9]. In addition, soybeans include a number of compounds that have been shown to have anticancer properties. Isoflavones and the Bowman–Birk protease inhibitor (BBI) or its less pure counterpart BBI concentrate are the most commonly investigated bioactive compounds (BBIC). Soybean isoflavones, chemically phytoestrogens, have chemopreventive properties that are related to a variety of biological processes, primarily their long-term estrogenic effects and antioxidant activity [9]. When a 43 amino acid sequenced peptide was isolated from soybean seeds three decades ago by, it was thought to have a wide range of biological activities . Galvez et al., in 1997 derived the name lunasin for the 43 amino acid sequenced peptide from the Tagalog word "lunas," meaning "cure." Since its discovery in 1997, lunasin has become one of the natural peptides found in soybeans and related foods with a better potential for treating chronic diseases. Lunasin was thought to be a good candidate to play a role in the anticancer characteristics attributed to soybean after its discovery in soybean and elucidation of its structure and antimitotic potential. Several research have been conducted since then to confirm this hypothesis [9].

In search of natural sources of lunasin besides soybean, a first screening has been carried out using different beans, grains and herbal plants. Lunasin has been found in cereal grains known for its health effects, such as barley, wheat and rye [10-13]. Several seeds of oriental herbal and medicinal plants have been analysed, finding that lunasin present in all of the Solanaceae family, except L. Chinese's[14]. This peptide has also been identified

in Amaranth, a plant well known and used by Aztecs for its high nutritional value and its biological properties [15]. A more rigorous and systematic search of Lunasin and lunasin homologues in different seats should be needed to carry out in order to establish relation between the presence of this peptide and taxonomic properties of the plants.

To produce a food that could be consumed on daily basis, soybean lunasin was inserted into the rice genome. This demonstrated that it was possible to express the exogenous lunasin in rice using the rice expression system. The improved antioxidant and anti-inflammatory activity of the trans-lunasin rice peptide extracts suggests that lunasin-overexpressing rice may be a viable resource for use in functional foods. The outcomes offer a fresh germplasm source for rice function improvement. Lunasin-rich rice known as black rice is good for human health and may one day be employed as a functional food in the diets of cancer and obesity patients.[16]

Some studies have suggested that the compounds found in hemp, such as cannabinoids and terpenes, may have potential anti-cancer properties. As lunasin, cannabidiol also shows the similar properties for inhibiting the angiogenesis. The non-psychoactive cannabinoid cannabidiol (CBD) effectively inhibits the growth of different types of tumours in vitro and in vivo and down-regulates some pro-angiogenic signals produced by glioma cells. As its anti-angiogenic properties have not been thoroughly investigated to date, and given its very favourable pharmacological and toxicological profile.[17]

### 3. *In vitro* and *In vivo* effects of Lunasin

Although its physiological significance remains to be established, Lunasin appears to be an ideal chemopreventive agent. Its chemopreventive properties both In vitro and in vivo have been demonstrated.

It has been proven that lunasin peptide given exogenously appears not to impact cell shape and proliferation in the absence of carcinogens, but delays transformation in the presence of carcinogens. Lunasin peptide at nanomolar quantities inhibited the transformation of mouse fibroblast (C3H10T1/2) cells caused by the chemical carcinogens 7,12-dimethylbenz(a)anthracene (DMBA) and 3-methylcholanthrene (MCA) [18]. Colony formation is a measure of anchorage-independent cell growth, one of the characteristics of transformed cells. Lunasin suppresses colony formation in NH3T3 cells, where it is 4-fold more effective, on a molar basis than the BBI, a known cancer preventive agent from soy [9, 19]. Further research with other synthetic lunasin-related peptides revealed that, whereas the Arg-Gly-Asp motif is responsible for lunasin internalization into the cell nucleus, the poly-aspartyl end is responsible for lunasin binding to chromatin. The putative helical region is thought to target lunasin to the chromatin. These investigations related lunasin's ability to bind chromatin to its anti-transformation capabilities.

Lunasin also prevents transformation of mammalian cells by viral oncogenes. It inhibits in a dose dependent manner, foci formation in C3H cells and NIH3T3 cells transfected with oncogene E1A, known to induce cell proliferation by inactivating the tumor suppressor protein Rb [20].

Interestingly Lunasin is effective even when add up to 15 days after transfection with E1A gene, suggesting its efficacy when applied even after the transformation event. Lunasin also suppresses colony formation induced by the ras-oncogene in MCF-7 cells stably transfected with an inducible form of oncogene[9, 19, 20]. The effect of Lunasin on cancer prevention has been also demonstrated using an in vivo mouse model. In this model, dermal application of Lunasin at 250μg/week reduced skin tumour incidence in SENCAR mice treated with DMBA and TPA by approximately 70% compared with untreated control [19]. This treatment also reduced the tumor multiplicity and delayed by two weeks, the appearance of papilloma in the mice, relative to the untreated control. Using a $2H_2O$-labelling method to measure cell proliferation in vivo, it has been found that on as in slows down epidermal cell proliferation in mouse skin in the absence and presence of DMBA [21]. Recent studies which were done by using data mining model including decision tree classification and association rule methods, for analysing 478 data collected from 201 research papers, stating that Lunasin and Bowman Brisk Protease Inhibitor from soy proteins has positive impact on different types of breast cancer, but still few soy phytoestrogens are inconsistent in breast cancer development [22].

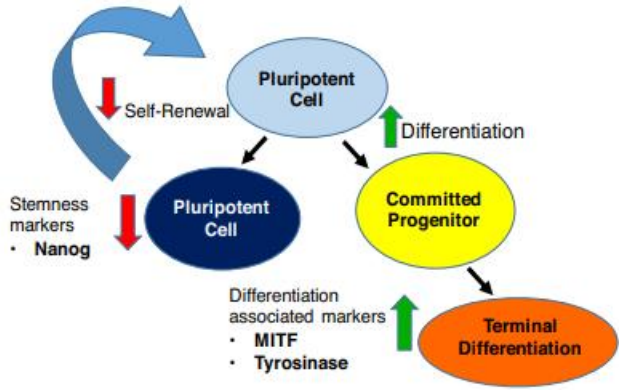


**Figure. 1: Lunasin's effects on melanoma cancer stem cells [23]**

Lunasin treatment of putative CSC's identified by virtue of high ALDH expression exhibit a decrease in expression of the stemness marker Nanog and increased expression of the differentiation markers MITF and tyrosinase. These results suggest that lunasin may have the capacity to induce highly metastatic and chemotherapy-resistant CSC to differentiate into less tumorigenic cells that are more susceptible to chemotherapy.[23]

Although most of the studies on lunasin have been conducted in vitro or in animal models, a few human studies have been conducted. In a randomized, double-blind, placebo-controlled study, 46 healthy adults were given a lunasin-enriched supplement for 12 weeks. The results showed a significant reduction in DNA damage in the group receiving the lunasin supplement compared to the placebo group [24].

Another study investigated the effects of a soy protein isolate containing lunasin on breast cancer biomarkers in postmenopausal women. The results showed a significant reduction in breast density, a risk factor for breast cancer [25].

***Ex vivo* effects of Lunasin**

The effects of lunasin on the viability and migration of human colorectal cancer cells (HCT-116) using an ex vivo model. The results showed that lunasin reduced cell viability and inhibited cell migration in a dose-dependent manner and confirmed that the potential use of lunasin as a dietary chemo preventive agent for colorectal cancer.[26]

**4. Mechanism of Action of Lunasin**

Changes in chromatin status is the most common mechanism for both chemical and viral oncogenesis. Lunasin, a soy peptide, known to exhibit anti-cancer effects by inhibiting the histone cores (H3 & H4) in mammalian cells, in presence of deacetylase inhibitor sodium butyrate [18, 19]. Recently, the histone acetylation inhibitory properties of different soybean and wheat varieties were demonstrated [14, 27].

This affinity of lunasin for hypoacetylated chromatin and its inhibitory effect on histone acetylation is relevant to the proposed epigenetic mechanism of action using the E1A-Rb-HDAC model [28]. This model stipulates that lunasin selectively kills cells that are being transformed by disrupting the dynamics of histone acetylation-deacetylation when a transforming event occurs. The tumor suppressor protein, retinoblastoma (Rb) functions by interacting with E2F promoter and recruiting histone deacetylase (HDAC) to keep the core histones in the deacetylated (repressed) state. The inactivation of Rb by the oncoprotein E1A dissociates the Rb-HDAC complex, exposing the deacetylated core histones for acetylation by histone acetyltransferases (HATs). When this event occurs, lunasin is triggered into action and binds to the deacetylated core histones competing with the HATs and turning off transcription.

We propose that the binding of lunasin to deacetylated core histones disrupts the dynamics of histone acetylation-deacetylation, which is perceived as abnormal by the cell and leads to apoptosis. This epigenetic mechanism suggests that lunasin can influence regulatory pathways involving chromatin modifications that may be fundamental to carcinogenic pathways in general, suggesting that lunasin could be effective against different types of cancers that involve chromatin modification.

One of the characteristics of an ideal cancer-prevention drug is the ability to be administered orally. This includes the ability to withstand breakdown by gastrointestinal and serum proteinases and peptidases and reach the target organ or tissue in an active state. The simulation of lunasin gastrointestinal digestion revealed that, while pure lunasin is quickly degraded by pepsin and pancreatin, lunasin in soy protein is resistant to the action of these enzymes [29, 30]. Animal bioavailability tests have confirmed the preliminary

results obtained from in vitro study. After rats consumed lunasin-enriched soy and lunasin-enriched wheat, lunasin was discovered as an intact and active peptide in their blood and liver [14, 27]. These findings imply that the combination protection given by BBI and other naturally occurring protease inhibitors, such as Kunitz trypsin inhibitor, plays a significant role in the availability of lunasin in soy and wheat protein. If a nutraceutical or dietary supplement is created in the future, this information must be considered.

Interestingly, the tumor suppressors Rb, p53 and pp32, function partly through chromatin modification. We propose that when these tumor suppressors are inactivated lunasin takes over as a surrogate tumor suppressor and selectively kills cells that are being transformed. The mechanism by which lunasin inhibits histone acetylation is not definitively known. Evidently, lunasin binds to deacetylated histone by ionic interaction with its negatively charged poly-D. Deletion of the coding region for poly-D in the lunasin cDNA nullifies its antimitotic activity when transfected into mammalian cells [31]. The N-terminus of lunasin that includes the helical region may play a role in targeting lunasin to deacetylated histones [27]. Experiments are being carried out to elucidate the histone acetylation inhibitory mechanisms of lunasin.

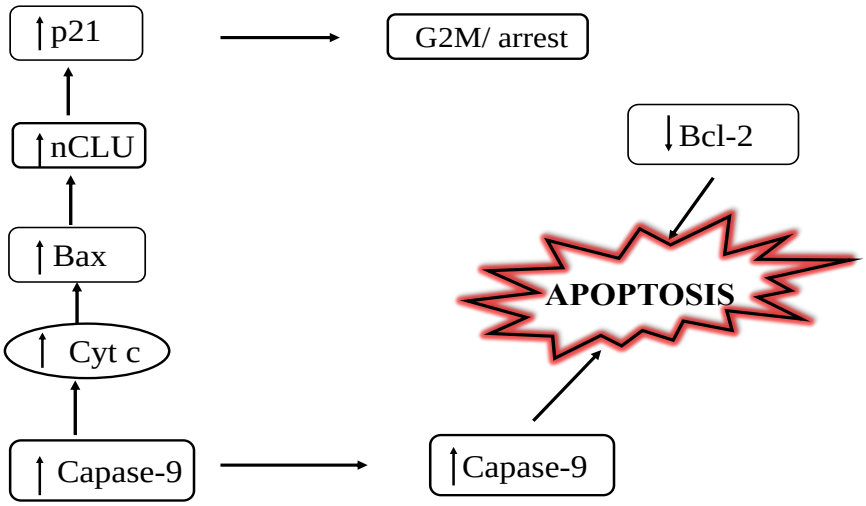


**Figure. 2: Lunasin inducing apoptosis** [4]

lunasin treatment might be beneficial in the inhibition of adipocyte inflammatory reactions through a decrease in IL-6 and MCP-1 secretions, and the retardation of obesity-related mediators that cause breast cancer cell metastasis, suggesting lunasin might block the cross-talk of these two cells.[32]

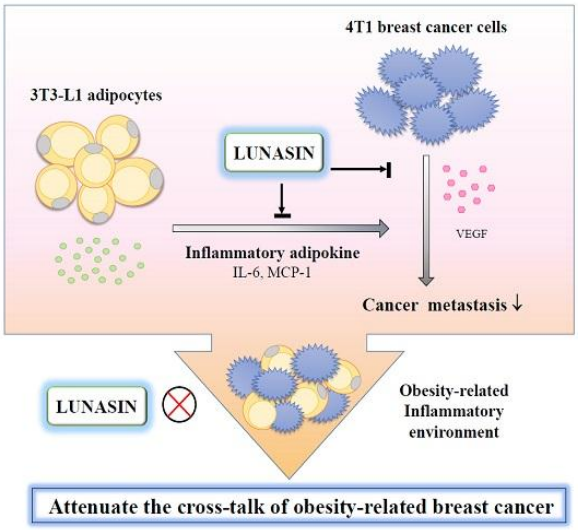


**Figure. 3: Mechanism of lunasin attenuating adipocyte inflammation and obesity-related breast cancer cell metastasis** [32]

Lunasin has an ability to inhibit angiogenesis, which is the formation of new blood vessels that tumors need to grow. Lunasin can inhibit the expression of vascular endothelial growth factor (VEGF), a protein that plays a critical role in angiogenesis.[32]

The expression of genes related to DNA damage repair, cell cycle regulation, and inflammation has also been shown to be altered by lunasin, indicating that it may have other modes of action in the fight against cancer.

Lunasin possesses antioxidant properties and can reduce intracellular reactive oxygen species (ROS). In addition, lunasin binds to and inhibits integrin-mediated signalling pathways such as Ras/MEK/ERK and PI3K/Akt. The anti-integrin activity of lunasin reduces phosphorylation of FAK, Src, ERK, and Akt. Lunasin can also suppress the NF-κB pathway by reducing IB kinase (IKK) activation due to integrin antagonism. The IKK complex phosphorylates and promotes IB breakdown, releasing the NF-κB p50 and p65 subunits for nuclear translocation and gene activation. Thus, the epigenetic and integrin-antagonistic actions of lunasin regulate the expression of genes involved in its anticancer properties, including anti-inflammation, immunomodulation and antiproliferation.[33]

## 5. Future Perspectives

Lunasin is a novel and promising chemopreventive peptide derived from soybean, wheat, barley, and other plant seeds. Its demonstrated cancer preventive properties in vitro make lunasin a perfect candidate to exert an in vivo cancer-preventive activity. Bioactive peptides have a limited usage in the market or at the global level. Though, new technologies are emerging now-a-days, to get the most active form of these peptides and incorporated to get the novel food product. The focus needs to be given on bioavailability of these peptides after its intake. Further studies, *in vivo* and *in vitro* need to be performed to demonstrate its use on a social level for the prevention of various chronic diseases. Also, to increase the market of value - added products or functional foods globally, bioactive peptides act as a potential candidate.

The preventive efficacy of lunasin administered in the diet and other routes needs be tested against different types of cancer. The Dose-Response relationship (Optimal dose) of Lunasin for chemoprevention is not finalized yet. Studies have used a range of doses, and it is not yet clear which dose is most effective for reducing cancer risk. In our laboratory, animal studies demonstrating the bioavailability are currently being carried out. There is still much to be learned about the effects of lunasin on cancer risks and this area of research holds considerable potential.

Clinical trials are lacking despite the fact that there have been several in vitro and animal research on the possible chemo preventive effects of lunasin. These studies have not examined lunasin's efficacy and safety in humans. Clinical trials are required to assess lunasin's potential negative effects and discover the best dosages and delivery strategies.

Limited understanding of mechanisms of action: While numerous mechanisms of action for lunasin's chemo preventive actions have been hypothesised, the precise molecular mechanisms underlying these effects are yet unknown. More research is needed to determine the molecular pathways and signalling processes involved in the putative chemo preventive effects of lunasin.

Limited understanding of possible interactions: Lunasin's efficacy and safety may be affected by possible interactions with other medications or dietary supplements. The best circumstances for administering lunasin require further investigation into potential medication interactions.

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