

## SHORT COMMUNICATION ΒΡΑΧΕΙΑ ΔΗΜΟΣΙΕΥΣΗ

# Immunomodulation due to the herbal mushroom, Ling Zhi, and its potential usefulness in oncology

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Ανοσοτροποποίηση από το μανιτάρι *Ganoderma lucidum* και χρήση του στην Ογκολογία

Περίληψη στο τέλος του άρθρου

**Key words:** Malaria, *Plasmodium knowlesi*

Ling Zhi is a very well known mushroom with its primary origin in China.<sup>1</sup> It has been used in Chinese herbal medicine for over 3,000 years and at the present time, Ling Zhi is still one of the most famous of Chinese herbal remedies. As a mushroom, Ling Zhi is classified in the phylum Basidiomycota, class Agaricomycetes and order Polyporales. Its scientific name is *Ganoderma lucidum*.<sup>1,2</sup>

Focusing on the active ingredients in this mushroom, the spores within the pileus (umbrella) contain several active ingredients that may have biological effects on the human body.<sup>3</sup> The most important active ingredients that have been identified include polysaccharides, triterpene, peptidoglycan, LZ-8 protein, protoalkaloids, nucleosides, ganodersterone and ergosterol.<sup>4</sup> Paterson said that "the therapeutic effects attributed to the fungus have been proven"<sup>5</sup> and "the next step is to produce some effective medicines which may be hampered by problems of mass production".<sup>5</sup>

This paper provides a brief review and discussion of the immunomodulatory effects of Ling Zhi. Further discussion on its potential usefulness in cancer management is also given.

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## THE IMMUNOMODULATORY EFFECT OF LING ZHI

Strong evidence has been documented showing that Ling Zhi can influence the cytokine production by the human peripheral blood mononuclear cells.<sup>6,7</sup> Many active gradients in Ling Zhi exert an immunomodulatory effect, of which the polysaccharide has been widely mentioned. Chan et al reported that polysaccharide from Ling Zhi could induce functional maturation of dendritic cells with significant production of IL-12 and IL-10,<sup>8</sup> although Li et al reported that the polysaccharide did not affect the production of IFN- $\gamma$ .<sup>9</sup> The specific polysaccharide, proved to be intact polysaccharide, has been identified as a complex beta-D-glucan consisting of a (1 $\rightarrow$ 6)-linked backbone chain, the immunomodulatory effect of which has been confirmed.<sup>10</sup>

In addition to polysaccharides, the important ingredient that is specific to Ling Zhi and is reported to have an immunomodulatory effect is LZ-8 protein (consisting of 110 amino acid residues with an acetylated amino end, and a molecular mass of 12,420 Da).<sup>11</sup> Van der Hem et al recently reported on the immunosuppressive activity of LZ-8, which is caused by reducing antigen-induced antibody formation.<sup>12,13</sup> Van der Hem et al proposed that this could be useful in transplantation medicine.<sup>12,13</sup> Kino et al reported that "LZ-8 prevents the production of systemic anaphylaxis reaction in mice if it has been administered repeatedly, and reduction of antibody production is the suggested mechanism."<sup>14</sup> In animal models, prolongation of graft survival in the experimental group receiving LZ-8 could be observed.<sup>15</sup> Haak-Frendscho et al concluded that "LZ-8 is a potent T cell activator, mediating its effects via cytokine regulation of integrin expression."<sup>16</sup>

## THE USEFULNESS OF LING ZHI IN PATIENTS WITH CANCER

As already noted, many recent reports confirm the possibility of future development of a new antineoplastic drug based on the active ingredients of Ling Zhi. Triterpene is the active ingredient that is usually mentioned for its potential usefulness in the treatment of cancer. Yue et al noted that the cytotoxicity exerted by triterpene is due to alteration of proteins involved in cell proliferation and or cell death, carcinogenesis, oxidative stress, calcium

signaling and ER stress.<sup>17</sup> As a conclusion, it is confirmed that triterpene is related to controlling signal transduction, that can result in the regulation of cancer cell growth.<sup>18</sup> The suppressive effect of triterpene on several kinds of cancer cells including breast cancer,<sup>19</sup> prostate cancer<sup>20</sup> and liver cancer<sup>21</sup> have been reported.

It should be noted that most of the publications related to the usefulness of Ling Zhi in the treatment of cancer are based on the animal model or cell culture study. Further studies, including human trials, are still required. Evidence has been published derived from a human study in Japan, where Oka et al<sup>22</sup> found that the mushroom mycelia could suppress the development of colorectal adenomas, pre-cancerous lesions of the large bowel.<sup>22</sup>

A further possible important role of Ling Zhi in cancer treatment is its usage as an agent providing cytoprotection. Zhuang et al recently noted that the use of several Chinese medicines, including Ling Zhi, in patients receiving chemotherapy or radiotherapy could lead to improvement of their immune function, increasing their ability to fight off the cancer itself, and secondary infections.<sup>23</sup> A recent laboratory study on a human cell line demonstrated a cytoprotective effect of Ling Zhi extract on the normal cells and a cytotoxic effect on the cancerous cells.<sup>24</sup> Improvement of the quality of life has been observed when Ling Zhi extract was used as an adjunct to conventional chemotherapy.<sup>25</sup>

## CONCLUSION

Ling Zhi is an interesting mushroom used in herbal medicine, for which there is evidence of immunomodulatory effects that could be useful in oncology.

## ΠΕΡΙΛΗΨΗ

### Ανοσοτροποποίηση από το μανιτάρι *Ganoderma lucidum* και χρήση του στην Ογκολογία

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Το μανιτάρι *Ganoderma lucidum* (Ling Zhi) είναι αρκετά γνωστό, με κύρια προέλευσή του την Κίνα. Οι σπόροι στο στέλεχος του περιέχουν αρκετά δραστικά συστατικά που ενδέχεται να έχουν βιολογικές δράσεις στον άνθρωπο. Αρκετά πρόσφατα δεδομένα δείχνουν ότι μπορεί να

εμφανίζουν ανοσοτροποποιητική δράση και πιθανότητα το συγκεκριμένο μανιτάρι να έχει θέση στις χώρες όπου εφαρμόζεται η εναλλακτική Ιατρική για μερικά νοσήματα ή και νεοπλάσματα.

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**Λέξεις ευρητηρίου:** Ανοσοτροποποίηση, Μανιτάρι Ling Zhi

## References

1. LINDEQUIST U, RAUSCH R, FÜSSEL A, HANSSSEN HP. Higher fungi in traditional and modern medicine. *Med Monatsschr Pharm* 2010, 33:40–48
2. ZHOU X, LIN J, YIN Y, ZHAO J, SUN X, TANG K. Ganodermataceae: Natural products and their related pharmacological functions. *Am J Chin Med* 2007, 35:559–574
3. SLIVA D. Cellular and physiological effects of *Ganoderma lucidum* (Reishi). *Mini Rev Med Chem* 2004, 4:873–879
4. BOH B, BEROVIC M, ZHANG J, ZHI-BIN L. *Ganoderma lucidum* and its pharmaceutically active compounds. *Biotechnol Annu Rev* 2007, 13:265–301
5. PATERSON RR. Ganoderma – a therapeutic fungal biofactory. *Phytochemistry* 2006, 67:1985–2001
6. JEURINK PV, NOGUERA CL, SAVELKOUL HF, WICHERS HJ. Immunomodulatory capacity of fungal proteins on the cytokine production of human peripheral blood mononuclear cells. *Int Immunopharmacol* 2008, 8:1124–1133
7. CHAN WK, LAM DT, LAW HK, WONG WT, KOO MW, LAU AS ET AL. *Ganoderma lucidum* mycelium and spore extracts as natural adjuvants for immunotherapy. *J Altern Complement Med* 2005, 11:1047–1057
8. CHAN WK, LAW HK, LIN ZB, LAU YL, CHAN GC. Response of human dendritic cells to different immunomodulatory polysaccharides derived from mushroom and barley. *Int Immunol* 2007, 19:891–899
9. LI L, LEI LS, YU CL. Changes of serum interferon-gamma levels in mice bearing S-180 tumor and the interventional effect of immunomodulators. *Nan Fang Yi Ke Da Xue Xue Bao* 2008, 28:65–68
10. WIWANITKIT V. A short review on beta-glucan, a substance for alternative therapy for cancerous patient. *Iran J Cancer Prev* 2009, 4:163–166
11. TANAKA S, KO K, KINO K, TSUCHIYA K, YAMASHITA A, MURASUGI A ET AL. Complete amino acid sequence of an immunomodulatory protein, ling zhi-8 (LZ-8). An immunomodulator from a fungus, *Ganoderma lucidum*, having similarity to immunoglobulin variable regions. *J Biol Chem* 1989, 264:16372–16377
12. VAN DER HEM LG, VAN DER VLIET JA, BOCKEN CF, KINO K, HOITSMA AJ, TAX WJ. Ling Zhi-8: Studies of a new immunomodulating agent. *Transplantation* 1995, 60:438–443
13. VAN DER HEM LG, VAN DER VLIET JA, KINO K, HOITSMA AJ, TAX WJ. Ling-Zhi-8: A fungal protein with immunomodulatory effects. *Transplant Proc* 1996, 28:958–959
14. KINO K, YAMASHITA A, YAMAOKA K, WATANABE J, TANAKA S, KO K ET AL. Isolation and characterization of a new immunomodulatory protein, ling zhi-8 (LZ-8), from *Ganoderma lucidum*. *J Biol*

- Chem* 1989, 264:472–478
15. VAN DER HEM LG, VAN DER VLIET JA, BOCKEN CF, KINO K, HOITSMA AJ, TAX WJ. Prolongation of allograft survival with Ling Zhi-8, a new immunosuppressive drug. *Transplant Proc* 1994, 26:746
  16. HAAK-FRENDSCHO M, KINO K, SONET, JARDIEU P. Ling Zhi-8: A novel T cell mitogen induces cytokine production and upregulation of ICAM-1 expression. *Cell Immunol* 1993, 150:101–113
  17. YUE QX, SONG XY, MA C, FENG LX, GUAN SH, WU WY ET AL. Effects of triterpenes from *Ganoderma lucidum* on protein expression profile of HeLa cells. *Phytomedicine* 2010, 17:606–613
  18. CHUNG WT, LEE SH, KIM JD, PARK YS, HWANG B, LEE SY ET AL. Effect of mycelial culture broth of *Ganoderma lucidum* on the growth characteristics of human cell lines. *J Biosci Bioeng* 2001, 92:550–555
  19. JIANG J, GRIEB B, THYAGARAJAN A, SLIVA D. Ganoderic acids suppress growth and invasive behavior of breast cancer cells by modulating AP-1 and NF-kappaB signaling. *Int J Mol Med* 2008, 21:577–584
  20. JOHNSTON N. Medicinal mushroom cuts off prostate cancer cells' blood supply. *Drug Discov Today* 2005, 10:1584
  21. CHANG UM, LI CH, LIN LI, HUANG CP, KAN LS, LIN SB. Ganoderiol F, a ganoderma triterpene, induces senescence in hepatoma HepG2 cells. *Life Sci* 2006, 79:1129–1139
  22. OKA S, TANAKA S, YOSHIDA S, HIYAMA T, UENO Y, ITO M ET AL. A water-soluble extract from culture medium of *Ganoderma lucidum* mycelia suppresses the development of colorectal adenomas. *Hiroshima J Med Sci* 2010, 59:1–6
  23. CHUNG WT, LEE SH, KIM JD, PARK YS, HWANG B, LEE SY ET AL. Effect of mycelia cell culture broth of *Ganoderma lucidum* on the growth characteristics of human cell lines. *J Biosci Bioeng* 2001, 92:550–555
  24. WANG DH, WENG XC. Antitumor activity of extracts of *Ganoderma lucidum* and their protective effects on damaged HL-7702 induced by radiotherapy and chemotherapy. *Zhongguo Zhong Yao Za Zhi* 2006, 31:1618–1622
  25. NONAKA Y, ISHIBASHI H, NAKAI M, SHIBATA H, KISO Y, ABE S. Soothing effect of *Ganoderma lucidum* antlered form on cyclophosphamide-induced adverse reaction. *Gan To Kagaku Ryoho* 2005, 32:1586–1588
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