

**ORGANIC SELENIZED COMPOUNDS IN GARLIC AS POTENTIAL CHEMOTHERAPY AGENT TO IMPROVE CANCER TREATMENT**

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**Abstract**

Garlic has been utilized since ancient times for both culinary and medicinal purposes. Recent research has identified selenium compounds in garlic, including  $\gamma$ -Glutamyl-Se-methylselenocysteine (GGMSC), leading to the hypothesis that GGMSC acts as a carrier for Se-methylselenocysteine (MSC). Experiments conducted on animals by researchers indicate that the effects of GGMSC in garlic and MSC on cancer cells in experimental models are equivalent. This finding suggests that garlic is a potential chemotherapeutic agent to enhance cancer treatment.

**Key words:** Garlic, Organic Selenium, Se-methylselenocysteine (MSC).

**Hợp chất Selen hữu cơ trong tỏi như tác nhân hóa trị liệu tiềm năng để cải thiện điều trị ung thư**

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**Tóm tắt**

Tỏi đã được sử dụng từ thời cổ đại cho cả mục đích ẩm thực và y học. Nghiên cứu gần đây đã phát hiện các hợp chất selenium trong tỏi, bao gồm  $\gamma$ -Glutamyl-Se-methylselenocysteine (GGMSC), dẫn đến giả thuyết rằng GGMSC đóng vai trò như một chất mang cho Se-methylselenocysteine (MSC). Các thí nghiệm được thực hiện trên động vật bởi các nhà nghiên cứu chỉ ra rằng tác dụng của GGMSC trong tỏi và MSC đối với các tế bào ung thư trong các mô hình thí nghiệm là tương đương nhau. Phát hiện này gợi ý rằng tỏi có thể là một tác nhân hóa trị liệu tiềm năng để hỗ trợ điều trị ung thư.

**Từ khóa:** Tỏi, Selenium hữu cơ, Se-methylselenocysteine (MSC).

**Introduction**

Garlic, scientifically known as *Allium sativum* L., belongs to the onion family (Alliaceae). It has been used by humans for thousands of years. In ancient Egypt, garlic was valued not only for its culinary applications but also for its health and therapeutic benefits.

The main chemical components isolated from garlic extracts include sulfur-containing compounds such as alliin, allicin, ajoenes,

vinyldithiols and sulfides

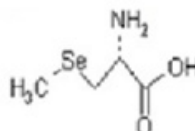
Garlic products are used by humans as a source of medicine in many ways in today's life. Researchers from various disciplines are currently working to explore the medicinal value of garlic for human health.

Researchers are primarily concerned with the medicinal value of garlic for its broad-spectrum therapeutic effects with minimal toxicity. Garlic extract exhibits antibacterial

activity against various types of bacteria, fungi and viruses. From the chemical composition of garlic, Numerous studies have highlighted the efficacy of garlic preparations in treating cardiovascular diseases, cancer, diabetes, hypertension, and atherosclerosis. Selenium, an essential trace element and antioxidant, is known for its cancer prevention properties. Extensive research has focused on the role of organic selenium in cancer treatment [1-2]. Evidence suggests that selenium intake is effective in cancer prevention. To biological enrich selenium-deficient areas, soil can be fertilized with selenium-rich compounds to increase the selenium content in garlic [3]. According to a study conducted at the Jiangsu Provincial Center for Disease Control and Prevention in China, individuals who consumed raw garlic at least twice a week over a seven-year period exhibited a 44% lower risk of lung cancer.

In Vietnam, garlic is grown throughout the country and is used as a culinary and medicinal ingredient. Recently, scientists have discovered

GGMSC can be considered as a carrier of Se-methylselenocysteine (MSC).



The authors of this study conducted experiments to demonstrate that GGMSC is a carrier of MSC. Selenomethionine (MSC) is a natural amino acid found in some plant materials such as cereals, soybeans, and enriched yeast, but it cannot be synthesized in animals or humans.

GGMSC is found naturally in garlic, accounting for ~31% of the total Se in garlic and ~53% in commercial garlic powder [5].

**2. Se-methylselenocysteine (MSC) reduces the toxicity and enhances the antitumor activity of anticancer drugs in chemotherapy**

Cancer is gradually becoming a “burden” for many countries in the world, including Vietnam. The rate of cancer in our country is

the cancer-treating effects of garlic. Therefore, it is necessary to study and research to improve the anti-cancer effects of garlic.

**1. Selenium and organic selenium in garlic**

We all know that the content of trace elements in plants, tubers, and fruits depends a lot on the content of those elements in the growing environment. In particular, plants containing a lot of sulfur such as garlic, if fertilized with a lot of fertilizer containing selenium, the selenium content in garlic increases [3]. This happens because the properties of sulfur and selenium are very similar, so selenium easily replaces sulfur in sulfur-containing compounds.

The major selenium-containing compound in natural garlic and selenium-fertilized garlic has been identified as  $\gamma$ -Glutamyl-Se-methylselenocysteine (GGMSC) and it is hypothesized that GGMSC mainly acts as a carrier of Se-methylselenocysteine (MSC)- an organic selenium with anticancer effects [4]. The structures of these two compounds are illustrated in the following figure:

increasing. There are about 100 types of cancer and this dangerous disease can occur at many different ages. However, middle-aged people often have a higher rate of disease.

Cancer is a dangerous disease, but if detected early and treated properly, cancer can be cured. Common cancer treatments today are surgery, radiotherapy, chemotherapy and some other treatments such as endocrine therapy, targeted therapy, etc.

Chemotherapy is a treatment method commonly used to treat patients with advanced cancer, when surgery or radiotherapy cannot be highly effective. Some drugs and chemicals for cancer treatment can prevent the development of cancer, but they are all toxic to cells. Toxicity

caused by chemotherapy is often a factor that hinders cancer treatment, limiting treatment time and increasing doses. Therefore, there is a need for new approaches to develop new agents or combination regimens to reduce toxicity and increase selectivity of cancer treatment drugs, counteract the toxicity caused by chemotherapy, bringing the potential for using higher doses of chemotherapy in the hope of overcoming drug resistance.

It has been shown that antioxidant compounds such as curcumin and some selenium compounds have protective effects against cisplatin (CDDP)-induced nephrotoxicity. In a study [6], the authors evaluated the effects of MSCs on the toxicity and antitumor activity of four drugs Cyclophosphamide (CTX), CDDP, oxaliplatin, and irinotecan in Fischer rats.

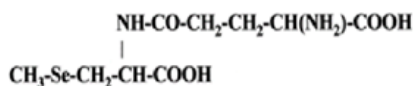
Cisplatin(cis-diamminedichloroplatinum)is a platinum complex used in the treatment of a variety of malignancies. The antitumor activity of CDDP is related to DNA synthesis through the formation of interstrand and intrastrand DNA cross-links. The known toxicities of CDDP are

nephrotoxicity, myelotoxicity, neurotoxicity, ototoxicity, aandagastrointestinalatotoxicity. Nephrotoxicity is the major dose-limiting toxicity. The major route of excretion of CDDP is via the kidneys, and it accumulates in the renal cortex, leading to renal failure, hypokalemia, and hypomagnesemia.

Cyclophosphamide(CTX)is often combined with other drugs to treat many malignant diseases such as: Ovarian cancer, Breast cancer, Small cell lung cancer... Reversible leukopenia, thrombocytopenia, anemia, anorexia, nausea, vomiting, diarrhea, stomatitis, mucositis, skin rash, flushing, urticaria, hair loss, aseptic cystitis, microscopic/gross hematuria, headache, conjunctivitis, jaundice...

Oxaliplatin - a platinum complex, is a drug used to treat advanced colorectal cancer. It is the only platinum compound active against colorectal cancer. Oxaliplatin is mainly used in combination with other chemotherapeutic agents, including irinotecan. Toxicities of oxaliplatin include neuropathy, diarrhea, myelotoxicity, and mucositis.

**$\gamma$ -glutamyl-Se-methylselenocysteine (GGMSC)**



Irinotecan (CPT-11) is used in combination for the treatment of patients with advanced colorectal cancer. Late-onset diarrhea is the dose-limiting toxicity of irinotecan. Although high-dose loperamide is used to prevent diarrhea caused by CPT-11, efficacy is limited. Neutropenia is another serious adverse event of irinotecan treatment, with transient neutropenia occurring in 80% of patients, severe neutropenia, and febrile neutropenia occurring in 47% and 15%, respectively.

The results of the mouse study of this study [6] showed that: The researchers combined MSCs with CTX, CDDP, oxaliplatin or irinotecan, orally daily for 14 days or 7 days before chemotherapy and for 7 days after drug administration. For the combination of MSCs and irinotecan, MSCs were administered orally for a total of 35 days.

The obtained data demonstrated that except for CTX, MSCs had a complete protective effect against toxicity induced by doses of CDDP, oxaliplatin and irinotecan, Optimal protection from chemotherapy-induced toxicity was achieved only when MSCs were treated prior to drug treatment.

Alopecia is another major side effect of patients treated with CTX. Alopecia is caused by the shedding of the rapidly dividing epithelium of the hair follicle. Currently, there is a lack of good animal models for studying chemotherapy-induced alopecia. Because it is difficult to demonstrate a direct protective effect of MSCs on CTX-induced alopecia, the researchers chose the post-shave hair regrowth method to evaluate the effects of MSCs. The data clearly demonstrated that when CTX was combined

with MSCs, normal hair growth occurred in mice that had been shaved prior to treatment.

In conclusion, the obtained research results clearly demonstrated that MSCs are highly selective and effective modulators of the therapeutic efficacy and toxicity of various chemotherapeutic agents in animal models.

### **3. Se-methylselenocysteine (MSC) is a Cancer Therapeutic Agent**

Selenomethionine (MSC) is highly bioavailable in humans and exhibits favorable pharmacokinetic properties with a short half-life and low risk of chronic selenosis. The tumoricidal activity of MSC has been demonstrated in several cancer cell lines.

All cancer cells exhibit an uncontrolled growth pattern and have the ability to metastasize, resulting in a lethal malignancy. To support this relentless cell division and proliferation, cancer cells undergo abnormal metabolic adaptations to promote their survival. Although the mechanisms of cellular transformation during carcinogenesis in different cell types may occur in different ways, the metabolic requirements of cancer cells are generally very similar. Equally remarkable for the energy adaptations that cancer cells have is their exceptional ability to withstand the increased environmental oxidation caused by their abnormal metabolism. Malignant cancer cells depend on high levels of intracellular reactive oxygen species (ROS) for proliferation, self-renewal, and metastasis. That is, these types of cancer cells maintain high levels of ROS compared to normal cells, creating oxidative stress. From here, scientists have proposed a new cancer treatment strategy called Modulation of oxidative stress as an anticancer strategy [7]. In this method, Selenomethionine (MSC) can be used. Selenomethionine (MSC) acts as a pro-oxidase [8]. MSC are metabolized by several distinct pathways that produce different Se metabolites, which in turn determine their specific biological activity. Among the metabolites generated, hydrogenselenide (HSe-) and methyl selenol (CH<sub>3</sub>Se-) act as antioxidants and play a central role in the redox cycle with glutathione (GSH) or the Trx/Grx

system (Trx-Thioredoxin); Grx glutaredoxin),, generating superoxide and hydrogen peroxide, which generate new ROS generation. Hydrogen peroxide is the key molecule that determines the fate of cancer cell survival. Because cancer cells already have high levels of ROS. MSCs continue to generate additional ROS. This causes cancer cells to die [7]. In contrast, healthy cells have steady-state levels of ROS. Therefore, in the case of increased ROS levels in normal non-cancerous cells, they can be neutralized by the body's antioxidant system.

Thus, Selenomethionine (MSC) has the effect of both reducing side effects in chemotherapy and destroying cancer cells.

To confirm that  $\gamma$ -Glutamyl-Se-methylselenocysteine (GGMSC) is a carrier of Se-methylselenocysteine (MSC) and has the same anti-cancer effect as MSC, scientists [4] conducted experiments comparing the anti-cancer effects of GGMSC with MSC in mice. The study was designed to compare the in vivo responses of GGMSC and MSC using various biochemical and biological endpoints, including: (a) tissue accumulation profiles; (b) urinary Se excretion following bolus doses; (c) anti-cancer efficacy; and (d) gene expression changes determined by cDNA array analysis. The results indicated that GGMSC primarily functions as a carrier for MSC. In carcinogenic mice, treatment with either GGMSC or MSC led to a lower incidence of premalignant lesions in the mammary gland and a lower occurrence of breast cancer as these early lesions progressed to malignancy.

### **4. Discussion**

Documents show that garlic contains the compound  $\gamma$ -Glutamyl-Se-methylselenocysteine (GGMSC) and GGMSC is a carrier of Se-methylselenocysteine (MSC)- and GGMSC has anti-cancer effects like MSC, thus garlic is a potential chemotherapy.

Since ancient times, garlic has been used as a spice and medicine, but little attention has been paid to the therapeutic effects of selenium and selenium compounds in garlic. Selenium has two sides. At reasonable levels, selenium is a medicine, but at high levels, selenium is toxic.

On the other hand, the selenium content in garlic depends on the selenium content in the soil where garlic is grown.

In Vietnam, garlic is used as a spice and medicine and is grown throughout the country.

Therefore, to make garlic a chemotherapy agent in cancer treatment, it is necessary to standardize the selenium content in garlic and choose a locality and garlic growing technique that meets that requirement.

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