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Clinical application of highly agglutinative staphylococcin in cancer treatment updates of the literature

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Abstract. – This review article summarized 100 published research papers and reviewed the application status of highly agglutinative staphylococcin in the clinical treatment of cancer. Highly agglutinative staphylococcin (HAS) derives from the superantigen of Staphylococcus aureus metabolite. Studies have shown that HAS can inhibit and kill tumors, repair tissues and cells, increase white blood cell count and improve the immune function. Its immunological effect acts through the following mechanism: activating T-cells and natural killer cells, enhancing phagocytes' phagocytosis and killing ability of lymphocytes, increasing white blood cell count in peripheral blood, repairing impaired histocytes, and inhibit the growth of tumor cells. Highly agglutinative staphylococcin is used in clinical treatment of tumors: intracavitary hyperthermic perfusion with single HAS is effective for malignant ascites; perfusion with HAS plus chemotherapeutics can remarkably improve the elimination rate of ascites. Highly agglutinative staphylococcin can also enhance the effect of and improve the response rate of chemotherapy and radiotherapy, and improve patients' immune function and relieve gastrointestinal reactions caused by radiotherapy and chemotherapy. Therefore, HAS is used to treat a malignant tumor, leucocytopenia, and malignant ascites, and relieve side effects caused by radiotherapy and chemotherapy and improve patients' immune function.

Key Words:
Highly agglutinative staphylococcin, Immune function, Cancer therapy, Combination therapy.

Introduction

Staphylococcal enterotoxin (SE) is a protein with high biological activity and a superantigen (SAg). It is a bacterial exotoxin with a strong stimulating capability and a variety of immunological activities. It stimulates a large number of T lymphocytes, promoting differentiation into viable cytotoxic T-cells, activating monocytes of NK cells, and promoting secretion of cytokines (including leukocyte interleukin-2, interferon, tumor necrosis factor, colony stimulating factor)[1,2]. Staphylococcal enterotoxin not only has substantial tumor-inhibiting effect, but also can elevate white blood cells simultaneously. Currently, it is known that SE has 14 serotypes (SEA, SEB, SEC, SED, SEE, SEG, SEH, SEI, SEJ, SEK, SEL, SEM, SEN and SEO), amongst which SEC has three subtypes, EC1, SEC2 and SEC3. SEP, SEQ, SER, and SEU[3]. Worldwide attention is focused on SE research, and more than 4500 related research articles have been identified from Medline database. In order to improve drugability of SE in tumor research, many researchers have focused on recombination of SEA, SEB, SEC, to obtain new SE products. Progress has been made in maintaining its anti-cancer activity and reducing gastrointestinal side effects. This practice is used mainly in the oriental medicine.

Highly agglutinative staphylococcin derive from the *Staphylococcus aureus* metabolite super antigen. Studies[4,5] that HAS inhibits and kills tumors, repairs tissues and cells, elevates white blood cell count, and improves immune function. Highly agglutinative staphylococcin is a biological bacterial response modifier extracted from *Staphylococcus aureus* metabolite which is efficient, has low toxicity and a significant enhancing effect on immunity. Highly agglutinative staphylococcin immunological effect acts by activating T-cells and natural killer cells, enhancing phagocytes' phagocytosis and destroying lymphocytes, increasing white blood cell count in peripheral blood, repairing impaired histiocytes, as

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well as directly inhibiting the growth of tumor cells[6].

Since 1998, studies on the clinical application of HAS have drawn attention in China and made significant progress. This article focuses on the pharmacological characteristics of HAS, the experimental anti-tumor therapy with HAS, the immunopharmacology research and the clinical application of HAS.

Immunopharmacological Characteristics

An antigen is a substance that can cause the immune response and stimulate immune cell proliferation. Antigens can be divided into two groups according to their ability to activate immune cells: ordinary antigens and super antigens. During the specified time, the common antigens, such as ganoderma, ginseng, aloe, nucleic acids, polysaccharides, chitosan and many other materials, can activate 1/10000-1/1,000,000 immune cells. The super antigens can enable 5-40% of the immune cells, about 2000-50000 times higher than the common antigens. Therefore, super antigens play a far greater roles in activating human immune cells and regulating the immune function. As early as 1970s, Peavy et al[7] and Langford et al[8] investigated the SE's stimulating activity with the mouse and human T-cells. With the development of modern immunology and further research on T-cells in 1960s, it has been gradually realized that both T-cells and B cells can produce tolerance independent of each other. based on the tolerance-producing principles. The T and B cells may be introduced in the treatment of autoimmune diseases and allograft. The immune function of SAg is achieved through TCR's two recognition functions. (1) SAg can be recognized by TCR after combining with MHC II molecules on the surface of APC or target cells to form complex (dual recognition effect on antigen Ag, and MHC I and II molecules). (2) Some specific molecules can recognize SAg that has combined with MHC II molecules called Vβ on the surface on TCR (V β specific). Thus, the T-cells can be activated and generate immune responses. White's experiment has found that stimulation of T-cells can be achieved when meeting the following two conditions: binding of SE and MHC II molecules; appropriate Vβ contained in T-cells. According to this fact, White proposed the concept of superantigen[9]. Since 1990s, there have been many investigations focusing on super antigens, which extensively investigated the immunologic, toxic, and anti-tumor mechanisms.

The generic name of HAS injection is staphylococcin injection. HAS is a super antigen, a new anti-tumor drug approved in China. It is the first anti-tumor super antigen biologics in the world[10]. The main ingredients of HAS include proteins, peptides, 18 kinds of amino acids, and free coagulase. Its active ingredient, SEC, can activate and proliferate T-cells, to produce cytotoxin and kill tumor cells. Meanwhile, it can also induce T-cells and other immune cells to produce various cytokines, directly or indirectly playing a role in killing the tumor cells. After years of clinical application, HAS showed its therapeutic characteristics in clinical pharmacological effects.

Anti-cancer Mechanism of HAS

The existing research concludes that the anti-cancer mechanism of the superantigens can be clarified from the following four aspects: 1) Apoptosis mechanisms of cancer cells: when the T-cells are activated, various cytokines, such as interleukin, interferon and tumor necrosis factor, can destroy vascular endothelial cells of the tumors, promote thrombosis and reduce blood supply to the tumor tissues, resulting in tumor cell necrosis and apoptosis. Cytokines also stimulate proliferation and differentiation of T-cells, which will in return produce more cytokines, so as to form endogenously circulating biological effects and speed up the apoptosis of cancer cells. 2) Dissolution mechanism of cancer cells: when the T-cells are activated by super antigens, CD4+ and CD8+T-cells are induced to produce cytotoxin. This super antigen-dependent cytotoxin-specific fusion protein has a strong affinity for the tumor cells, and are able to dissolve the cancer cells in a rapid way. 3) Clearance mechanism: when the T-cells are activated, the resulting interleukin can induce the activation of LAK cells that have broad anti-tumor effects. After being activated, LAK cells can clear cancer cells that are difficult to be eliminated. 4) Anti-metastasis mechanism: SAg activates NK cells. The protein and cytolysin released by NK cells can perforate the tumor cell membrane, resulting in intracellular fluid outflow and apoptosis. This mechanism plays a significant role in the immune surveillance against cancer cells and can prevent cancer metastasis when the cancer cells sharply increase.

Zhao et al[11] investigated the inhibiting effect of HAS on bladder cancer growth in mice in 2003. In the experiment, BT3 tumor cells were inoculated into Tm mice, to establish the test models; observe the local inhibiting effects of different radiation doses and HAS on the tumors. The mice were treated after inoculation with highly agglutinative staphylococcin and the results showed on day 16 that the tumor inhibition rates in the HAS group,

radiation 5Gy group and radiation 5Gy + HAS group were 34%, 3.2% and 52.9%, respectively. The mice were treated seven days after inoculation with highly agglutinative staphylococcin and the corresponding results showed that the tumor inhibition rates in the HAS group, radiation 5Gy group and radiation 5Gy + HAS group were 27.0%, 84.9% and 84.6%, respectively, and 80.7% and 84.1% in radiation 8Gy group and radiation 8Gy+HAS group, respectively. The experiment concluded that HAS would not interfere with the tumor-inhibiting effect of the radiotherapy.

Fan et al[12] randomized 230 medium and advanced cancer patients to the treatment and control group. One hundred and 16 patients from the treatment group, received combination therapy with HAS + chemotherapy; 114 patients from the control group received single chemotherapy. Changes in quality of life, white blood cell count, T cell subsets, NK cell activity and tumor volume in the two groups were observed. Thirteen indicators (including appetite, strength, weight, sleep quality, mental status) of the patients were evaluated. Results showed that the post-treatment quality of life in both groups improved, with an effective rate of 70.7% in the treatment group and 41.1% in the control group. There was an extremely significant difference between the two groups ($p < 0.01$). The post-treatment white blood cell counts decreased in both groups by varying degrees, including 39 (33.6%) cases in the treatment group and 65 (57.0%) instances in the control group; counts which decrease below 4.0×109/l were significantly different between the two groups ($p < 0.01$). In the treatment group, the pre-treatment CD3, CD4, CD8, CD4/CD8 and NK activity were 43.77 ± 10.5, 27.06 ± 9.0, 19.71 ± 8.20, 1.48 ± 0.71 and 25.18 ± 13.2, respectively. The post-treatment values were 44.0 ± 12.7, 32.36 ± 9.2, 19.12 ± 6.20, 1.67 ± 0.76 and 25.221 ± 5.1, respectively. In the control group, the pre-treatment values were 44.61 ± 10.84, 29.4 ± 37.95, 18.21 ± 7.80, 1.60 ± 1.36 and 24.79 ± 14.09, respectively. The post-treatment values were 36.75 ± 11.0, 25.20 ± 7.37, 18.95 ± 8.01, 1.33 ± 1.02 and 21.36 ± 12.86, respectively. The results showed that the post-treatment CD4 and CD4/CD8 values in the treatment group apparently increased compared to the pre-treatment values, with significant difference. The post-treatment CD3, CD4, CD4/CD8 and NK cell activity in the control group significantly decreased compared to the pre-treatment values, with significant difference. Comparing the post-treatment values of the two groups, CD3, CD4, CD4/CD8 and NK cell activity values in the treatment group were higher than the corresponding values in the control group, with statistically significant difference ($p < 0.01$). The response rate (CR+PR) after one treatment course was 58.6% in the treatment group, and 36.8% in the control group, with highly significant difference in the tumor volume change between the two groups ($p < 0.01$). The clinical data showed that HAS plays an important role in improving immune function in cancer patients, inhibiting tumor cell growth, protecting bone marrow haematopoietic function of patients undergoing chemotherapy, and improving the quality of life of the patients, with curative short-term effect.

Application in Tumor Therapy

By retrieving the Chinese Core Technical Journal, we identified 100 research papers related to clinical applications published by Chinese researchers between 2001 and 2007, involving clinical observations results of the HAS application in tumor treatment in nearly 3000 cases (Table I).

The significant effect of HAS has been confirmed in the clinical application in 10,000 patients with various types of cancers. The adverse reactions were mild, and no severe reactions were observed. The effect was particularly satisfactory when used in combination with radiotherapy or chemotherapy. The efficacy of single HAS had the following characteristics which could distinguish HAS from other anti-cancer drugs. The response rate for the 1000 cancer patients (various types) is 42.5%, calculated according to the volume change of solid tumors, not associated with normal organ damage and white blood cell count decrease. The quality of life was also greatly improved. This was the best effect so far that is difficult to achieve with chemotherapy or radiotherapy alone. Results from a comparative study (involving 378 cases) in which HAS was used in combination with chemotherapy or radiotherapy showed that, HAS can significantly improve the response rate when used in combination with chemotherapy or radiotherapy (Table II)[13].

Chen et al[14] treated advanced gastrointestinal tumors with superantigen HAS in combination with chemotherapy in the clinical studies, and the results showed that HAS can effectively increase and maintain white blood cell count, improve neutrophil levels, prevent bone marrow suppression induced by chemotherapy drugs, and enhance patients' tolerance to chemotherapy. The Karnofsky score in the treatment group increased with a significant difference compared to the control group. The main results can be reflected in the following aspects: 1) changes in peripheral hemogram: blood routine parameters before and after treatment im-

Table I. Clinical application of highly agglutinative staphylococcin in cancer therapy

Number	Therapeutic applications	Cases	Reference No.
1	Injection at tumor area as interventional treatment of liver cancer	22	13
2	Injection at intrahepatic tumor area as collaborative treatment of liver cancer	86	(14,15)
3	Local injection into the tumor body as treatment of bronchogenic carcinoma	10	16
4	Intrathoracic injection therapy for lung cancer resection patients	58	17
5	Intratumoral injection therapy for radiotherapy -resistant malignant neck cancer	33	18
6	Highly agglutinative staphylococcin therapy for malignant pleural effusion	955	(19-35)
7	Highly agglutinative staphylococcin therapy for recurrent pneumothorax	29	36
8	Highly agglutinative staphylococcin therapy for malignant hydrothorax and ascites	261	(37-41)
9	Therapy for malignant advanced ovarian cancer and malignant ascites	119	(42-44)
10	Highly agglutinative staphylococcin therapy for malignan hydropericardium	21	45
11	Intractable subcutaneous hydrops	5	46
12	Used with platinum-based preparations	858	(47-70)
13	Combination therapy of bleomycin and highly agglutinative staphylococcin	32	71
14	Combination therapy with 5-fluorouracil for esophageal cancer	52	72
15	Combination therapy of highly agglutinative staphylococcin (HASL) and VP-16 for lung cancer complicated by hydrothorax	136	(73, 74)
16	Combination therapy of highly agglutinative staphylococcin and hydroxycamptothecine for lung cancer	102	(75, 76)
17	In combination with chemotherapy for non-small cell lung cancer	61	77
18	Highly agglutinative staphylococcin combination therapy for esophageal squamous carcinoma	28	78
19	Highly agglutinative staphylococcin in combination with chemotherapy for cancerous ascites	100	39
20	Highly agglutinative staphylococcin in combination with chemotherapy for colon cancer	222	(79, 80)
21	Highly agglutinative staphylococcin therapy for myelosuppression and gastrointestinal reactions caused by chemotherapy drugs	68	81
22	Highly agglutinative staphylococcin combination therapy for medium and advanced liver cancer	108	82
23	Intratumoral injection of highly agglutinative staphylococcin in combination with radiotherapy for cervical lymph node metastasis	32	83
24	Intratumoral injection of highly agglutinative staphylococcin in combination with radiotherapy for cervical lymph node metastasis	60	84
	In total	3458	

Table II. Effect of highly agglutinative staphylococcin combined with chemotherapy or radiotherapy

Types of cancers	Therapeutic methods	Number of cases	CR+PR (%)	Decrease in WBC count (%)	Improvement in quality of life (%)
Various cancers	Chemotherapy alone	114	36.8	57	41.1
	Combination therapy	116	58.6	33.6	70.7
Nasopharynx cancer (50Gr)	Radiotherapy alone	40	35.6*		
	Combination therapy	108	80.6*		

*Disappearance rate of lesions.

proved in 30/42 patients, and percentages of the white blood cells and neutrophils increased in all the patients who used HAS during chemotherapy.

Post-chemotherapy blood routine results of patients who received HAS during chemotherapy: a decrease in 8 cases (8/30), with no significant changes in the rest of the cases. The WBC levels of 28 instances in the single chemotherapy group were determined before and after chemotherapy (within 2 weeks after chemotherapy), and the WBC levels of the 17 cases (17/28) decreased after chemotherapy in varying degrees, $p < 0.025$, with significant difference between the two groups. (2) The Karnofsky scores of 57.4% of the 48 patients increased while

37.5% in the control group, with a significant difference ($p < 0.025$). (3) Efficacy evaluation: 31 non-surgical patients in the treatment group, including two cases (2/31) of CR, 12 cases (12/31) of PR, 11 cases (11/31) of SD, and six cases of (6/31) PD, constituting a total response rate of 45.5%. 30 non-surgical patients in the control group, including one case (1/29) of CR, 11 cases (11/30) of PR, 12 cases (12/30) of SD, and eight cases (8/30) of PD, constitute a total response rate of 40%. The study concluded that HAS, as an adjuvant therapy to chemotherapy for advanced gastrointestinal cancer patients, can improve and maintain the number of white blood cells, prevent bone marrow suppression induced by chemotherapy drugs, enhance patients' tolerance to chemotherapy, and significantly improve the patients' quality of life.

The primary adverse reaction is fever, which can vanish with no treatment. The drug can be used safely in clinical practice. It is considered that the superantigen produces effective anti-tumor effect through immune enhancement, and studies show the following characteristics of HAS application in tumor patients: combination therapy with chemotherapy or monotherapy in tumor patients who were not suitable for chemotherapy can both strengthen the anti-tumor efficacy, increase white blood cells, improve patients' quality of life and tolerance to chemotherapy. However, the super antigen has high ability to activate lymphocytes. Thus, even a trace of super antigen can enable a large number of T-cells, which will further secrete a variety of cytokines. Therefore, inaccurate dosage in clinical application may cause immune disorders of the body[15]; long-term repeated use can also cause immune tolerance of the body[16]. Therefore, there are still many problems with the application of super antigen in clinical treatment of tumors that need to be solved. Questions about accurately controlling the dosage of the super antigen and course of treatment, combined with chemotherapy or radiotherapy (in order to maximize the synergistic anti-tumor effect) are worth discussing and require extensive experimental and clinical studies.

Clinical observation results from intrathoracic injection of HAS in combination with cisplatin for the treatment of malignant pleural effusion have been published. Forty cases of malignant pleural effusion were confirmed through pathological diagnosis. They received intrathoracic injection of 10 ml HAS and 80 mg-100 mg cisplatin after ejecting pleural effusion through transthoracic intubation tube. The procedure was repeated after two weeks, to observe the efficacy, improvement in quality of life and toxicity reaction. The clinical results showed marked effect in 25 cases and effect in 12 cases in the treatment group, constituting a total response rate of 92.5%, and 32 cases and 26 cases in the control group, constituting a total response rate of 81%, with significant difference between the two groups ($p < 0.05$). It was concluded that intrathoracic injection of HAS in combination with cisplatin was an effective and a well-tolerated therapeutic approach for malignant pleural effusion, with few side effects[17].

The efficacy of intraperitoneal administration of HAS in combination with chemotherapy drugs (FEM) in the treatment of ascites of patients with malignant gastrointestinal tumors. They randomized 140 patients with gastrointestinal tumors and malignant ascites to HAS treatment group (group A), FEM chemotherapy group (group B) and FEM+HAS treatment group (group C) according to the random numbers. The following results were obtained: the response rate of group C (34.5%) was higher than that of group A (13.3%, p=0.027), while no significant difference was observed between group C and group B (20.2%) (p>0.05). The efficacy of gastric cancer was the highest, followed by pancreatic and colon cancer; liver cancer had the poorest efficacy. Group A had the fewest side effects (22.2%), while group B had the most side effects (97.5%); side effects in group C (56.4%) were decreased compared to group B ($p < 0.001$). It was concluded that intraperitoneal administration of HAS in combination with chemotherapy drugs in the treatment of ascites of patients with malignant gastrointestinal tumors not only improves the anticancer efficacy of chemotherapy drug, but also reduces the side effects of chemotherapy drugs[18].

Malignant pleural effusion refers to pleural metastasis of malignant tumors or pleural effusion caused by malignant tumors of the pleura itself. Pleura is not sensitive to systematic chemotherapy due to its special anatomic features. Thus, it is difficult to achieve effective drug concentration in the pleura, which is a difficult point in clinical practice. However, intrapleural administration routine can ensure the high concentration chemotherapy drugs act directly on the pleural cancerous nodes and exfoliating cancer cells, to enhance the killing ability of chemotherapy drugs to tumor cells, without increasing the toxicity. Cisplatin is a non-cell cycle-specific drug, especially with strong killing ability to cells during mitosis and DNA synthesis phase and extremely powerful penetrating ability. After intrathoracic administration, high concentration cisplatin can enter into the tumor body directly or indirectly

through the transport of capillaries, to kill tumor cells in a wider site. In recent years, the response rate of cisplatin (monotherapy) has been reported to be 45%-67%; this rate may be improved to some degree when used in combination with other chemotherapy drugs. In the data control group, cisplatin and vindesine were used to treat patients with malignant pleural effusion, and a total response rate of 81% was achieved, but the toxicity was significantly increased[18]. Patients with malignant pleural effusion are usually of higher ages, and most of them are unwilling to receive the treatment. The cellular immune function in patients with malignant tumors is generally reduced to varying degrees and will be further reduced to the deteriorating conditions. Worse immune function of the cells suggested poorer prognosis of the patients. The T cell subset is the most important cell population of the immune system. Although chemotherapy is a therapeutic approach for tumors, it can further decrease immune function of the patients, especially the cellular immune function, which is not conducive to long-term tumor control and easy to induce tumor recurrence and metastasis[19]. Highly agglutinative staphylococcin is a new novel anti-tumor biological response modifier and its main ingredient is enterotoxin C. It can strength activity of NK cells and LAK cells, and increase transformation rate of the lymphocytes, with particular strong stimulating effect on T-cells, which will produce interleukin (IL), interferon (IFN), tumor necrosis factor (TNF), colony stimulating factor (CSF), and many other cytokines, to activate activity of the body's immune system and enhance the ability to kill tumor cells, without any damage to healthy cells. Furthermore, it can repair the damaged cells, so as to restore immune function of the body, reduce tumor recurrence, and reduce the incidence of distant metastasis[20,21]. Intrathoracic insertion of central venous catheter is simple to use, characterized by minor damage, thorough drainage and long-term retention (reducing pain of repeated puncture). Intrathoracic chemotherapy with combined HAS and cisplatin can produce synergic effect and kill cancer cells, able to induce aseptic adhesion of pleura and prevent re-increase in pleural effusion. HAS can also reduce gastrointestinal side effects caused by chemotherapy and improve the general condition of the patients. In summary, the total response rate in this group (HAS + cisplatin) was 92.5%, significantly higher than 81% of the data control group ($p < 0.05$), and the quality of life was improved, with significantly reduced side effects, indicating that this treatment method is simple and efficient.

Cisplatin is a cell cycle-specific drug, able to kill various tumor cells and induce apoptosis, as well as stimulate pleura cell proliferation, fibrosis, and stop vicious exudation[22]. Cisplatin is a new novel anti-tumor biological response modifier applied in clinical practice in recent years. Yang et al[23] investigated the clinical value of combination therapy of HAS and cisplatin in the treatment of advanced cancer complicated by malignant ascites. Their clinical results showed that the response rate of the combination therapy of HAS and cisplatin was as high as 81.30%, significantly higher compared to single use of HAS or cisplatin ($p < 0.05$). This response rate (81.30%) was also higher than the response rate of the novel recombinant human interleukin-2 reported by Wu et al[24] in treatment of malignant pleural effusion (73.33%), and similar to the response rate (83%) of thoracic injection of cisplatin and fluorouracil reported by Sui et al[25] in treatment of 58 cases of malignant pleural effusion. But patients treated in this group (HAS and cisplatin) reported no alopecia, fewer leukopenia, nausea and other adverse reactions, which was related to the fact that high biological activity of HAS can promote increase of white blood cells and platelets of the body. Ma et al[26] observed the efficacy and adverse reactions of combination therapy of HAS and cisplatin in the treatment of malignant pleural effusion. They randomized 48 patients with malignant pleural effusion to two groups. Pleural effusion of patients in both groups was ejected as thoroughly as possible. Twenty-four patients in the treatment group received HAS+ cisplatin; 24 patients in the control group received monotherapy with cisplatin. Results: the response rate was 87.5% in the treatment group, significantly higher than 58.3% of the control group. It was also concluded that HAS+ cisplatin was quite effective in the treatment of malignant pleural effusion, with fewer adverse reactions. Recently, Li et al[27] demonstrated the therapeutic value of HAS in treatment of 200 cases of malignant tumors.

Conclusions

Clinical applications for many years have demonstrated the following six clinical pharmacological effects of HAS: (1) Activating T-cells and promoting their proliferation, to improve immune function of the body. (2) Using HAS alone to prove its anti-cancer effects, which endow HAS with extremely broad application prospects. (3) Elevating white blood cells have a strong WBC elevating ef-

fect, and is especially suitable for chemotherapy-induced WBC decline. (4) Eliminating malignant hydrothorax and ascites: intravesical infusion of HAS alone is significantly effective; combination therapy with chemotherapy drugs can significantly improve elimination rate of pleural effusion. (5) Improving the efficacy of radiotherapy and chemotherapy: HAS can significantly improve the response rate of single chemotherapy or radiotherapy when used in combination. (6) Improving immune function of the patients and reducing gastrointestinal side effects caused by radiotherapy and chemotherapy; the main indications include malignant tumors, leukopenia, malignant pleural effusion, side effects caused by radiotherapy- and chemotherapy-induced immune dysfunction. The main side effects include fever and local swelling, which can vanish within a short time without any treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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