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Article Review: Lunasin's Mechanism as an Antioxidant And *Hypocholesterolemic Agent*

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Abstract . Several ways that can help lower cholesterol levels in the blood include using drugs (pharmacotherapy) or by modifying lifestyle and consuming certain foods. One of them is lunasin. Lunasin is a peptide found in soybean plants and is a promising drug candidate because it has broad health effects such as antioxidant, anti-inflammatory, anti-cancer, and lowering blood cholesterol through various mechanisms. This paper aims to examine the role and mechanism of action of lunasin as an antioxidant and its ability to lower blood cholesterol levels due to the unique peptide structure of lunasin as well as the bioavailability of lunasin starting from degradation, absorption, translocation and distribution of lunasin to target organs or target tissues after oral administration . This paper also discusses soybean plants as the main source of lunasin and the optimal content of lunasin in soybeans.

Keywords : antioxidant; soybean; hypercholesterolemic agent; lunasin

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Introduction

Lunasin is a bioactive peptide first identified in soybeans and has attracted scientific attention due to its potential health benefits. As a compound composed of 43 amino acids, lunasin is known to have a wide range of biological activities, including antioxidant, anti-inflammatory, and anticancer effects, as well as the ability to lower blood cholesterol levels (hypocholesterolemic effect) (Lule et al., 2015; Liu et al., 2014). The mechanism of action of lunasin as a therapeutic agent is thought to be related to its ability to inhibit histone acetylation, bind to chromatin, and neutralize free radicals (Jeong et al., 2007; Hernandez-Ledesma et al., 2009).

In its role as an antioxidant, lunasin is able to capture excess reactive oxygen species (ROS) in the body, which if uncontrolled can cause oxidative damage to DNA, proteins, and lipids, and contribute to various degenerative diseases, including cardiovascular disease and cancer (Hernandez-Ledesma et al., 2014; Li & Li, 2013). In addition, lunasin is also reported to have a hypocholesterolemic effect by inhibiting the expression of key enzymes in cholesterol biosynthesis and improving lipid metabolism, as shown in various in vivo and in vitro studies (Dia et al., 2009; Sirtori et al., 1993; Zhong et al., 2007).

Research on lunasin is increasingly developing with a multidisciplinary approach, ranging from biochemistry and molecular biology to food technology. Lunasin's ability to remain active after consumption of soy-based foods also contributes to its development as a functional agent in healthy diets (Guijarro-Díez et al., 2014; Vermont et al., 2009). Therefore, further understanding of lunasin's mechanism of action is crucial to support its development as a nutraceutical supplement and natural therapeutic agent.

This article will discuss in depth the mechanism of lunasin as an antioxidant and hypocholesterolemic agent based on various recent literature, and evaluate its potential in the prevention and management of chronic diseases through molecular and clinical approaches.

Literature review

Structural and Physiological Characteristics of Lunasin

Structural Characteristics

Lunasin (derived from the word 'Lunas' in Tagalog which means 'to heal') is a special peptide sequence with 43 amino acids encoded in the soybean gene *Gm2S* -1. [1]

The isolated *Gm2S -1* gene encodes for a methionine-rich protein and three other peptides as a ' *signal peptide* ', a small subunit called lunasin and a linker peptide. [1] (Figure 1)

Lunasin was discovered accidentally through collaboration in Dr. De Lumen's laboratory at UC Berkeley in 1996. [1]

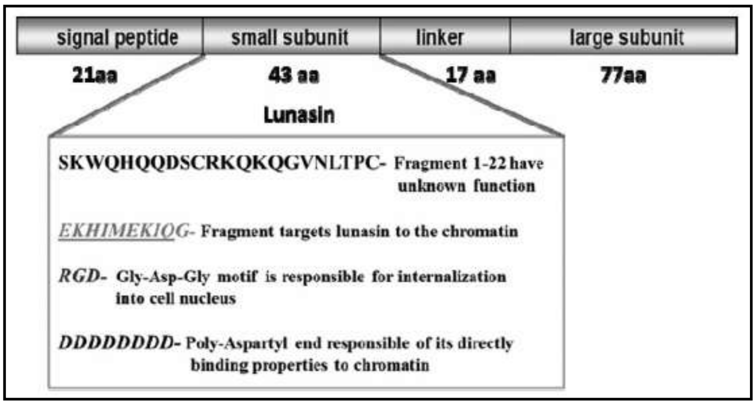


Figure 1. Lunasin (small subunit) [1]

Figure 2. Domain Settings from Lunasin [2]

Lunasin is a unique peptide consisting of 43 amino acid residues (with the sequence SKWQHQQDS CRKQKQGVN LT PCEKH IME KI QGRGDDDDDDDDD) with a molecular weight of 5.5 kDa. This peptide contains 8 negatively charged Asp(D) residues at the carboxyl terminal, which results in histone binding and is able to work as a potent inhibitor of the acetylation of positively charged histones H3 and H4. [3] (Figure 1)

The poly-D chain is immediately followed by the Arg-Gly-Asp (RGD) cell attachment motif sequence responsible for lunasin attachment to the extracellular matrix, and it is suspected that the structurally homologous *helical region* (EKHIMEIQG) functions to maintain the part of the protein that binds to chromatin, this causes *the helical region* to be a target for lunasin to the histone core. This allows *the helical region* to function to increase the ability to bind to the histone core (Figures 2 and 3). The RGD motif also facilitates the internalization of lunasin into mammalian cells within minutes, followed by localization into the nucleus within hours. Based on several studies, the cell attachment function of the RGD motif is specific to certain cell lines, seen attachment in CH3 cells but not in NIH3T3 cells. The RGD motif can induce cell apoptosis in different cell lines through its own caspase mechanism. In addition, lunasin is also involved in the process of cell proliferation and growth, cell maintenance functions, cell interactions and cell *signaling* . Based on previous research, the primary function of lunasin as a potent inhibitor of the acetylation of positively charged histones H3 and H4 is seen in the position of the *poly-D chain* , the RGD motif and the possible helical structure of the region, while the function of other amino acids and other structures in lunasin remains unknown. Further research is still needed to determine whether smaller peptides contained in the functional domain of lunasin also have the ability to maintain health or can be used for treatment. [3]

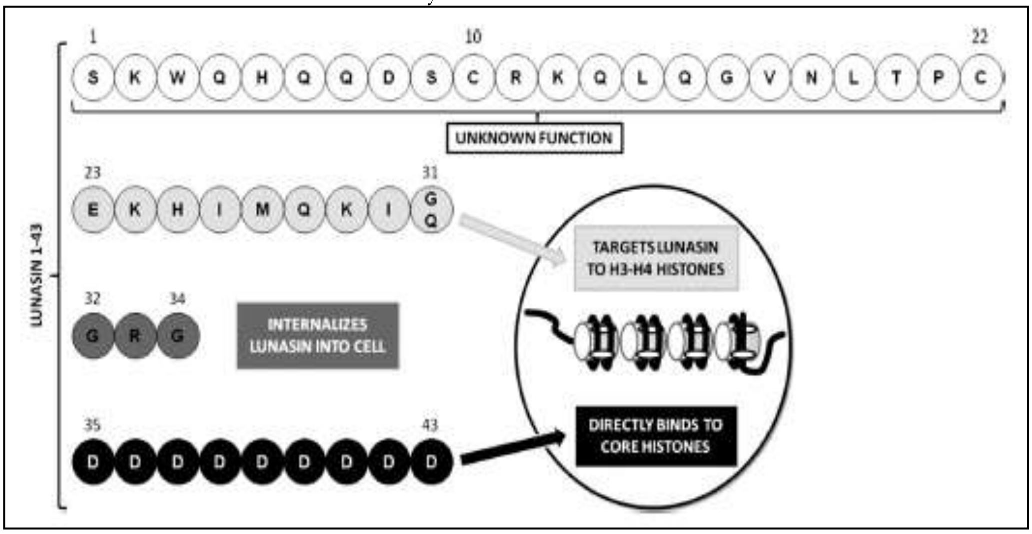


Figure 3. Lunasin Sequence and Function of Its Peptide Parts [4]

Physiological Characteristics

Because lunasin is a peptide, it is important to understand its degradation, absorption, translocation, and distribution in target organs or tissues after oral administration. Therefore, the bioavailability of lunasin has been studied both in *vitro* and *in vivo* . Preliminary studies have shown that the bioavailability of lunasin in mice and rats fed a diet enriched with soy protein-lunasin was 35%. [5,6] Also, studies of the bioavailability of lunasin in adult males showed it was 4.5%. [97] The high ability of lunasin to not be degraded in the gastrointestinal tract and by serum proteinases or peptidases, and to maintain its bioactive form during translocation into the blood and other organs, makes lunasin a promising drug candidate. Furthermore, *circular dichroism analysis* shows that lunasin has high thermostability, with a temperature range of 25-100 ° C without changes in its secondary structure or bioavailability. [8]

But actually lunasin was first isolated in 1987 at Niigata Medical School, Japan, in the process of screening protease inhibitors from soybeans, which was then identified as a promising anticancer candidate. It was first described as a small polypeptide with a poly-Asp(D) residue located at the carboxyl terminal end, and was later found to be present in legumes, grains, medicinal plants, including wheat, rye, *sunberry, wonderberry, bladder cherry, jimson weed, Solanum ningrum L, amaranth* and *triticale* , with concentrations ranging from 0.013 to 70.5 mg lunasin protein/g protein. [3] (Table 1)

Table 1. Lunasin Content in Soybeans, Rice, and Medicinal Plants [9]

Plant (Latin name)	Plant (General name)	Lunasin content (mg/g protein)	Lunasin content (mg/g seed)
Triticum aestivum	Wheat		0.2-0.3
Hordeum vugare L.	Barley	5.9-8.7	0.01-0.02
Glycine max[3]	Soybean	4.4-70.5	0.5-8.1
Amaranthus hypochondriacus	Amaranth	9.5-12.1	
Physalis alkekengi var. francheti	Bladder-cherry	17.0	0.1
Solanum lyratum	Hyyodori-jogo	22.3	0.4
Solanum nigrum L.	Sunberry	36.4	1.8
Datura starmonium	Jimson weed	10.3	0.3

Soybeans are the primary source of lunasin, with contents ranging from 4.4 to 70.5 mg lunasin/g soy protein across various soybean gene varieties. [9] (Table 1) Lunasin levels increase during ripening and begin to decline at the time of sprouting and are influenced by the soaking period. The planting process, growth temperature, and soil moisture conditions also significantly influence lunasin content. [1]

Benefits of Lunasin for Health

Several clinical trials on soy protein have prompted the FDA to issue a statement stating that consuming 25 g of soy protein per day may reduce the risk of cardiovascular disease. This is based on existing epidemiological evidence that soy as a dietary supplement, such as soy protein and its non-protein components, such as saponins and isoflavones (e.g., genistein and diadzein), may help regulate cholesterol levels and reduce risk factors for coronary heart disease in some individuals and laboratory animals. [10,11,12,13]

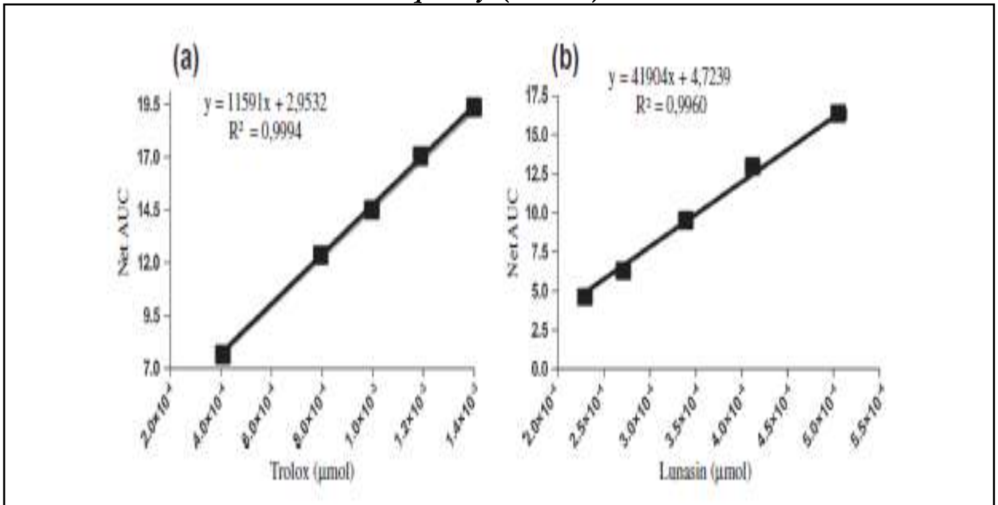
2.1 Lunasin's Ability as an Antioxidant

In a study conducted by Hernández-Ledesma et al., lunasin can reduce the production of *reactive oxygen species (ROS)* in macrophages induced by lipopolysaccharide (LPS) in a dose-dependent manner, based on *in vitro assessment* of the inhibitory activity of linoleic acid oxidation and ABTS $^{+}$ free radical scavenging ability . Lunasin showed potent ABTS scavenging activity . [14]

The antioxidant capacity of lunasin is assessed by its ability to capture peroxyl and superoxide radicals, as well as its ability to bind iron ions. Table 3 shows the linearity of the area under the curve (*AUC*) and the antioxidant concentration (Trolox or lunasin). To determine the value *The Oxygen Radical Absorbance Capacity* (ORAC) of lunasin is the slope of the AUC versus concentration curve divided by the slope of the Trolox calibration curve. The ORAC value of lunasin is 3.44±0.07 µmol Trolox equivalents/µmol lunasin. This value is higher than natural antioxidants such as vitamin C (1.65 µmol Trolox equivalents/µmol vitamin C) [15] , or synthetic antioxidants such as *butylated hydroxyanisole* (BHA) (2.43 µmol Trolox equivalents/µmol BHA). [16] According to existing ORAC data, the length of peptides derived from food sources with the ability to scavenge peroxyl radicals is 4 to 20 amino acids. [17] From previous research, we know that lunasin has 43 amino acids, the first peptide containing more than 20 amino acids that has this antioxidant ability. The antioxidant ability of lunasin is due to the presence of the amino acids Trp, Cys, and Met in its sequence. [18] This amino acid is also thought to be responsible for the ability of this peptide to capture ABTS radicals. [14]

The results of this study open up the possibility for further research into the antioxidant capacity of lunasin in other cell lines and demonstrate the ability of lunasin as [a] *cardioprotective agent.*

Table 3. Antioxidant Capacity of Lunasin Measured Using *Oxygen Radical Absorbance Capacity* (ORAC) Assessment [19]



2.2 Lunasin's Ability to Lower Blood Cholesterol Levels

Lunasin works in two ways to lower LDL cholesterol levels:

a. **Specifically interfering with the steps in the formation of HMG-CoA reductase** . Lunasin inhibits the acetylation of the histone H3 tail at the K14 position by Poly -*Caffeyl alcohol* (PCAF) [20,21] , this will decrease the expression of the HMG-CoA reductase gene, which will make the liver unable to synthesize cholesterol.22 (Figure 4)

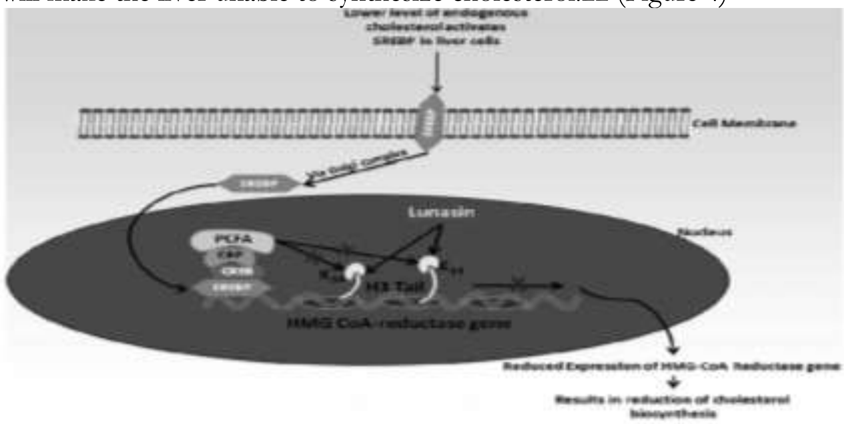


Figure 4. Regulation of Lunasin in Reducing Cholesterol Biosynthesis [1]

b. **Increases LDL receptor gene expression** , which increases the number of receptors and clears LDL cholesterol from the bloodstream. In the presence of lunasin, levels of the SP1 protein (a coactivator of SREBP (Sterol Regulatory Element-Binding Protein) for LDL receptor production) are doubled compared to those without lunasin.（Figure 5)

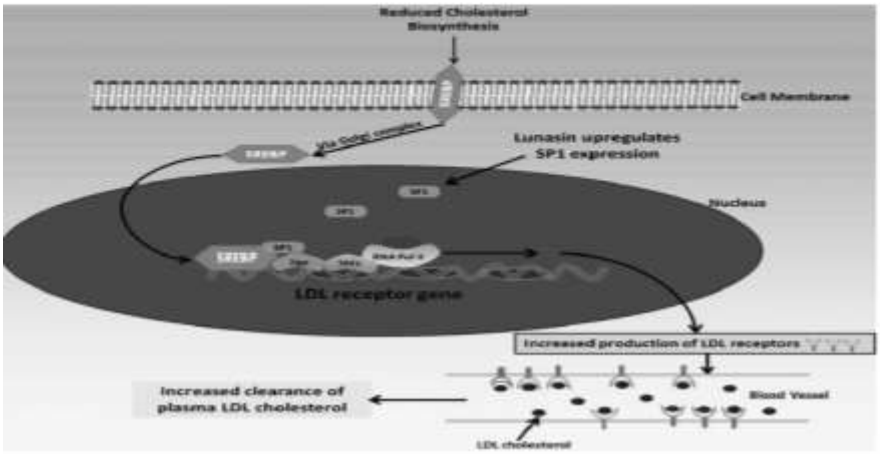


Figure 5. Upregulation of LDL-Receptor Gene by Lunasin [3]

In vitro research conducted on HepG2 liver cells showed that lunasin can significantly reduce the expression of HMG-CoA reductase by inhibiting the acetylation of PCFA (Poly-Caffeyl Alcohol) of H3-lysine 14 and increasing the expression of SP1 protein. [1]

In vivo research shows that supplementation of LSE (lunasin-enriched soy extract) with casein can reduce LDL cholesterol levels compared to those receiving a casein-only diet in pigs that have mutations in the LDL receptor gene. [1]

RESEARCH METHODS

This literature review was made with a search strategy for this study using English and Indonesian using databases, Proquest, Google Scholar, and PNRI. The keywords used were " antioxidants", "soybeans", hypercholesterolemic agents", "lunasin".

RESULTS AND DISCUSSION

1. Antioxidant Activity of Lunasin

Lunasin exhibits significant antioxidant activity through its ability to scavenge free radicals and reduce oxidative stress in cells. A study conducted by Hernández-Ledesma et al. (2009) showed that lunasin was able to inhibit the production of reactive oxygen species (ROS) in activated RAW 264.7 macrophages, as well as reduce the expression of inflammatory molecules. Furthermore, a study by García-Nebot et al. (2014) demonstrated that lunasin was able to protect Caco-2 intestinal cells from oxidative stress by increasing cell viability and reducing intracellular ROS levels.

The lunasin structure is rich in negatively charged amino acids, such as glutamic acid and aspartic acid, allowing electrostatic interactions with transition metal ions that play a role in the formation of free radicals, so that lunasin is effective in neutralizing the effects of hydroxyl and superoxide radicals (Li & Li, 2013). In addition, based on ORAC (Oxygen Radical Absorbance Capacity), lunasin has a high radical absorption capacity, similar to several other antioxidant peptides from animal and plant protein sources (Dávalos et al., 2004; Huang et al., 2010).

2. Hypocholesterolemic Activity of Lunasin

Lunasin also shows potential in lowering blood cholesterol levels, making it a candidate for a natural hypocholesterolemic agent. Studies by Sirtori et al. (1993) and Wang et al. (2004) reported that consumption of soy protein containing lunasin contributed to a decrease in low-density lipoprotein (LDL) cholesterol and blood triglycerides. This effect is largely attributed to lunasin's ability to reduce the expression of the HMG-CoA reductase enzyme, a key enzyme in cholesterol biosynthesis (Zhong et al., 2007).

A study by Dia et al. (2013) developed an immunochemical method to measure plasma lunasin concentrations after soy protein consumption, and the results showed that lunasin can be absorbed into the systemic circulation in its active form. This supports the hypothesis that lunasin can work systemically to lower cholesterol levels, while also acting at the molecular level as an epigenetic modulator that influences the expression of lipid metabolism genes (Jeong et al., 2007; Hernández-Ledesma et al., 2011).

3. Epigenetic Mechanisms and Cancer Prevention

The mechanism of action of lunasin as an epigenetic agent is also relevant in the context of its antioxidant and hypocholesterolemic effects. Lunasin is known to inhibit the acetylation of histones H3 and H4, which is a crucial process in regulating gene expression (Jeong et al., 2007; Jones & Srivastava, 2014). This inhibition is related to lunasin's ability to prevent abnormal cell proliferation and increase the expression of protective genes against oxidative stress and lipid metabolism.

Furthermore, a study on *the Drosophila melanogaster model* by Jones & Srivastava (2014) showed that lunasin can modulate signaling pathways associated with cancer cell growth and cholesterol metabolism. This supports the multifunctional role of lunasin as a bioactive compound with not only nutraceutical properties but also pharmacological potential.

CONCLUSION AND SUGGESTIONS

Lunasin works in two ways to lower LDL cholesterol levels: first, by specifically interfering with the steps in HMG-CoA reductase formation, and second, by increasing the expression of the LDL receptor gene. The highly variable lunasin content across Glycine max species suggests that levels of this important bioactive peptide can be genetically manipulated. Furthermore, soybean isolates and hydrolyzed soy protein have the highest lunasin concentrations. Studies have shown that lunasin can be absorbed by the human body, a key factor in reaching the target tissues. Lunasin content varies depending on the seed type, developmental stage, and production standards. Lunasin's resistance to gastric enzymes enhances its utility due to its good bioavailability. These factors make lunasin one of the most sought-after molecules for future therapeutic research. However, it is crucial to gather information on the mechanisms and actions of lunasin in the host. Molecular and proteomic tools/techniques are still needed to elucidate the molecular mechanisms of the course of various diseases and to ensure its safety and efficacy.

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