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THE ROLE OF LENTINAN IN CANCER TREATMENT: IMMUNOMODULATORY EFFECTS AND THERAPEUTIC SYNERGY

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ABSTRACT
Lentinan, a polysaccharide extracted from the edible mushroom Lentinula edodes (shiitake), has received considerable attention in cancer research owing to its immunomodulatory as well as anticancer properties. The article represents a review aiming at summarizing our current understanding of the mechanisms of action of lentinan, its efficacy against different types of cancers, and its promise as an adjunct therapy. The therapeutic potential of lentinan is convincingly supported by a thorough review of the most recent scientific studies as a guide to future research. Mushrooms, it is estimated, number about 140,000 species on Earth; only 10% have been identified with around 14,000 named species, and mushrooms are a vast, relatively unexploited source of powerful new pharmaceutical products. They are of the greatest importance for modern medicine by providing an unlimited source of polysaccharides with antitumor and immune-stimulating properties. Most, if not all, species of Basidiomycetes fungi contain biologically active polysaccharides in their fruit bodies, cultured mycelium, and culture broth. Data on mushroom polysaccharides have been accumulated from 651 species and 7 infraspecific taxa representing 182 genera of higher Hetero- and Homobasidiomycetes. These polysaccharides show varying chemical composition; nevertheless, the largest percentage is categorized as β-glucans. These have β-(1→3) linkages in the main chain and, in addition, other β-(1→6) branch points, which are important for their antitumor effect.

KEYWORDS: Lentinan, cancer , Immunomodulatory, antitumor , mushroom, polysaccharide.

INTRODUCTION

Despite the years put into cancer research, it is still a significant source of disease and death worldwide. New therapeutic agents have been specifically of interest, and among these, lentinan has garnered attention because it can enhance immune response as well as inhibit tumors. This review comments on the pharmacology, mechanisms, and clinical uses of lentinan in the treatment of cancer.[1]

Chemical Structure and Properties of Lentinan: Lentinan is a β-glucan that primarily consists of D-glucose units joined by both β-(1→3) and β-(1→6) glycosidic bonds. Its specific structure might be the main cause for its biological activity, which may comprise immunomodulation and anticancer effects. Shiitake is a mushroom that people have been using as an edible fungus in traditional Chinese medicine for nourishing blood and qi. Lentinan (LNT) is a very potent active principle isolated from shiitake mushrooms, responsible for its antioxidant, antiinflammatory, and anti-tumor activities. The leading causes of death in many parts of the world include inflammatory diseases and cancers; hence an urgent need exists for more effective treatments.

LNT has gained recognition as an adjunctive treatment to chemotherapy in China and Japan, and from the conducted studies, it would appear that LNT has significantly contributed towards the management of inflammatory and oncological conditions. Findings from clinical trials reveal that LNT administered with chemotherapy reagents improve the patients' prognosis, amplify the immune response, and inhibit other side effects for lung, colorectal, and gastric cancers. The detailed mechanisms by which the LNT pathway is involved in inflammatory diseases and cancers remain undetermined.[2]

Structural features of polysaccharides responsible for their bioactivity

Studies on the polysaccharides' structure and functions highlighted crucial structural features important to play an immune activator role. The form and structure of such polysaccharides, for example: influences from glycosidic linkages, the formation of helical structures, etc., play a great role in the biological functions of these polymers. For instance, glucans have been shown to possess crucial biochemical properties through their (1→3)-β-linkages in the main chains. This specific configuration has been identified as critical for the immunoenhancing and antitumor activities of the polysaccharides. Other β-glucans that have both mixed linkages (1→4) in addition to the (1→3) linkages, however, have very little, or no activity towards either immune enhancement or anticancer uses.

Triple helical conformation is another major structural feature of (1→3)-β-glucans. The capacity of these polysaccharides to be recognized by specific receptors of the body is associated with their ability to elicit an immune response, and this may be an important function of these polysaccharides. A third factor affecting their immunostimulatory potential is the degree of branching of these polysaccharides. As a general rule, more highly branched β- (1→3)-glucans that are more branched at the (1→6) branch points—that is, a branching degree around 0.33—display greater immunostimulatory and anticancer potency than their more lightly branched or even linear counterparts. It is significant that the greater the branching in β-(1→3)-glucans, the tighter will be the triple helical structure they exhibit and thus the higher the effective immune-enhancing effect.[3]

Further, β-(1→3)-glucans substituted with peptides or proteins have been known to increase their immunopoten-tiation capacity. Polysaccharides of higher molecular weights also tend to show greater immunoenhancing effects. Further studies on α-(1→4)-D-glucans, sharing structural forms and similar molecular weights, reported that a lesser degree of branching favors immunostimulatory activities. In doing so, the issues regarding the complexity of polysaccharides in the structure-function relationship, as well as these glycoproteins and their accompanying functions in health and disease, are further ascertained. Different species of mushrooms express these polysaccharides, which are also established to have antioxidant properties, establishing the importance of such biological molecules in nature.[4,5,6]

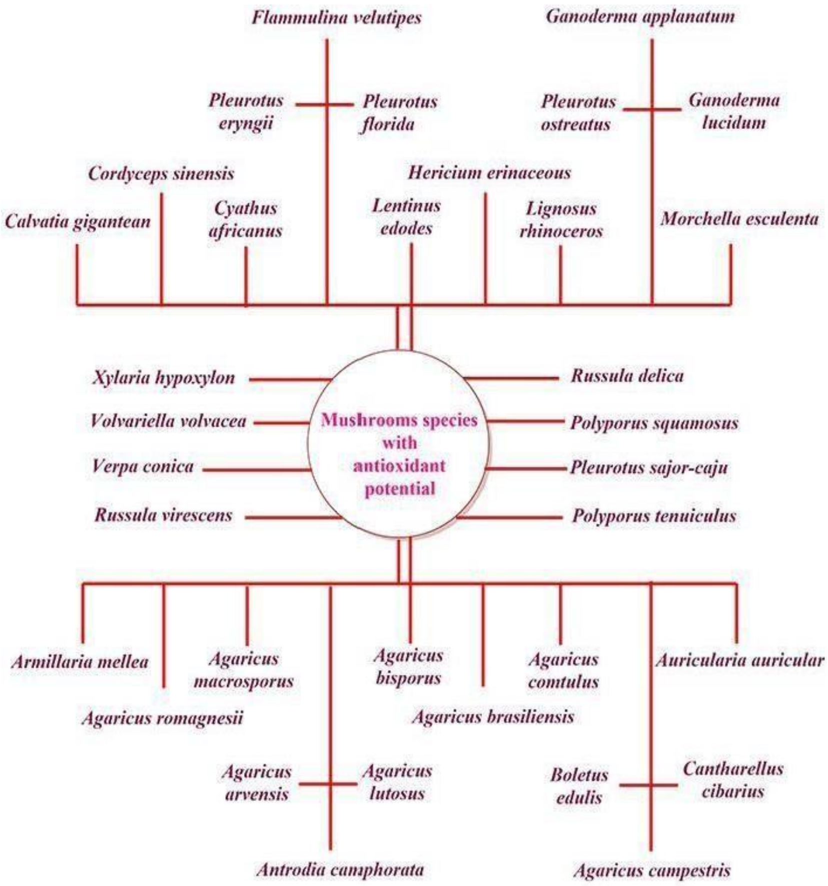


Fig. 1: Different varieties of mushrooms showing antioxidant potential.

Structure of lentinan

Examined the different structures and components found in lentinan. Among these elements, β-glucan is particularly significant due to its connection to immune function, a link that has been well-established in earlier studies. Notably, Sasaki and Takasuka provided an in-depth analysis of the primary structure of β-glucan in lentinan. Their research showed that it consists of a β-(1-3)-glucose backbone with (1-6)-β-glucose branches occurring after every two glucose units, as depicted in Figure 1. These structural complexities highlight the distinctive characteristics of β-glucans and their influence on biological activities. The variations in biological activity seen in different β-glucans can be traced back to their unique structural features, emphasizing the need for further research to fully understand these compounds and their implications for the immune system.[7]

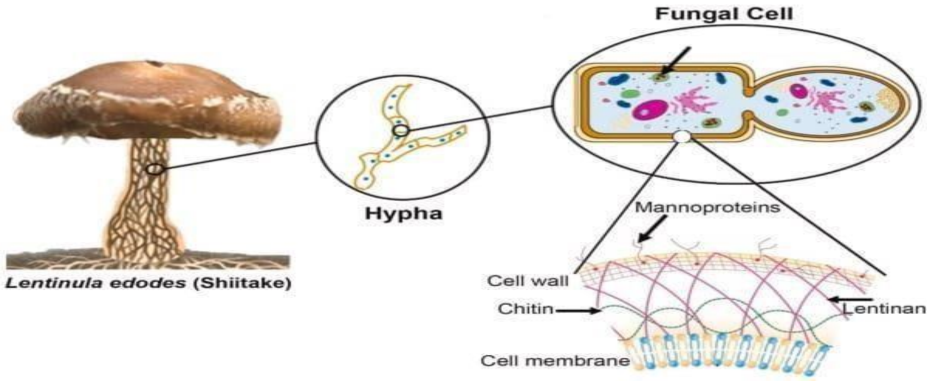


Fig. 2; Structure of lentinan.

Lentinan as anti cancer agent

Lentinan has shown encouraging results in treating various cancers, such as breast cancer, lung cancer, brain tumors, lymphomas, and more. Research has explored the mechanisms behind lentinan, emphasizing its role as an inducer of reactive oxygen species, a mitotic kinase inhibitor, an antimitotic agent, an angiogenesis inhibitor, and a topoisomerase inhibitor. These characteristics of lentinan ultimately lead to apoptosis, which helps inhibit cancer proliferation. Recent studies have highlighted how lentinan exhibits significant antitumor potential. A thorough understanding of lentinan's anti-tumor and immunomodulatory mechanisms has been well-documented in numerous studies and publications, underscoring its significance in cancer treatment and research.[8,9,10]

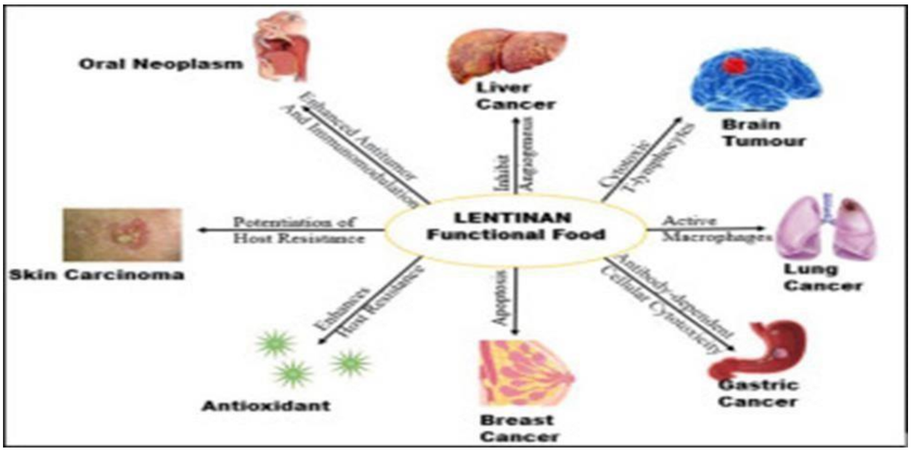
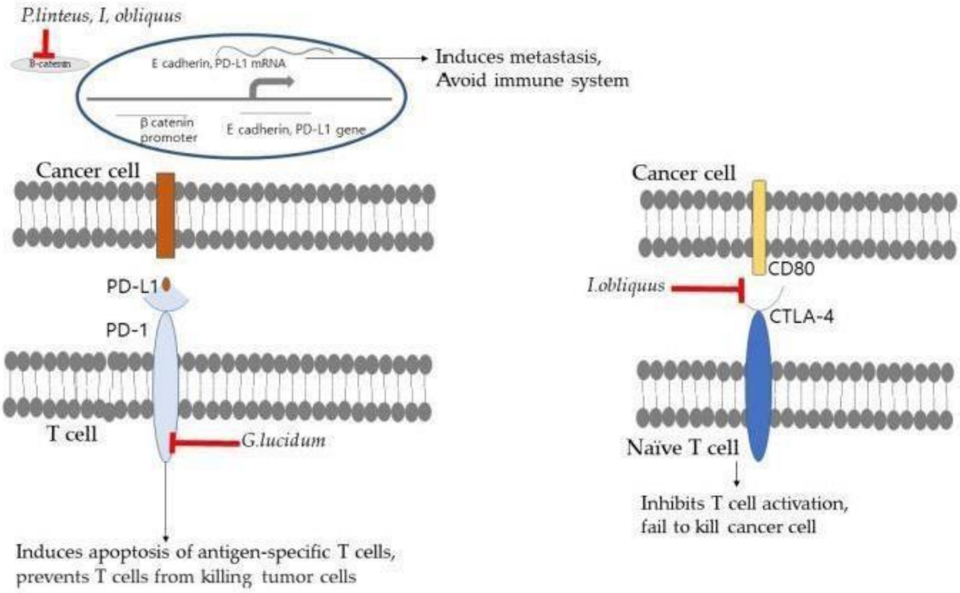


Fig. 3: Lentinan as functional food.

Immunostimulatory effect

Research has shown that β-glucan, the main component of lentinan, plays a vital role in the immunoregulation process linked to lentinan. Its significance lies in its ability to trigger various signaling pathways, such as MAPK-NFκB and Syk-PKC, by engaging with different pattern recognition receptors like TLR2/4/6/9 and Dectin-1, as well as other important membrane receptors like CD11b. This interaction activates key immune cells, including NK cells, macrophages, and T cells. A detailed study by Peng et al. used self-prepared lentinan to stimulate mouse spleen lymphocytes, providing further insights into the immunomodulatory effects of lentinan and its influence on immune cell activity.[11,12,13]

Mechanisms of Anticancer Activity

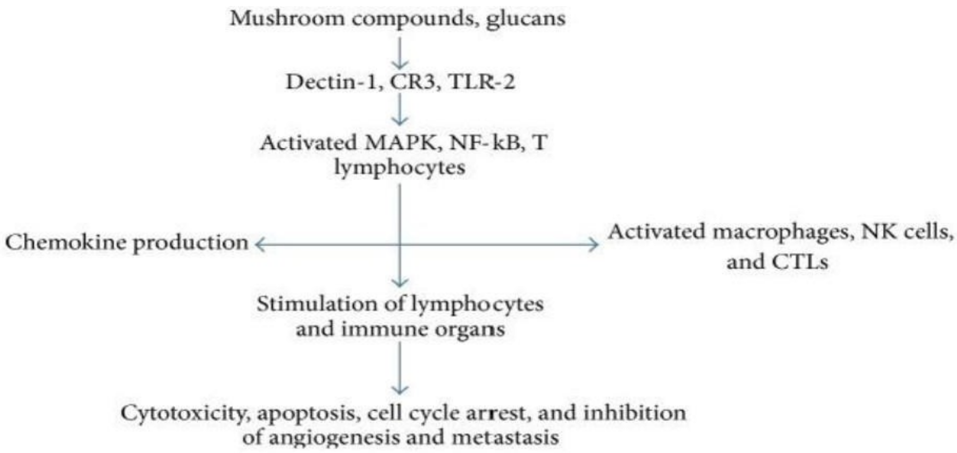


Lentinan exhibits anticancer activity by multiple mechanisms.

This includes the description of how mushroom compounds act on the PD-1 pathway and the CTLA-4/CD80 pathway.

2.1. Immunomodulation

Mushroom compounds can interact with innate and adaptive immunity in fighting cancer. The response of the immune system to antigens is very crucial. The engagement of host PRRs and pathogen-associated molecular patterns (PAMPs) plays a critical role in the effectiveness of immune responses. Maybe one of the most important PAMPs is β-glucans; they are the most significant molecules for induction of an immune response. These compounds are located at dendritic cells, macrophages, neutrophils, and monocytes. It activates the signal transduction pathways that activate T cells, MAPK, and NFkB when Dectin-1 binds to β-glucans to produce cytokines. PRRs such as Dectin-1, TLR-2, and CR3 detect mushroom-derived compounds that activate adaptive immunity and the interaction between PAMP and PRR in innate immune cells. Lentinan promotes the activation of several immune cells, including macrophages, NK cells, and T lymphocytes. This immunostimulatory effect is required to slow and impede the growth of tumors and metastasis.[14,15]



2.2. Induction Apoptosis

Lentinan has been demonstrated by many researchers to induce apoptosis in cancerous cells by the activation of intrinsic pathways of apoptosis. It is a cascade reaction attributed by an increase in the level of protein expression of pro-apoptotic proteins and caspase activation. Being proved to induce apoptosis, lentinan thus classifies it as a molecule capable of being used as a medicine in the cancer war. These observations open the possibility of further investigation into complex molecular interactions and help to better explain the mechanisms involved in the action of lentinan in exerting its anti-cancer effect. Increased pro-apoptotic proteins accompanied by caspase activation are significant indicators of a complex mechanism of action of this agent; hence, lentinan is placed high on the list of promising candidates to be used in new anti-cancer therapies. By further inceptions of the molecular mechanisms induced by lentinan, researchers may clearly ascertain through this process and thereby develop targeted approaches using lentinan's power to induce apoptosis.[16,17]

2.3, Inhibition of Tumor Angiogenesis

In other words, lentinan is known as a bioactive compound within certain mushrooms that have a notable capability to inhibit tumor angiogenesis. This mechanism acts by downregulating the expression of vascular endothelial growth factor (VEGF), which effectively inhibits angiogenesis or new blood vessel formation that nourishes tumors. Targeting specifically VEGF, lentinan interrupts an important pathway connecting neoplastic growth and metastasis. Its ability to inhibit angiogenesis stands to be a promising therapy approach since it limits the all-important blood supply directly fueling tumor growth. Because lentinan modulates VEGF expression, it represents a strategic avenue to limit the nutrition supply to the tumors; thus limiting further tumor growth and metastasis. Given its targeted actions on angiogenesis, lentinan becomes a potential adjuvant therapy, besides the conventional therapies, to retard tumor proliferation and the onset of metastases. In short, its capability to modulate the complex phenomenon of angiogenesis by regulating the expression of VEGF heralds it as an invaluable asset in the fight against cancer.[18,19,20]

2.4. Modulation of Cytokine Production

Lentinan is a polysaccharide which modulates the release of critical cytokines involved with the modulation of the immune response and progression of tumors. Such cytokines include interleukin-1 (IL-10), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-a) responsible for orchestrating different immune defenses against harmful diseases like infections and cancer. The modulation of these levels of cytokines by lentinan would assist in maintaining the fine balance of immune responses as well as tumor growth. This modulation illustrates the possible role of lentinan in the regulation of immunity and modification of tumor biology through association with prominent signaling pathways.[21,22,23]

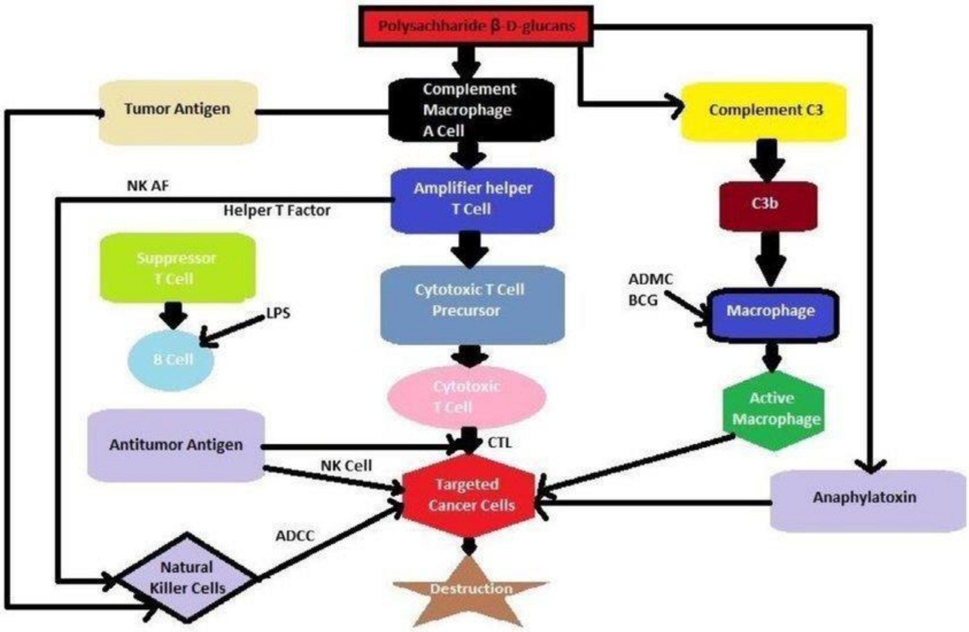


Fig. Basic mechanism of polysaccharides destroyed cancer cells.

2. Efficacy of Lentinan in Various Cancers

2.1. Gastric Cancer

Lentinan has been shown in clinical trials to enhance survival rate of Patients suffering from gastric cancer when used in conjunction with chemotherapy.

2.2. Colorectal Cancer

Both animal and clinical research suggests that the compound strong>lentinanstrong>, may help synergistically boost the effects of 5- fluoro-uracil by common chemotherapy agent for colorectal cancer, fluoro-uracil by enhancing Immune response, and decreasing side effects.

2.3. Lung Cancer

Potential of lentinan in inhibiting involves Preclinical studies proliferation of lung cancer cells and enhanced effectiveness in radiotherapy.

2.4. Hepatocellular Carcinoma

Lentinan has shown Promising results in hepatocellular carcinoma by Citation: Sanjose et al. induces afoptosis and decreases the tumor growth in vitro as well as in vivo.[24,25,26]

3. Synergistic Effects with Chemotherapy

Lentinan, a polysaccharide molecule from mushrooms, has been studied in depth as an adjunct in chemotherapy for various cancers, such as gastric, colorectal, and lung cancer. Initial results from clinical trials have been promising when this polysaccharide molecule has been used in combination with standard chemotherapy. It is now evident that lentinan can be an adjunct to conventional chemotherapy, so its use is beneficial for all patients with these various types of cancers. It is believed that the mechanism for lentinan boosting chemotherapy involves improvements in the immune function of the host and in its response to chemotherapy. Lentinan, therefore, is administered by health care professionals to chemotherapy patients in the hope that it will maximize the benefits obtained from their treatment while minimizing those adverse effects associated with the treatment of cancer. Overall, lentinan's inclusion in cancer treatment protocols would appear to hold much promise for further improving outcomes and quality of life in patients diagnosed with gastric, colorectal, and lung cancers. Chemotherapy agents have been shown to significantly improve patient outcomes with increased survival rates and reduction in tumour size accompanied by overall improvement in quality of life. One major development of this sort is the remarkable role polysaccharides now play in mitigating the side effects of chemotherapy, particularly in inhibiting immunosuppression and fatigue. Innovations in the form of treatment handling have not only helped patients but also encouraged improvements in their health and wellness. Essentially, it's an exciting step forward in cancer therapy towards more effective and patientoriented treatment.[27,28,29]

4. Clinical Applications and Trials

There have been many clinical trials which have been conducted to study the efficacy of lentinan to treat cancer. Common and extensive meta-analyses reveal that the sole administration of lentinan can significantly improve survival rates and quality of life. The research work further discloses that lentinan, one of the beta-glucans extracted from certain mushrooms, has significant importance in determining improved outcomes and well-being for cancer patients. The findings suggest the potential utilization of lentinan in concert with the therapeutic programs for cancers since it provides a useful benefit like extended survival and improved quality of life for treated patients. Secondly, aside from the survival issue, lentinan has been associated with better symptom control and overall well-being of cancer patients.

The positive results from these trials suggest that lentinan is a potential adjunctive agent in integrated approaches to cancer therapy further emphasizing the drugs' ability to enhance treatment outcomes as well as offering alternative options that help overcome the obstacles of cancer. In general, the existing evidence supports lentinan in management of cancer care to maximize outcome benefits of treatment and to enhance the quality of life of patients suffering from this complex disease.[30,31,32,33]

5. Safety and Side Effects

Based on the findings of many clinical experiments, lentinan, and the polysaccharide originating from the shiitake mushroom, has been reported to be generally well-tolerated. Clinical studies show that side effects related to lentinan are relatively rare. Its most commonly reported side effects, however, are mild gastrointestinal disorders such as bloating and gas or changes in bowel habits. There have also been instances of allergic reactions experienced by a few people who are very sensitive to the compound. While side effects are rare and generally mild, a high index of suspicion is recommended, and lentinan should be used with caution, in order not to provoke a possible adverse reaction. Moreover, taking into account the several potential health benefits attributed to lentinan, for instance, its immune system-modulating capability, together with the proposed anticancer activity, the risk-benefit profile is positive. As the scientific studies regarding lentinan are expanded, further clarification on the mechanism and therapeutic potential of this compound will provide key insights into the role that the natural compound can play in enhancing health and wellness.[34,35,36]

6. Future Perspectives

More research would be required in order to clearly define what the most effective dosages and innovative delivery methods are for lentinan when given in conjunction with other conventional cancer treatments. This means a lot of groundwork has to be done to ensure that outcomes for cancer treatment are optimized. More importantly, though is to understand it in the further complex interaction it has with other cancer therapies. Perhaps through this route one may better appreciate how such therapies might be combined in order to kill cancer. Again one has to follow up the potential for synergy between lentinan and immunotherapies, and the development of these combinations could radically improve the treatment of cancer. With this all-encompassing journey of research, we can learn answers to how lentinan works with other therapies or immunotherapies and change the field of treatment of cancer and open new avenues for improvement in patient outcomes.[37]

DISCUSSION

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CONCLUSION

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