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MiniReview

Role of Soy-derived Peptide Lunasin in Cancer Therapy: A Review

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Abstract

Innovative nutritional strategies represent a promising frontier in the prevention and treatment of cancer. Among these, soy-derived compounds have gained significant attention due to their potential health benefits. One promising agent is Lunasin, a bioactive peptide found in soy that exhibits notable anticancer properties. Lunasin operates primarily by inhibiting histone acetylation, a critical process in gene regulation. This inhibition leads to reduced cell proliferation, controlled cell cycle progression, and induction of apoptosis in cancer cells, establishing Lunasin as a powerful epigenetic modulator. Additionally, its multifunctional domains impact integrin signaling, influencing key cellular pathways involved in tumorigenesis. Incorporating Lunasin-rich soy products into the diet offers a novel nutritional intervention. Research suggests that dietary Lunasin not only provides chemo-preventive effects against a range of carcinogens but may also complement conventional cancer therapies. This review examines the molecular mechanisms underlying Lunasin's anticancer effects and discusses its emerging role as a nutritional tool in cancer prevention. By harnessing the natural properties of soy peptides, we aim to pave the way for innovative, diet-based approaches to cancer therapy, ultimately contributing to enhanced global public health.

Keywords: histone acetyl transferases, phosphatase and tensin homolog, lunasin targeted extract, arginylglycylaspartic acid, lunasin, cancer therapy

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1 INTRODUCTION

Cancer is a prominent cause of death and a significant impediment to expanding life expectancy statistics globally[1]. The health crisis of cancer knows no geographical boundaries and the number of people diagnosed with cancer is projected to increase by almost 50% over the next two decades[2]. In 2020, about 19 million individuals worldwide were diagnosed with cancer, and nearly 10 million died from the disease. It is projected that there will be roughly 28 million new cases and 16 million deaths by the year 2040[3,4]. Cancer cells originate from normal cells that have multiplied out of control, leading to genetic instabilities and mutations within cells and tissues. Although several treatments exist for cancer, the prognosis for each patient is unique based on factors such as disease type and progression[5,6]. The most frequent treatments for cancer are surgery to remove the tumor or affected tissues. The gold standard for cancer treatment is conventional cytotoxic therapy, which includes radiation and chemotherapy. Although these therapies are helpful in treating a wide range of cancers, they are associated with certain drawbacks, such as disease recurrence and patient non-compliance owing to severe adverse effects such as pain, exhaustion, anaemia, nausea, emesis, and hair loss[7,8]. These therapies aren't as effective due to several factors. One of the biggest problems with chemotherapeutic medicines is drug resistance, which may be either inherited or developed over time. In tumour cells, metabolic heterogeneity is one of several causes of medication resistance, which may develop at the cellular and tissue levels. Furthermore, cancer might grow due to the existence of several tumour cell populations with different metabolic profiles, which can increase resistance to chemotherapy. Other common routes that cause cancer cells to become resistant to drugs include disruptions or changes to apoptotic or growth signalling pathways, upregulation of drug transporters, and deregulation of DNA damage repair. Another big problem with chemotherapy is that anticancer medications aren't very precise; they may harm healthy human cells as well as cancer cells, and they cause a plethora of unpleasant side effects. Molecular

targeting of cancer cells offers a way to avoid harming healthy cells, in contrast to conventional radiation and chemotherapy. Additionally, targeted drug delivery can be achieved through immunotherapy by administering antibodies that specifically target antigens on cancer cell surfaces. However, a significant hurdle that limits the effectiveness of immunotherapy is the expression of the same target antigens on healthy cells. Because of these constraints, scientists have been looking at natural based molecule for combatting cancer. Therefore, there is an urgent need for the ongoing research and development of new herbal anticancer medications derived that are both effective and reasonably priced[9]. There has been a recent surge in interest from the academic and industrial research communities in the use of herbal medicines to treat and prevent cancer. Several different types of medicinal plant extracts or phytochemicals have been documented as having anticancer efficacy in a variety of tumor types and development stages. Medicinal plants account for a considerable portion of around 60 percent of all the chemotherapeutic drugs used in cancer treatment[10].

Various ancient therapeutic practices involve plants or plant-based preparations. Traditional medical practitioners treat a wide range of illnesses using a variety of herbal remedies each of which has its own history, philosophy, and cultural context[11]. Phytomedicines promote health and happiness, and it is rooted in Indian Vedas. It's a compilation of several cultural and traditional approaches to health care. Ayurvedic principles have been integrated into the modern medication development program, which has found widespread acceptance in the current healthcare system[12]. Because they are less likely to cause side effects in healthy people, natural compounds produced from plants are gaining interest in the field of medication research[13]. Roots, leaves, flowers, stems, and bark contain phytochemicals and derived metabolites that have pharmacological effects on the human body. Several substances contribute to plant health, including flavonoids, alkaloids, phenol compounds, tannins, glycosides and gums, resins, and oils[14,15]. Several well-recognized herbal compounds are established in cancer therapy for their diverse antitumor mechanisms. Curcumin, resveratrol, epigallocatechin gallate (EGCG) from green tea, thymoquinone, baicalin, berberine, and extracts from Oldenlandia diffusa and Salvia miltiorrhiza have consistently demonstrated anticancer activities in preclinical and clinical models. Their mechanisms typically include induction of apoptosis, suppression of cell proliferation, inhibition of metastasis and angiogenesis, modulation of immune activity, and the targeting of critical signaling pathways such as NF-κB, PI3K/AKT, and p53. Curcumin, for example, is widely studied for its ability to suppress tumor initiation, promotion, and metastasis, while resveratrol and EGCG have shown similar broad impact across multiple cancer types, and berberine is noted for both its anti-inflammatory and antitumor activities. Soy presents a distinct position among natural anticancer agents owing to its complex matrix of bioactive compounds, notably isoflavones like genistein and daidzein, saponins, phenolic acids, peptides such as lunasin, Bowman-Birk inhibitors, and phytic acid. Extensive research has demonstrated that soy and its derivatives inhibit cancer progression through several convergent mechanisms: antioxidant effects, modulation of hormone signaling, epigenetic regulation, suppression of angiogenesis, cell cycle arrest, apoptosis induction, and direct inhibition of malignant proliferation. Soy-derived isoflavones are effective for hormone-sensitive cancers such as breast and prostate cancer and serve to complement or synergize with conventional therapies and other phytochemicals, such as curcumin, to enhance anticancer outcomes. Compared to other herbal agents, soy's uniqueness lies in its multiple active components that act at different stages of carcinogenesis, the breadth of its effects across various cancer types, and its established safety as a dietary staple. Emerging evidence also highlights that combinations of soy phytochemicals with agents like curcumin or EGCG can yield synergistic effects, further intensifying anticancer activity. In this way, soy's anticancer efficacy is robust, multi-targeted, and supported by both epidemiological evidence and mechanistic studies, positioning it as a key candidate in functional food-based cancer prevention and adjunctive therapy. Peptides offers more benefits over other chemotherapeutic compounds and hence peptides have caught the interest of researchers as potential new anticancer drugs. Aside from having minimal toxicity, high affinity, and great target specificity, peptides also have good tissue penetration, unlike chemotherapeutic antibodies, due to their small size[16,17]. Polypeptides have increased tissue permeability and possess superior affinity, selective targeting capabilities, and reduced toxicity in comparison to available treatments. Rusdi et al.[16] investigated the toxicity of soyabean extract with targeted Lunasin (ET-Lun) in Sprague Dawley (SD) rats. Single oral doses of ET-Lun at 2000mg/kg and 5000mg/kg weight was administered to two groups. Distilled water for vehicles was administered to control group as treatment, and the rats was sacrificed. Following the collection of blood for haematological assessment, the histology of the liver and kidneys was also performed. After giving 2,000 and 5,000mg/kg of ET-lun, no harmful side effects was seen. In terms of liver and kidney histology, there was no discernible difference between the two groups. In addition, there was no significant difference in the levels of creatinine, urea, AST, and ALT between the treatment group and the control group. ET-Lun was essentially non-toxic[16]. Therefore, polypeptides are considered a promising class of naturally occurring anti-cancer compounds with the ability to halt the disease at various points in its genesis and progression. Due to their health benefits, people have taken an interest in soybean and related products following their widespread extraction and use[18].

Researchers' attention has been sparked by epidemiological studies indicating a correlation between greater soy intake and lower risks of breast, prostate, colon, and

lung cancers[19]. Specifically, in the case of breast cancer, it has been hypothesized that secondary metabolites like isoflavone are responsible for the anticancer benefits of soy components. Recent research has shown that a bioactive peptide is responsible for much of soy's anticancer action[20]. A 43-amino-acid peptide found in soy, known as Lunasin, has been demonstrated to block the transformation of mammalian cells triggered by carcinogens and the viral oncogenes *E1A* and *RAS*[21,22]. Topical use of Lunasin was found to inhibit tumor growth in a mouse model of skin cancer. Lunasin was found in 144 out of 144 soy genotypes tested, with quantities ranging from 6 to 7mg of lunasin/g of protein, according to a screening of the United States Department of Agriculture, Soybean Germplasm Collection. Jeong and colleagues conducted an analysis on several types of soybeans in Korea and these soybeans were found to have lunasin concentrations ranging from 4.40 to 70.49mg of lunasin per gram of protein. These changes demonstrate that the amounts of this peptide in soybeans may be genetically modified, implying the potential to selectively develop soybean types with elevated lunasin content. Furthermore, it has been shown that soy can be processed on a big scale to develop various soy protein products. Reports have identified and isolated lunasin from barley and wheat, which are other natural sources of this compound besides soybean. The crude extracts of eight kinds of wheat contain lunasin in quantities ranging from 211 to 249µg per gramme of seed. The different levels of lunasin found in wheat food items indicate the amount of lunasin that is accessible to consumers. Lunasin are also found in the Solanaceae family, which includes amaranth and pepper[23,24]. The present review examines the existing literature on the molecular processes and possible benefits of Lunasin in context of cancer prevention and treatment.

2 LUNASIN

Lunasin, a diminutive peptide discovered in soybeans, has surfaced as a captivating molecule with the capacity to potentially inhibit and combat cancer. The progression of this compound from its first discovery to its present condition as a potential anticancer drug is a captivating one, characterised by continuous study and noteworthy advancements. The discovery of Lunasin was an instance of serendipity. While researching to enhance the methionine levels in soy proteins, Dr. Galvez fortuitously stumbled onto the soy peptide present in minute amounts inside soybean seeds, which effectively halts cellular proliferation[25]. Research findings indicate that this peptide, present in maize, wheat, and barley, has an inhibitory impact on mammalian cells during early stages of carcinogenesis. Furthermore, unlike other substances that prevent cancer, the peptide effectively eliminates potentially malignant cells without causing any harm to nearby healthy cells. Moreover, it substantially diminishes the likelihood of those cells undergoing malignant transformation. The group coined the name "Lunasin," derived from the Filipino word "lunas," which translates to "cure." Upon observation, it was found that certain fractions of soybean had significant anti-tumor effects. This prompted the researchers to isolate and analyse the active compound, known as lunasin[25,26].

The peptide Lunasin comprised of four distinct regions, namely the N-terminus, which encompasses the initial 22 residues; the central segment, which exhibits resemblance to chromodomains found in chromatin-binding proteins; the arginylglycylaspartic acid (RGD) motif; and the C-terminus, which is abundant in aspartic acid (D). The peptide's distinctive properties have been traced down to its last three functional regions. According to de Mejia et al.[26] the tripeptide RGD serves as an extracellular matrix that facilitates the availability of Lunasin intracellularly. The internalization of Lunasin seems to be facilitated by the integrin recycling pathway, wherein the integrin αVβ3 plays a crucial role, as reported by Cam et al.[27], Inaba et al.[28], and McConnell et al[29]. Moreover, the RGD motif enhances the capacity of Lunasin to rival the integrins in binding to extracellular matrix, thereby inhibiting the integrin-mediated signaling pathway, including the regulation of cellular processes such as proliferation, migration, invasion and apoptosis[30,31]. The antimitotic properties of Lunasin have been ascribed to its ability to bind to regions of positively charged deacetylated histones and cellular regions, such as hypoacetylated chromatin present in telomeres and kinetochores in centromeres, through the interaction of its poly-D carboxyl end with highly negatively charged 8 D-residues[32]. Consequently, due to the improper formation of the kinetochore complex, the microtubules are unable to attach to the centromeres, resulting in the cessation of mitosis and ultimately culminating in cell death.

The amino acid sequence of Lunasin, a unique peptide entailing 43 amino acids is notated as: SKWQHQQ-DSCRKQKQGVNLTPC-EKHIMEKIQG-RGD-DDDDDDDD[33]. This peptide has structural similarities with the conserved area of chromatin-binding proteins, and its carboxyl terminus contains eight Asp residues[34]. Soybean cotyledon Lunasin was first discovered when a cDNA from soybean seeds was at its mid-maturity stage[33]. The *Gm2S-1* gene codes for a methionine-rich protein with a signal peptide, a small subunit (named Lunasin, after the Tagalog word "lunas" for cure), a linker peptide, and a large subunit. In mammalian cells, transfection and expression of the Lunasin gene cause mitotic arrests and eventual cell death[35]. According to the theory behind its antimitotic activity, this peptide achieves its goal by attaching its poly-D carboxyl terminus to hypoacetylated chromatin in kinetochores and centromeres. The microtubules are unable to bind to the centromeres, causing mitotic arrest and cell death because of improper formation of the kinetochore complex[36].

2.1 Mechanism of Action: Anticancer Activity

Lunasin was first investigated as a therapeutic agent

for its capacity to bind hypoacetylated core histones and prevent histone acetylation. The epigenetic action of Lunasin involves interactions with histones. The use of histone acetyltransferases (HATs) to acetylate histones H3 and H4 is hindered by Lunasin. As a result, Lunasin is in direct competition with HATs for the role of ligand to deacetylated histones. This competition leads to cell cycle pauses at various stages such as Sub-G0/G1, G1/S, and G2/M cell cycle which ultimately leads to cell apoptosis. Modifying chromatin structure and regulating gene expression are both impacted by histone acetylation and deacetylation. The chromatin structure undergoes a relaxation process upon acetylation which contributes to the activation of transcription; therefore, deacetylation leads to condensation of chromatin and supercoiling which are associated with transcriptional regression. By blocking chromatin acetylation and oncogene activation, Lunasin prevents the transition of normal cells into malignant cells by displacing kinetochore proteins from hypoacetylated chromatin. Lunasin inhibits histone acetylation primarily in cancer cells while sparing normal cells due to differences in their chromatin state and cellular context. In normal cells, core histones are largely kept in a deacetylated state by tumor suppressor proteins such as Rb, which recruit histone deacetylases to maintain chromatin condensation and prevent unnecessary gene activation. As a result, lunasin does not significantly affect the cell cycle or induce apoptosis in these normal cells. In contrast, during carcinogenic transformation or in actively dividing cancer cells, oncogenic signals inactivate Rb, causing the release of deacetylated histones and their subsequent exposure. Lunasin binds to these exposed deacetylated histones, competes with histone acetyltransferases, and inhibits further acetylation, thereby blocking transcription of genes essential for tumor growth and inducing apoptosis. This selective mechanism explains why lunasin can exert anti-cancer effects while largely sparing healthy tissues, offering a therapeutic advantage over less discriminating epigenetic modifiers. Typically, acetylation promotes transcription, whereas deacetylation inhibits gene expression. By preventing histones from being acetylated, Lunasin suppresses gene activity as shown in Figure 1.

Additionally, Lunasin may increase gene expression by favouring the acetylation of certain lysine (K) residues while simultaneously deacetylating other residues. Therefore, it seems that its histone binding controls gene expression. The acetylation of histone H4 at lysine 16 (H4K16ac) is a key factor in the regulation of apoptotic genes, transposable element transcription activation, promotion of S phase entry, and the modulation of the cis-regulatory landscape of a substantial portion of the mammalian genome which in turn causes downregulation of acetylated histones (H4K8Ac and H4K12Ac). To bind to the deacetylated N-terminus of H4, Lunasin relies on its N-terminus, middle region, and aspartic acid (D)-tail[37]. Yu et al synthesized Lunasin and investigate the mechanism of Lunasin on MDA-MB-231 human breast cancer cells. The intracellular regulation of MDA-MB-231 cells following co-cultivation with lunasin was thoroughly investigated by doing a simultaneous transcriptome and proteome study. The study also investigated the impact of lunasin exposure on global changes in MDA-MB-231 cells at both the transcript and protein levels. This was done to illustrate the potential regulatory mechanisms of the lunasin peptide in its anti-proliferation actions. Lunasin demonstrated a dose-dependent inhibition of cell growth in human breast cancer MDA-MB-231 cells during the cell proliferation experiment. The suppression of cell growth was observed, with inhibition rates ranging from 15.1% to 56.8% at doses ranging from 0.25mg/mL to 1.0mg/mL, in comparison to the control group. Isolating total RNA and protein from MDA-MB-231 cells in the control group and the 0.25mg/mL lunasin group allowed for subsequent transcriptomic and proteomic analysis, which aimed to additionally investigate the overall intracellular regulation in MDA-MB-231 cells, reveal its anti-cancer function, and identify potential molecular mechanisms. In order to comprehend the variations in the manner of expression between the lunasin and control group, the differentially expressed genes was analyzed using GO and KEGG enrichment analysis. The expression levels of genes associated to *CASP*, including *CASP 3*, *7*, and *14*, was up-regulated respectively, compared to the control group. *CASP 3*, an effector of programmed cell death, plays a pivotal part in the process of cellular apoptosis. The findings suggest that lunasin exposure may trigger cell apoptosis in MDA-MB-231 cells. The RGD motif, in conjunction with integrin receptors, forms a significant recognition system for cell adhesion. This system plays crucial functions in controlling cell proliferation, differentiation, and death. The presence of the RGD motif in the lunasin peptide is likely to facilitate its binding to the extracellular matrix and trigger cell death via a mechanism that relies on caspase activation. The expression levels of pro-apoptotic genes, including *Bak1, Bax, cytochrome C,* and *apoptotic peptidase activating factor 1* was dramatically increased in MDA-MB-231 cells after co-culture with lunasin. The expression of *Bcl-2* was significantly reduced. Augmenting the Bax/Bcl-2 ratio would enhance the permeability of the mitochondrial outer membrane, leading to mitochondrial outer membrane permeabilization (MOMP) and triggering the intrinsic apoptotic cascade. After undergoing Mitochondrial Outer Membrane MOMP, proteins located in the intermembrane space of mitochondria, such as Smac and Cytochrome c, are discharged into the cytosol. Cytochrome c interacts with Apaf-1, initiating the formation of apoptosome, which ultimately leads to caspase-mediated apoptosis. The Bax/Bcl-2 ratio rose from 22.9 to 210.6, indicating that lunasin suppressed the growth of MDA-MB-231 cells via the mitochondria-mediated intrinsic apoptotic mechanism. The expression of genes involved in DNA replication was markedly reduced upon exposure to lunasin, particularly the genes connected to the minichromosome maintenance (MCM) complex. The expressions of MCM was down-regulated respectively. DNA unwinding is an essential process in DNA replication. The MCM complex, which

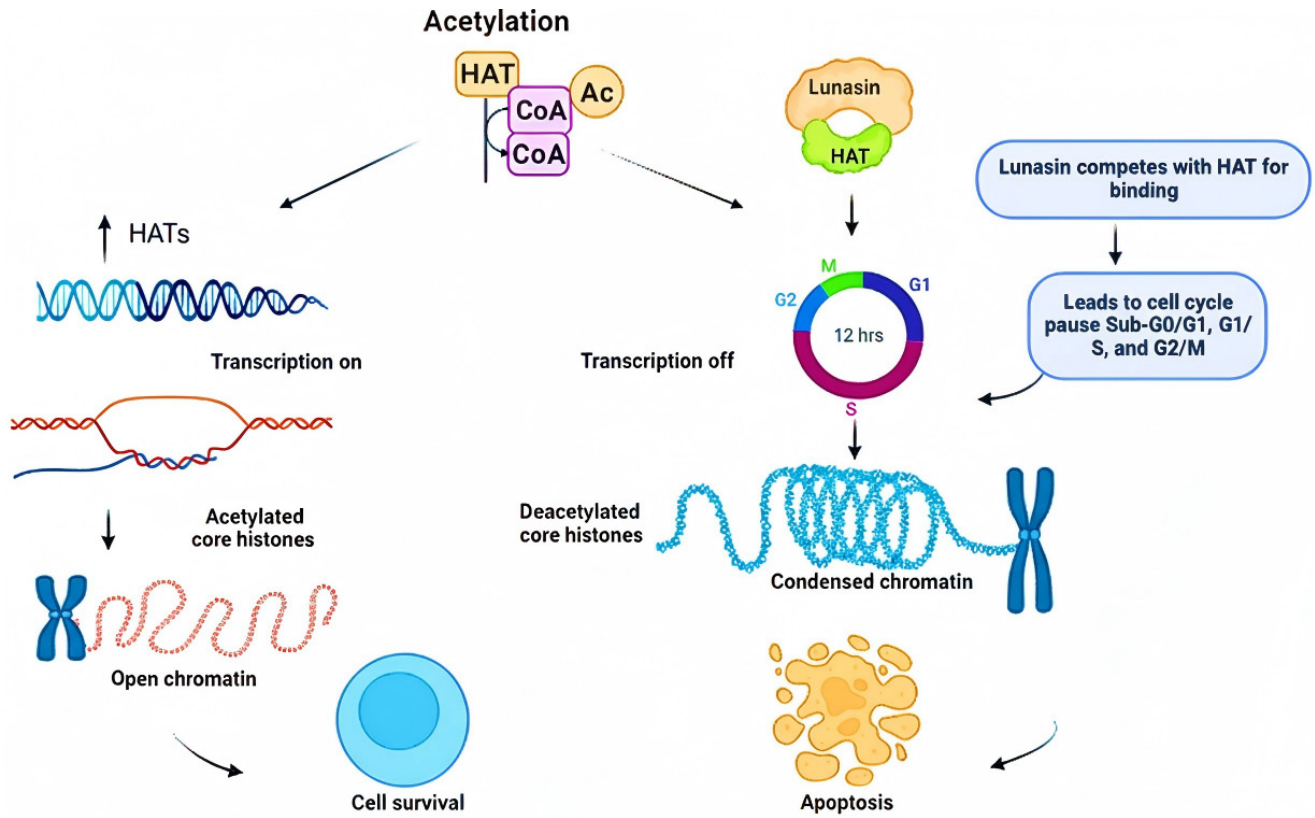

Figure 1. Mechanism of Action of Lunasin. First, lunasin inhibits histone acetyltransferase (HAT) activity by binding directly to deacetylated histones in chromatin, preventing histone acetylation. This chromatin binding leads to alterations in gene expression by maintaining a repressive chromatin state, thereby inhibiting transcription of oncogenes and genes involved in cell proliferation. Second, lunasin contains an RGD (Arg-Gly-Asp) motif that binds to integrin receptors on the cell surface, disrupting integrin-mediated signaling pathways which regulate cell survival, migration, and invasion. This RGD-integrin interaction impairs cytoskeletal organization and reduces invasive potential. Collectively, these effects induce cell cycle arrest (commonly at G1/S or G2/M phases) and promote apoptosis through activation of caspases and mitochondrial pathways, selectively targeting cancer cells while sparing normal cells due to differences in chromatin states and inhibit tumor cell proliferation and metastasis. Thus, lunasin acts epigenetically and via cell surface receptor modulation to exert multifaceted anticancer activities.

serves as the central component of DNA helicase, plays a crucial role in facilitating the formation of replication forks and the recruitment of associated proteins. In addition, the expression of genes involved in the DNA polymerase α-primase complex POLA1, POLA2, PRIM1, and PRIM2 was reduced after lunasin administration. The DNA polymerase α-primase complex, which demonstrates RNA polymerase activity in the 5'-3' direction, has a crucial function in the commencement of DNA replication. The findings indicated that lunasin significantly suppressed cell mitosis and DNA replication in MDA-MB-231 cells. The qRT-PCR study revealed a considerable up-regulation in the transcript levels of *CASP 3*, *7*, *Bak1*, *Bax*, and *Cyc1* genes, whereas *Bcl2*, *MCM6*, and *POLA2* showed a strong down-regulation compared to the control group. The cancer-preventing action of the lunasin peptide was likely due to its poly-D structure and RGD cell adhesion motif, which allowed it to block DNA replication and induce cell death via the lysosome-mitochondrial axis Additionally, the helical domain, which mimics chromatin-binding proteins, facilitates interaction with histones, leading to the inhibition of histone acetylation and subsequent transcriptional repression of genes involved in tumor progression. The polyaspartic acid tail is considered significant for targeting chromatin and possibly aiding nuclear localization of Lunasin. These roles have been substantiated through truncation and mutation studies, with experiments that remove or alter the RGD sequence resulting in substantial loss of anticancer function. Furthermore, studies on Lunasin derived from transgenic soy indicate that post-translational modifications, such as glycation at lysine residues in the helical domain, can occur. These modifications have the potential to influence Lunasin's biological activity, particularly its epigenetic regulatory functions, although current evidence indicates that the overall effects of such modifications are not yet fully understood. Increasing Lunasin content through genetic engineering often enhances its biological activity, but fine details regarding the impact of glycosylation and other structural changes on anticancer efficacy remain subjects of ongoing investigation[38,39].

3 CURRENT RESEARCH ENVISAGED ON LUNASIN AS AN ANTICANCER PEPTIDE

According to research conducted by various researchers on animals and into vitro cell line models it has been

proved that Lunasin can be used as an anticancer peptide as illustrated in Table 1. Anti-inflammatory action of Lunasin was investigated in breast cancer cells by examining its effects on inflammatory markers. The researcher used estrogen-dependent MCF-7 and estrogen-independent MDA-MB-231 breast cancer cells for this study. The beta-estradiol was a substitute for natural oestrogen. Apoptosis, cell vitality, and apoptosis-related gene expression was investigated. The growth of normal cells was unaffected by Lunasin; however, the growth of breast cancer cells was suppressed. *Interleukin* (*IL*)*-6* gene expression and protein synthesis was both raised at 24h, and secretion was reduced at 48h. Lunasin inhibited VEGF release, reduced cell viability, and triggered apoptosis in both breast cancer cell lines. Leptin receptor (Ob-R) mRNA expression was solely downregulated by Lunasin in MCF-7 cells. It was shown that the seed peptide Lunasin reduced the development of breast cancer cells by modulating inflammatory, angiogenic, and estrogen-related chemicals, making Lunasin a potentially useful chemo-preventive drug[40].

Anti-proliferative effect of Lunasin was also investigated in breast cancer MDA-MB-231 cell lines. The MDA-MB-231 cells was subjected to a combined transcriptome and proteome analysis. The results showed that the expression of cysteinyl aspartate specific proteinases *CASP 3*, *CASP 7*, and *CASP 14* was significantly up regulated after exposure to Lunasin. The lysosomal pathway was also highly downregulated in response to Lunasin, which suggests that lysosomes may work along with mitochondria during apoptosis. Additionally, Lunasin inhibited DNA replication-related gene expression in MDA-MB-231 cells. The findings suggest that Lunasin peptide's anti-proliferation action is driven by its ability to prevent cell mitosis, DNA replication as well as its ability to promote lysosome-mitochondrial mediated cell death[41].

Cancer stem-like cells (CSC) have significant clinical and preventative implications due to their role in tumor development. The cytotoxic impact of the peptide Lunasin on HCT-116 cells was investigated specifically in the CSC of colorectal cancer. Flow cytometry data showed that the inhibitory effects was connected to G1 cell cycle arrest and apoptotic induction. In addition, the majority of tumor cells entered the sub-GO/G1 phase earlier due to Lunasin, which was associated with the apoptotic events seen. By activating caspase-3 and cleaving PARP, immunoblotting data demonstrated that Lunasin triggered apoptosis and that it can regulate cell cycle progression by way of the cyclin-dependent kinase inhibitor p21. These findings indicate that the peptide Lunasin may affect both the parental and the tumor sphere-derived subsets of HCT-116 cells exhibiting chemo-preventive effect of Lunasin against colorectal cancer[42].

To deliver Lunasin into melanoma cell lines and to enhance its bioavailability, Castaneda-Reyes et al.[43] l developed liposome-based formulations. Amaranth oil was utilized to develop an unsaponifiable, squalene-rich composition, which was then integrated into liposomes. The optimized formulation containing the unsaponifiable substance was further evaluated on A-375 and B16-F10 melanoma cells. Treatment of melanoma cells with liposomes containing lunasin was observed to have a protective effect. Compared to treatments with free Lunasin, treatments with liposomal Lunasin increased the cytotoxicity of Lunasin in melanoma cells by 31.81% and 41.89% in B16-F10 and A-375 melanoma cells, respectively[43].

A transgenic soybean was developed by overexpressing the bioactive peptide lunasin, which has several physiological uses. Following PCR confirmation that lunasin had been effectively introduced into the soybean genome, three transgenic lines — L12, L43, and L45 — was chosen for further investigation. Ultra-performance liquid chromatography coupled with tandem mass spectrometry and Western blot was used to characterise the expression of lunarsin in the lines. Lunasin levels was considerably greater in the L12, L43, and L45 lines compared to soyabean wild type. The teasgenic lunasin shows greater DPPH, ABTS+, and oxygen radical scavenging potential. In addition, it aslo exhibited greater anti-inflammatory efficacy on lipopolysaccharide-induced macrophage cells in comparison to LEW. It notably inhibited the production of nitric oxide (NO) and pro-inflammatory cytokines such as IL-1 and IL-6. Furthermore, LET exhibited superior anti-proliferation efficacy on MDA-MB-231 cells compared to LEW. To summarise, it is both viable and effective to generate lunasin using a transgenic soybean expression system. In the future, soybean that has been genetically modified to produce higher levels of lunasin might potentially be used as a functional food in the diets of individuals to treat cancer[44].

To examine the influence of Lunasin on the expression of intercellular adhesion molecule 1 (ICAM-1) and epithelial cadherins (E-Cadherin) markers in breast cancer, twenty-four Sprague-Dawley rats were employed. The animal groups were classified as either "normal," "positive control," "negative control," "adjuvant," "curative," or "preventive" depending on the kind of treatment they received. The H-score was used to quantify the results of the collection, processing, staining (with anti-E-Cadherin antibodies, anti-ICAM-1), microscopy examination, and quantification of tissue samples. Overall, ICAM-1 expression was downregulated while E-Cadherin expression was upregulated due to the preventive dosage of Lunasin. The scientists ascertained the cancer-preventive effects of Lunasin. Further investigation is needed to determine its anticancer effect on different markers and an equivalent impact on other cancers[45].

The pharmacological action of lunasin targeted extract is to reduce inflammatory responses by reducing cyclooxygenase and inducible NO synthase production. The extract has

Table 1. Current Perspectives on Lunasin as an Anticancer Peptide

No.	Aim of study	Method	Result of the investigation	References
1	The purpose of this research is to discover how lunasin inhibits the growth of breast cancer cells by targeting estrogen-related molecules and inflammatory mediators.	Researchers used MCF-7 (estrogen-dependent) and MDA-MB-231 (estrogen-independent) breast cancer cell lines, substituting β-estradiol for physiological estrogen. The study investigated the effects on apoptosis, mediator secretion, gene expression, and cell viability in breast cancer cells	Lunasin inhibited VEGF release, reduced cell viability, and induced apoptosis in both breast cancer cell lines. It also downregulated leptin receptor (Ob-R) mRNA in MCF-7 cells and modulated inflammatory and estrogen-related pathways.	[40]
2	Anti-proliferative effect of Lunasin was investigated in breast cancer MDA-MB-231 cell lines	MDA-MB-231 cells were subjected to a combined transcriptome and proteome analysis after being treated with lunasin	The results showed that lunasin significantly upregulated cysteinyl aspartate specific proteinases *CASP 3, CASP 7*, and *CASP 14* expression, and downregulated the lysosomal pathway. It also inhibited DNA replication-related gene expression in MDA-MB-231 cells, suggesting that lunasin inhibit cell mitosis and promotes lysosome-mitochondrial mediated cell death.	[41]
3	The cytotoxic impact of the peptide Lunasin on HCT-116 cells was investigated specifically in the CSC of colorectal cancer.	Flow cytometry and immune blotting assays was used to determine the efficacy of lunasin on HCT-116 cells	Flow cytometry revealed that lunasin induces G1 cell cycle arrest and apoptosis, with cells entering the sub-G0/G1 phase earlier. Immunoblotting showed that lunasin triggers apoptosis via caspase-3 activation and PARP cleavage, while also regulating cell cycle progression through p21, indicating its potential as a chemopreventive agent in colorectal cancer.	[42]
4	To deliver Lunasin into melanoma cell lines and to enhance its bioavailability	Amaranth oil was utilized to develop an unsaponifiable, squalene-rich composition, which was then integrated into liposomes. The optimized formulation containing the unsaponifiable substance was further evaluated on A-375 and B16-F10 melanoma cells	Treatment of melanoma cells with liposomes containing lunasin was observed to have a protective effect. Compared to treatments with free Lunasin, treatments with liposomal Lunasin increased the cytotoxicity of Lunasin in melanoma cells by 31.81% and 41.89% in B16-F10 and A-375 melanoma cells, respectively	[43]
5	To examine the influence of Lunasin on the expression of ICAM-1 and E-Cadherin markers in breast cancer	Twenty-four Sprague-Dawley rats was employed. The animal groups were classified as either "normal," "positive control," "negative control," "adjuvant," "curative," or "preventive" depending on the kind of treatment they received. The H-score was used to quantify the results of the collection, processing, staining (with anti-E-Cadherin antibodies, anti-ICAM-1), microscopy examination, and quantification of tissue sample	Overall, ICAM-1 expression was downregulated while E-Cadherin expression was upregulated due to the preventive dosage of Lunasin. The scientists ascertained the cancer-preventive effects of Lunasin. Further investigation is needed to determine its anticancer effect on different markers and an equivalent impact on other cancers	[44]
6	To investigate the acute toxicity of targeted lunasin (ET-Lun).	The SGOT-SGPT ratio, liver histology, and central vein width was measured in Sprague Dawley rats after 91 days of administration of the extract	No statistically significant change in SGOT-SGPT levels as well as in the diameter of the central vein in the rat liver was observed between the experimental and control groups (P>0.05)	[46]

the potential to enhance apoptosis and reduce dysplasia. Furthermore, it might inhibit EGFR expression in rats with breast cancer. ET-Lun was shown to have an acute toxicity LD50 of above 5,000mg/kg BW, making it non-toxic. The SGOT-SGPT ratio, liver histology, and central vein width were measured in Sprague Dawley rats after 91 days of administration of the extract. No statistically significant change in SGOT-SGPT levels as well as in the diameter of the central vein in the rat liver was observed between the experimental and control groups (P>0.05)[46].

4 BIOAVALABILITY ASPECTS

Bioavailability refers to the crucial quality of a food-derived chemical to retain its structural integrity and biological activity even after being absorbed, distributed, and metabolised. The term "bioavailability" refers to the fraction of a compound that is absorbed into the bloodstream after ingestion. Studies on in vitro bioavailability have shown that isolated lunasin, whether synthetic or refined from soybeans, undergoes rapid digestion within 2 minutes when exposed to simulated stomach or intestinal fluids. However, when found in crude protein extracts separated from soybeans, lunasin at least partly withstands the impact of digestive enzymes, retaining 60% and 80% of its original form after being proteolyzed for 120 minutes by pepsin and pancreatin, respectively[47]. The findings indicated that lunasin might be protected from digestive enzyme proteolysis by naturally occurring protease

Table 2. Marketed formulation of Lunasin in Category Health and Nutrition

No.	Marketed formulation	Country of Origin	Company	Dose	Health Claim	References
1	*LunaCell*	United States	Simplesa	6 capsules per day	Combat inflammation and oxidative damage with Simplesa LunaCell, a cutting-edge lunasin supplement. This potent soy peptide protects against free radicals, preventing cellular damage and promoting overall well-being.	[54]
2	*LunaCol*	New Zeland	Vita Care	1 capsule twice a day	LunaCol is a prophylactic supplement that has three really critical ingredients that our immune system needs**.** LunaCol is comprised of Lunasin, Lysozyme, and Beta-D-Glucans and helps in strengthening our immune system.	[55]
3	*Lunasin*	United States	CareFast	1 capsule per day	Lunasin aids in maintaining optimal LDL cholesterol levels by inhibiting the activity of HMG-CoA reductase, a key enzyme in liver cholesterol synthesis, and supports cellular well-being through epigenetic mechanisms.	[56]
4	*Lunasin enrich your code*	United States	Luna Code	2 capsules in the morning and 2 capsules in the evening	Enhances the expression of beneficial genes. Modulates a healthy inflammatory response and it contains active lunasin for enhanced absorption	[57]
5	*LunaRichX*	United States	Reliv International	One capsule	LunaRich® X, a concentrated non-GMO soy lunasin supplement, supports healthy cholesterol levels, offers antioxidant benefits, and boosts immune function and cellular health.	[58]

inhibitors as Kunitz-trypsin inhibitor or Bowman-Birk inhibitor (BBI). Hernández-Ledesma et al. discovered that BBI provides protection to lunasin in soybean-derived meals throughout the process of sequential digestion with pepsin and pancreatin. This finding highlights the significance of the lunasin:BBI ratio in determining the level of protection[48]. Cruz-Huerta and colleagues have verified this idea, demonstrating the protective impact of the primary isoinhibitor from the Bowman-Birk family (BB1) on the simulated physiological digestion of synthetic lunasin in laboratory circumstances. When BB1 is not present, lunasin is fully broken down by digestive enzymes[49]. However, when the isoinhibitor is present, only a partial breakdown of lunasin occurs. The identification of peptides produced from lunasin during a simulated digestion process has recently been accomplished[50]. These scientists also examined the bioavailability of lunasin and released fragments by utilising Caco-2 cell monolayers, indicating that both lunasin and fragment RKQLQGVN18 were absorbed intact across the intestinal epithelium by a process involving paracellular passive diffusion. Hsieh et al.[37] provided evidence that lunasin exhibited bioavailability after oral administration in mice and rats. CD-1 mice was administered synthetic 3H-labeled lunasin, which was subsequently absorbed and distributed in several organs, including the lung, mammary gland, prostate, and brain. Furthermore, the scientists also documented that lunasin obtained from the blood and liver of rats fed with soy flour enriched with lunasin was able to successfully inhibit the development of foci, comparable to an equal quantity of synthetic lunasin[51]. Notably, the presence of lunasin has been observed in the plasma of healthy male volunteers after the ingestion of soy protein. During these investigations, participants were administered a 50g dosage of soy protein for a duration of 5 days, after a one-week interval of abstaining from the substance. At time intervals of thirty and sixty minutes after the consumption of soy protein, blood samples were obtained and examined for the presence of lunasin. The amounts of lunasin detected ranged from 50.2 to 110.6ng/mL of plasma. This quantity corresponds to the assimilation of 4.5% of lunasin from a 50g portion of soy protein[52]. A novel technique has been developed to directly extract and measure lunasin from plasma utilising an ion-exchange microspin column and a validated immunoassay methodology. The encouraging findings regarding the bioavailability and the advancements in methods for detecting and measuring lunasin levels in human samples are crucial for bolstering clinical trials that validate the chemopreventive properties of this peptide, as shown by cell culture and animal research[53].

5 MARKETED FORMULATIONS OF LUNASIN

Inflammation and oxidative damage may be mitigated with the use of the most cutting-edge Lunasin supplements currently available in the market. They shield the body against free radicals, which induce cell death, and prevent neurological diseases, cardiovascular problems, and visible apparent aging. The marketed formulations of Lunasin as health supplement in the category of health and nutrition are listed in Table 2.

6 PATENTS GRANTED FOR LUNASIN

In recent years, several research teams have investigated Lunasin for potential use in a wide range of contexts. Table 3 provides a summary of patent applications that have been

Table 3. List of Patents on Lunasin

No.	Patent No.	Inventor	Summary	References
1	W02005091823A2 (2005)	Raymond Rodriguez, Mark Magbanua	This invention includes gene expression patterns induced by lunasin, linked to cellular anti-cancer activity. These patterns can be used to test potential anti-cancer drugs, develop preventive and therapeutic strategies, and monitor patients with or at risk for cancer. It also includes microarrays for analyzing specific gene sets.	[59]
2	KR20070093758A (2006)	Hyungjin Jeong, Benito O de Lumen, Alfredo F. Galvez	A method is provided for isolating and purifying Lunasin from soybean and barley. This approach produces a cancer-suppressing medicinal component. Methods entail the following steps: (a) Extract soybean and barley seeds using secondary distilled water, protease inhibitor, sodium acetate, and sodium phosphate buffer and then followed by centrifugation. (b)Using distilled water, dialyze the separated supernatant from step (a) to eliminate proteins below 3,000 Da and then lyophilize to get a crude extract. (c) Finally, purify the crude extract using ion exchange, high-speed liquid, and immuno-affinity columns.	[60]
3	W02009051662A2 (2009)	Raymond Rodriguez, Alfredo F. Galvez	This study outlines techniques for evaluating the potential anti-neoplastic properties of a test compound. The methodology involves administering the test compound to a cancerous cell and subsequently assessing the acetylation levels of Lysine 16 located on the N-terminal tail of histone H4. A test compound and a cell are supplied, the acetylation of Lysine 16 of the N-terminal tail of histone H4 is assessed, the cell is exposed to the test drug, and the cell is re-evaluated. Increased acetylation of Lysine 16 of the N-terminal tail of histone H4 in the cell is proportionate to the test compound's anti-neoplastic efficacy. Lunasin derivatives and other antineoplastic medicines may be evaluated using this method. A test medication may also be evaluated by measuring the expression of target genes such UGTIA and thrombospondin.	[61]
4	US9066906B2 (2015)	Keith Davis etal, Brian Barnett, Jian Cai Elizabeth, McConnell	This invention covers a process for making Lunasin by extracting and purifying wild-type Lunasin from soybeans or other plants that naturally produce Lunasin. This method involves obtaining plant material from the plant and then isolating the lunasin-containing complex from the plant material. Additionally, the method also involves the release of lunasin from the lunasin-containing complex.	[62]
5	CN108034670B (2017)	Chi Yan, Chen Yuhua, Li Mingying	A cost-effective method for preparing soybean-derived Lunasin bioactive peptide without columns involves obtaining the Lunasin gene fragment via Overlapping Extension PCR. The fragment is fused with NpuC to form a fusion protein expressed in the pET 26 vector. Using elastin-like protein (ELP) and a DnaE split intein, the N-terminal Lunasin polypeptide is separated and purified through trans-splicing and reversible ELP phase change, offering a rapid and economical purification process.	[63]
6	CN106831999A (2017)	Ren Guixing, Zhu Yingying	The present invention describes a technique for producing lunasin-multiple tandem polypeptides. This involves genetically linking multiple lunasin genes in a sequential manner after optimising their codons using genetic engineering methods. This invention utilises yeast-preferred codons to synthesise lunasin-multi-tandem gene fragments, which are then fused with histidine tags. These gene fragments are integrated into the Pichia pastoris expression system to produce lunasin-multi-tandem polypeptides. This process enhances the efficiency of lunasin production and purification.	[64]

submitted for Lunasin showing anticancer property and its synthesis from plant sources.

7 FUTURE OPPORTUNITIES AND CHALLENGES

Lunasin exhibits potential as a bioactive agent for preventing cancer and as a potent epigenetic modulator. It enhances the efficacy of conventional treatments like chemotherapy and radiation therapy while reducing their side effects. Lunasin's ability to influence cellular processes related to cancer development, such as cell proliferation, inflammation, and angiogenesis suggests that it could have a role in cancer prevention and risk reduction. Further investigations may provide an insight regarding its potential value in high-risk population. Lunasin's bioactive properties and advances in personalized medicine

may pave the way for targeted therapies. Identifying patients who are more likely to benefit from Lunasin treatment based on specific genetic or molecular profiles could optimize its therapeutic potential. It is important to emphasize that more comprehensive research, including well-designed clinical trials, is necessary to fully understand potential of Lunasin and determine its role in cancer prevention and treatment. Despite promising in vitro and preclinical studies, there is a lack of robust clinical data demonstrating the effectiveness of Lunasin in cancer treatment. Clinical trials are necessary to establish its efficacy, safety, optimal dosage, and potential side effects in human subjects. Delivering Lunasin in an active form to targeted tissues in the body remains a challenge. Further research is needed to elucidate the precise molecular pathways through which Lunasin exerts its effects on cancer cells. The optimal dose and administration of Lunasin as an anti-cancer agent is still unknown. Although Lunasin has been shown to have promising anti-cancer properties, further research is needed to determine the most effective dose, route of administration, and stability studies of the peptide.

Lunasin holds considerable promise as a bioactive agent for cancer prevention and as a potent epigenetic modulator, capable of enhancing the efficacy of conventional therapies such as chemotherapy and radiation while potentially reducing associated side effects. By modulating key cellular processes, including proliferation, inflammation, and angiogenesis, Lunasin may play a crucial role in cancer prevention and risk reduction, particularly in high-risk populations. Effective delivery remains a major hurdle, and strategies beyond liposomes such as nanoparticle encapsulation, peptide conjugation, and polymer-based systems could improve stability, bioavailability, and tissue specificity. Translating preclinical findings into the clinic requires well-designed trials; a Phase I study would focus on safety, tolerability, and pharmacokinetics, with secondary endpoints evaluating biomarkers of epigenetic activity, preliminary anti-tumor effects, and interactions with standard therapies to define optimal dosing. Moreover, Lunasin may act synergistically with conventional chemotherapeutics like doxorubicin or cisplatin, as well as other bioactive dietary compounds such as curcumin or resveratrol, enhancing anti-cancer effects through complementary mechanisms. Overall, while preclinical studies are promising, further research is needed to optimize delivery, dosing, and combination strategies, and to elucidate the precise molecular pathways through which Lunasin exerts its therapeutic effects.

8 CONCLUSION AND OPINIONS

Galvez and de Lumen fortuitously discovered that the expression of Lunasin in *Escherichia coli* resulted in the development of anomalous elongated bacterial filaments. Subsequently, they demonstrated that the expression of a fusion of Lunasin with green fluorescent protein in mammalian cells caused cell death and mitotic arrest. Numerous preclinical studies have demonstrated the favourable response of various types of cancer to the chemo preventive and chemotherapeutic effects of Lunasin. There is now substantial preclinical evidence that has been independently verified by many researchers, demonstrating that lunasin has both chemopreventive and therapeutic effects against a wide range of cancer types. Preliminary investigations in mouse models suggest that lunasin exhibits no toxicity and is present in the body at levels that are enough to show effectiveness to advance the exploration of Lunasin's potential as a chemo-preventive and therapeutic agent, it is imperative to proceed with translational research that culminates in the initiation of human clinical trials. It is now necessary to conduct translational research to begin human clinical trials to evaluate both the chemo preventive and therapeutic effects of lunasin. Therapeutic techniques will likely include the creation of new versions of lunasin that have improved stability and are more easily absorbed by certain cells, to boost their bioavailability. Furthermore, further research is required to examine the synergistic effects of combining lunasin with other anticancer drugs to assess its increased effectiveness. Given the recent findings about the possible anti-cancer properties of the Lunasin peptide, we eagerly anticipate the forthcoming research on lunasin biology and its progression into clinical trials. The encouraging outcomes of initial investigations on the anticancer properties of the Lunasin peptide have generated anticipation for subsequent biological inquiries and the eventual commencement of clinical trials.

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Conflicts of Interest

The authors declared no conflict of interest.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Authors Contribution

The idea and design of the research was a collaborative effort by all authors. Kaur SD, designed the outline and organization of the paper. The first draft was written by Kaur SD who also developed all the accompanying tables and graphics. The article was updated based on feedback from Dr Kapoor DN. The manuscript has been finalized by Kaur SD and Kapoor DN. Kapoor DN oversaw the manuscript editing process. After several rounds of revisions, all authors agreed on the final draft.

Abbreviation List

EGCG, Epigallocatechin gallate

SD, Sprague Dawley
ET-Lun, Extract with targeted Lunasin
HATs, Histone acetyltransferases
MOMP, Permeabilization
MCM, Minichromosome maintenance
CSC, Cancer stem-like cells
NO, Nitric oxide
ICAM-1, Intercellular adhesion molecule 1
E-Cadherin, Epithelial cadherins
BBI, Bowman-Birk inhibitor

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