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The Role of Mushroom Polysaccharides in Cancer Prevention and Therapy

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Abstract: Cancer remains a leading cause of mortality worldwide, with millions of deaths each year. One emerging area of interest in cancer prevention and treatment is the effect of gut microbiota and how dietary interventions can modulate its composition to exert anti-tumor effects. The gastrointestinal tract hosts a diverse community of microorganisms, collectively known as the gut microbiota, which is vital for human health maintenance. When dysbiosis occurs, it can contribute to diseases such as colorectal cancer (CRC). Recent studies have identified mushroom polysaccharides as promising agents with potent anti-tumor properties. Mushroom polysaccharides act as indigestible polysaccharides that can serve as prebiotics to maintain gut health and regulate the immune system. In this article, we review and record studies about the effects of mushroom polysaccharides in anti-tumor. They stimulate and activate immune responses and induce tumor cell death through apoptosis and necrosis. They also affect angiogenesis, thereby inhibiting the nutrient absorption of cancer cells. This paper describes the structure of polysaccharides that can influence bioactivity and anti-tumor effects and summarizes the functions of mushroom polysaccharides in clinical settings.

Keywords: mushroom polysaccharides, cancer, anti-tumor, immune, gut microbiota.

1. Introduction

Cancer, or malignant tumor, is a disease that still has a fairly high mortality rate. Several million people continue to die from cancer each year. When cancer occurs, normal cells become cancerous and multiply. The growing cells form a tumor. Distribution of tumor will potentially lead to organ failure n the organs to which they are dispersed. As a result, the patient's system deteriorates, and the immune system weakens. Eventually, the patient d-evelops complications that can lead to death. It is always one of the most feared diseases due to its high mortality rate. People try various methods to treat cancer and achieve an anti-tumor effect. Cancer has many types, which usually depend on the tumor's location and varying rates of growth.

A diverse ecosystem of microorganisms, known as the gut microbiota, lives within the gastrointestinal tract and plays an important role in maintaining human health. With over 1,000 common species, the gut microbiota play a key role in stimulating the immune system, helping to defend the body against numerous diseases. However, an imbalance in the gut microbiota, known as dysbiosis, can result in various. On the other hand, an imbalance in the gut microbiota can result in

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gastrointestinal diseases. Colorectal cancer (CRC) is one such condition, prompting numerous studies to explore ways of lowering CRC risk through gut microbiota modulation. [1-4]

The gut microbiota can also be influenced by diet. Numerous studies on the anti-tumor effects of different macro and micronutrients and have revealed that polysaccharides found in mushrooms can affect the gut microbiota, control the immune response, strengthen the body's defenses, and prevent tumor growth and metastasis. An increasing number of studies highlights the potential of mushroom polysaccharides for cancer prevention and therapy by influencing gut microbiota, thereby triggering anti-tumor responses and modulating immune functions. For instance, Lentinus edodes, a common mushroom rich in β-glucan, is widely used in colorectal cancer therapy due to its promising anti-cancer properties. In addition to this, it has many other anti-tumor mechanisms. [1,3,4]

2. Literature Review

2.1. Diet and Gut Microbiota

Diet is crucial in shaping gut microbiota and lowering cancer risk, as highlighted by various studies. According to Cindy D. Davis and John A. Milner, incorporating prebiotics, probiotics, and synbiotics into the diet is beneficial for gut health. [5] These components help reduce risk of colon cancer by lowering DNA damage, enhance immune responses, and promote apoptosis in damaged cells. Prebiotics encourage the proliferation and activity of certain gut bacteria, which leads to an enhanced population of helpful bacteria. Probiotics contribute growth of beneficial bacteria and inhibition of harmful bacteria. It regulate the gut microbiota. Synbiotics combine prebiotics and probiotics to enhance the viability and activity of beneficial bacteria. [5-8] They increase beneficial cells and decrease harmful cells. Similarly, polysaccharides, as discussed by Qianqian Song, act as prebiotics that contribute to disease prevention and management. When polysaccharides reach the large intestine, specific gut microorganisms ferment them, generating short-chain fatty acids (SCFAs) that contribute to the modulation of immune responses. [9] Type 2 diabetes mellitus (T2DM), obesity, and inflammatory bowel disease (IBD) have all been demonstrated to benefit from this fermentation process and the SCFAs that are produced. Thus, the consumption of prebiotics, probiotics, synbiotics, and polysaccharides can make people more health and lower risk of disease by influence gut microbiota. Colon cancer is a good example.

2.2. Antitumor Effects of Edible Plants

To study the antitumor effects of diet further, attempts have been made to test the impact of various foods on tumors. The antitumor effects of some foods will be discussed.

Watercress, a cruciferous vegetable,are abundant glucosinolates and lutein and beta-carotene. It can be converted into isothiocyanates (ITCs). It has been demonstrated that ITCs and carotenoids inhibit cancer by lowering cell growth, stopping angiogenesis, and inhibiting metastasis. Reducing cell growth and suppressing metastasis can decrease the spread and progression of cancer. If cancer cell metastasis is prevented, treating cancer becomes much easier. Preventing angiogenesis stops the formation of blood vessels that support cancer cell growth. Ultimately, these factors lead to cancer cell death. [19]

Anisi Stellati Fructus (ASF), a traditional Chinese medicinal herb, is known for its applications in treating inflammation, pain, and insomnia. Additionally, it exhibits antitumor properties, especially in inhibiting metastasis and angiogenesis. Metastasis occurs when cancer cells migrate from their original location to distant areas of the body, complicating efforts to target and eliminate these cells. Angiogenesis is the process by which new blood vessels form from existing ones, supplying tissues with oxygen and nutrients. In cancer, it will support tumor by oxygen and nutrients. It was mentioned earlier that ASF inhibits metastasis and angiogenesis. then the mRNA levels and activity of matrix

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metalloproteinases (MMPs) -9, -13, and -14, as well as urokinase plasminogen activator (uPA) are also reduced. MMP-9 is particularly important for both metastasis and angiogenesis.

Star anise, commonly used in Indian cuisine, is known for its antioxidant properties. Its antioxidant activity is attributed to N-nitrosodiethylamine (NDEA) and is promoted by phenobarbital (PB). NDEA and PB reduce oxidative stress and enhance the activity of antioxidant enzymes like catalase (CAT), thereby increasing antioxidant defenses. At the same time, erythrocyte glutathione (GSH) and glutathione S-transferase (GST) levels are significantly boosted. These compounds strengthen detoxification processes and minimize toxic metabolite formation, thus supporting antitumor activity.

2.3. Mushroom Polysaccharides and the Immune System

According to numerous studies, mushroom polysaccharides have many beneficial functions for the human body, including antimicrobial effects, antioxidant effects, and the reduction of cholesterol and blood sugar levels.

Among the key functions of mushroom polysaccharides is their antimicrobial activity. Its primary mechanism involves stimulating the immune system to produce antimicrobial effects through neutrophils and macrophages. For example, in Marijana Kosanić's research, mushroom polysaccharides exhibit antimicrobial activity against Enterococcus faecalis. [16] Next is the antioxidant effect. When Reactive oxygen species (ROS) levels become excessively high and exceed the cell's antioxidant defenses, they can damage proteins, lipids, and DNA, leading to a state known as oxidative stress. Oxidative stress potentially leading to cell damage and contributing to various diseases. As a result, it is important for people to consume foods rich in antioxidants. Mushroom polysaccharides are already well known for their benefits. Hericium erinaceus has demonstrated antioxidant and neuroprotective properties.18 Many mushroom polysaccharides are indigestible and enter the intestines as dietary fiber, which has the ability to lower blood sugar and cholesterol levels. [17]

Furthermore, mushroom polysaccharides enhance the immune response by increasing cytokine secretion and immune cell activity. They also enhance the cytotoxic effects on tumor cells by generating reactive oxygen species (ROS). Clinically, one of their most critical abilities is enhancing the efficacy of chemotherapy and radiation therapy, which improves patient outcomes and reduces treatment-related toxicity by increasing response rates to chemotherapy. However, it is essential to note that while mushroom polysaccharides provide substantial benefits, they may also cause adverse effects in some patients, warranting careful consideration and monitoring during use. [10]

3. Mechanism of the Anti-tumor Effect of Mushroom Polysaccharides

3.1. Polysaccharide Structure and Anti-tumor Effect

The anti-tumor effects of polysaccharides are influenced by their structural composition. According to previous studies, high molecular weight polysaccharides may exhibit stronger anti-tumor effects. In the branching structure of polysaccharides, a branching frequency of 0.2 to 0.33 (1 in 5 to 1 in 3 backbone residues) demonstrates the strongest anti-tumor effect.10,14 In terms of conformation, the triple-helical tertiary structure of polysaccharides is the most important, as it helps maintain stability and facilitates interactions with immune cells, contributing to their anti-tumor effects. Regarding solubility, increasing the solubility of polysaccharides enhances their activity and amplifies their anti-tumor effects. In chemical modification, carboxymethylation and sulfation transform β-glucans into water-soluble forms, which enhance their immunomodulatory and anti-tumor properties. [4,10,11,12]

Most mushroom polysaccharides cannot be digested by the intestine; they act as dietary fiber. Although dietary fiber cannot be digested, fermentation by gut microbiota results in the formation of short-chain fatty acids (SCFAs). In the previous section, it was mentioned that SCFAs also possess

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anti-tumor effects. SCFAs primarily boost the activity of natural killer (NK) cells, which contributes to their anti-tumor effects. For example, butyrate's function is inhibiting the proliferation of cancer cells. Butyrate can accomplish the function of maitain the integrity of the intestinal barrier by having G-protein coupled receptors (GPCRs) that control the immune response. It also functions as a histone deacetylase (HDAC) inhibitor, and blocking HDAC activity can slow the growth of cancer cells. [20] Similarly, SCFAs have been found to influence the release of extracellular vesicles (EVs) from NK cells. EVs can carry substances that help kill cancer cells or modulate the immune response. [21] Additionally, NK cells generate cytotoxic substances that boost T cell (immune cell) activity. Increased cytotoxicity results in the death of more multiple myeloma cells (a type of cancer cell).[22]

Additionally, NK cells affect the anti-inflammatory cytokine IL-10. SCFAs decrease IL-10 secretion from NK cells, which is significant since IL-10 dampens immune activity and can facilitate tumor cell growth. Thus, lowering IL-10 levels may help to inhibit tumor cell proliferation. [21]

3.2. Immune System

Mushroom polysaccharides display anti-tumor effects through mechanisms such as halting the cell cycle, triggering tumor cell death by apoptosis and secondary necrosis, macrophage activation, and blocking angiogenesis (antiangiogenic activity). Their bioactivity and resulting anti-tumor properties are greatly influenced by structural factors such as composition, molecular weight, conformation, backbone structures, and branching patterns. [10- 12]

The numerous anti-tumor effects of mushroom polysaccharides arise from their interaction with the immune system. In Lu Ren's words, Mushroom polysaccharides function as biological response modifiers, influencing the immune system. They bind with receptors on immune cells to enhance immune activity against tumors. [10] When mushroom polysaccharides bind with immune system receptors, it will regulate the expression of pro-apoptotic and anti-apoptotic proteins via apoptosis. After then, growth of tumor cells will be inhibited. Mushroom polysaccharides stimulate the immune system, which in turn leads to anti-tumor effects. In addition to the previously mentioned modulation of pro-apoptotic and anti-apoptotic proteins, the immune system reacts with cell cycle arrest, secondary necrosis, stimulation of macrophages, and anti-angiogenetic activity. and anti-angiogenetic activity

In more detail, Mushroom polysaccharides stimulate both the innate immune system and the adaptive immune response components. In the innate immune system, mushroom polysaccharides interact with pattern recognition receptors (PRRs) on immune cells, including Dectin-1 and Complement Receptor 3 (CR3), thereby activating innate immune responses. Dectin-1 activates macrophage responses. Macrophages are essential to the innate immune system, where they function by capturing and destroying pathogens. CR3 recognizes β-glucans and produces tumor cytotoxicity by enhancing adhesion to microbial cells. [10,11,2,13] Moreover, The adaptive immune response is made up of B cells and T cells. B cells generate antibodies that target specific antigens, whereas T cells orchestrate the immune response against abnormal cells. Mushroom polysaccharides specifically boost T-helper cells (Th1 and Th2) and stimulate the production of cytokines, including TNF-α, IL-1, IL-3, and interferons (IFNs). These cytokines allow immune cells to mature and proliferate rapidly and help differentiate abnormal cells to better defend against them. [10]

3.3. Direct and Indirect Tumor Cell Death

In addition to the effects of mushroom polysaccharides on the immune system, they can also have direct or indirect effects on cells, leading to their death. Regarding the direct effects on cells, there are two types: apoptosis and necrosis. Apoptosis is a controlled and regulated process of cell death that prevents the release of harmful substances into the surrounding tissues. Polysaccharides can

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regulate the expression of pro-apoptotic and anti-apoptotic proteins. In apoptosis, polysaccharides increase the expression of pro-apoptotic proteins (Bax, Bad, Bak) and decrease the expression of anti-apoptotic proteins (Bcl-2, Bcl-xL, and Bcl-w), resulting in the initiation of apoptosis. [10]

On the other hand, Necrosis is a form of cell injury where cells die in an uncontrolled way. During necrosis, dying cells lose membrane integrity, causing their contents to spill into the surrounding tissue. This release of cellular debris, enzymes, and other molecules triggers an immune response. Then the inflammation happened. In this situation, Polysaccharides promote the production of tumor necrosis factor-alpha (TNF-α), a substance that is cytotoxic to tumor cells and induces necrosis. Because the destruction of the cell membrane is uncontrolled, necrosis itself is also uncontrollable. [9-12]

Moreover, the indirect effect on tumor cells is anti-angiogenesis. Tumor cells, like common cells, also need blood vessels to support their survival. Therefore, if tumor cells lose their blood supply, it will lead to cell death. Research by Q.-Z. Cao and Z.-B. indicates that mushroom polysaccharides may inhibit angiogenesis by reducing the secretion of angiogenic factors, including vascular endothelial growth factor (VEGF), angiostatin, endostatin, interferons, thrombospondin-1 (TSP-1), tissue inhibitors of metalloproteinases (TIMP), and tumstatin. [10,15] When angiogenesis is suppressed, the proliferation and metastasis of tumor cells are reduced.

3.4. Clinical Applications

The clinical applications and mechanisms of mushroom polysaccharides will be discussed. Mushroom polysaccharides were mentioned earlier as aids to chemotherapy and radiation therapy, and now these applications will be detailed. There are many types of mushroom polysaccharides, and some examples include Schizophyllan, which has abundant β-glucans. Schizophyllan-derived β-glucans facilitate the infiltration of numerous immune cells, including T lymphocytes and macrophages, into the tumor and surrounding affected areas. Following their destruction of cancer cells, these macrophages and lymphocytes strengthen the interleukin-2 (IL-2)/interleukin-2 receptor (IL-2R) system. IL-2's primary purpose is to activate lymphocytes to eliminate cancer cells.

In a related context, β-glucans from maitake promote granulopoiesis and stimulate the production of granulocyte colony-stimulating factor (G-CSF). They also regulate CXCR4 (C-X-C chemokine receptor type 4) and SDF-1 (stromal cell-derived factor-1) expression. One kind of white blood cell that aids in the fight against infections is the granulocyte. β-glucans from maitake enhance granulopoiesis via G-CSF. After chemotherapy and radiation therapy, patients often need to produce granulocytes through G-CSF because these therapies have the potential to dramatically lower immune and white blood cells. In this situation, weakens the body’s immunity, making granulopoiesis essential for restoring immune function. According to a study by Koichi Ito, MD-Fraction (purified β-glucans from maitake) reduces CXCR4/SDF-1 expression. CXCR4/SDF-1 is responsible for binding to various immune cells to regulate them, thereby playing a critical role in cancer progression and immune cell trafficking.[23] In cancer, tumor cells often utilize CXCR4/SDF-1 expression to migrate to SDF-1-rich organs. Saima Hassan provides an example related to breast cancer. When individuals exhibit elevated p-CXCR4 expression alongside reduced plasma SDF-1 levels, cancer cells face an increased risk of metastasis, potentially migrating to organs with higher SDF-1 levels due to the SDF-1 gradient. [25] According to SDF-1 gradient, Decreasing CXCR4/SDF-1 expression prevents cancer cells from exploiting this pathway to migrate to other organs,[23,24] thereby reducing the metastatic risk, which is beneficial for cancer therapy.

β-glucan from P. linteus is also useful for clinical therapy. Chemotherapy is a well-known cancer treatment that interferes with the division and replication of cancer cells, targeting fast-growing cells in the body. The impact of β-glucan from P. linteus on clinical cancer treatment is notable. It has the ability to activate caspases-3 and -8.[26] Caspases play a central role in apoptosis; when a caspase is

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activated, it initiates a cascade that activates more caspases, ultimately leading to cell death by cleaving specific cellular proteins.[27] When β-glucan from P. linteus is used alongside chemotherapeutic drugs, it can enhance the drugs' effectiveness in killing cancer cells. However, chemotherapeutic drugs often have side effects, such as anemia, which may result from the suppression of bone marrow and direct damage to red blood cells (RBCs). This can alter the biophysical properties of RBCs, making them fragile and more prone to destruction, ultimately affecting patients' health. By utilizing β-glucan, patients may require a lower dosage of chemotherapeutic drugs, enhancing the drugs' cancer-killing ability while reducing their side effects.[26,28]

4. Discussion and conclusion

In recent years, attention has been drawn to the relationship between diet and cancer. Nutrition is becoming increasingly important in cancer prevention and treatment. The antitumor effects of different foods have been the subject of numerous studies and articles; the main focus of this essay is on the polysaccharides found in mushrooms. To begin with, gut microbiota has a significant role in cancer. Dysbiosis of the gut microbiota can contribute to diseases like colorectal cancer (CRC), indicating that mushroom polysaccharides may impact gut microbiota to produce antitumor effects. They function as prebiotics, probiotics, and synbiotics improve gut microbiota. Production of short-chain fatty acids (SCFAs), which decrease the release of the anti-inflammatory cytokine IL-10, increase the cytotoxicity and proliferation of natural killer (NK) cells, and stimulate antitumor immune responses.

Mushroom polysaccharides induce cancer cell death through three additional mechanisms. One well-known mechanism involves their interaction with the immune system to activate immune responses. Additionally, they can cause cancer cell death both directly and indirectly. Indirectly, they promote cancer cell death through an anti-angiogenesis effect.

Moreover, various studies indicate that structure of mushroom polysaccharides affect their antitumor efficacy, such as the molecular weight, branching patterns, solubility, and tertiary conformation. It suggests that structural modifications can enhance their effects. Furthermore, in clinical treatment, mushroom polysaccharides can be used in conjunction with chemotherapy to improve therapeutic outcomes.

5. Limitations and Future Directions

To completely comprehend the therapeutic effects of mushroom polysaccharides on cancer, more information and investigation are required. Future studies should explore their potential as adjuncts in cancer treatments.

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