Effects of Water-Soluble *Ganoderma lucidum* Polysaccharides on the Immune Functions of Patients with Advanced Lung Cancer

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**ABSTRACT** Preclinical studies have established that the polysaccharide fractions of *Ganoderma lucidum* have potential anti-tumor activity. Recent clinical studies have demonstrated that *G. lucidum* polysaccharides enhance host immune functions [e.g., enhanced natural killer (NK) cell activity] in patients with advanced solid tumors, although an objective response was not observed. This open-label study aimed to evaluate the effects of water-soluble *G. lucidum* polysaccharides (Ganopoly®, Encore International Corp., Auckland, New Zealand) on immune functions in patients with advanced lung cancer. Thirty-six patients were enrolled and treated with 5.4 g/day Ganopoly for 12 weeks. In the 30 cancer patients who completed the trial, treatment with Ganopoly did not significantly alter the mean mitogenic reactivity to phytohemagglutinin, mean counts of CD3, CD4, CD8, and CD56, mean plasma concentrations of interleukin (IL)-2, IL-6, and interferon (IFN)-γ/H925, or NK activity in the patients, but the results were significantly variable. However, some cancer patients demonstrated markedly modulated immune functions. The changes in IL-1 were correlated with those for IL-6, IFN-γ/H925, CD3, CD8, and NK activity (P<0.05), and IL-2 changes were correlated with those for IL-6, CD3, CD8, and NK activity. The results suggest that subgroups of cancer patients might be responsive to Ganopoly in combination with chemotherapy/radiotherapy. Further studies are needed to explore the efficacy and safety of Ganopoly used alone or in combination with chemotherapy/radiotherapy in lung cancer patients.

**KEY WORDS:** • efficacy • *Ganoderma lucidum* • immune function • polysaccharide • tumor

**INTRODUCTION**

At present, the major forms of cancer treatment are surgery, radiation, chemotherapy, and immunotherapy.1,2 However, these therapies are only successful when the cancer is detected at an early stage, or limited to certain types of cancer (e.g., leukemia). Because of limited diagnostic means for detecting precancerous status and cancers at early stages, most patients present in the advanced stage of cancer or with extensive local infiltration. For advanced tumors, in particular those tumors developed from epithelial tissues such as lung, colon, breast, prostate, and pancreas, these therapies are less successful. Drug resistance and dose-limiting toxicities are the major problems for the success of cancer chemotherapy.2,3 Therefore, novel therapeutic approaches are needed to kill cancer cells more effectively and selectively.

The use of natural medicines for treatment of advanced cancers has drawn much attention recently.4 Indeed, some natural medicines have been investigated as anti-cancer agents with encouraging findings, although objective responses have rarely been found. A number of natural medicines have been reported to be immune stimulants in *in vitro* and in animal studies,5,6 in which they have been shown to enhance cell-mediated immunity and natural killer (NK) cell activity, facilitating the killing the tumor cells by the body. For example, *Ganoderma lucidum*, a medicinal mushroom, has been reported to have anti-tumor activity in mice.7–11 Further studies suggest that the *G. lucidum* polysaccharide (PS) fractions are involved in this anti-tumor action.12,13 *G. lucidum* PS is able to activate macrophages, T lymphocytes, and NK cells, and induce the production of cytokines such as tumor necrosis factor (TNF)-α, interleukins (ILs), and interferons (IFNs) *in vitro* using human immune cells and *in vivo* in mice.11,14–16 However, it is unclear whether *G. lucidum* PS has immunomodulating effects in humans.
vivo. This study aimed to investigate the effects of Ganopoly® (Encore International Corp., Auckland, New Zealand), the PS fractions extracted from *G. lucidum*, on the immune function of advanced-stage cancer patients.

Herbal preparations have been widely used for cancer therapy in Asian countries, in an attempt to assist in killing tumor cells and for reducing the toxicity of combined chemotherapeutic agents. Indeed, some natural medicines have been investigated as anti-cancer agents in cancer patients, and some encouraging findings have been observed, although objective responses have rarely been found. Herbal medicines appear to work as biological response modifiers, which modify the relationship between the host and tumor by modifying the host’s biological response to tumor cells with resultant therapeutic effects. Most biological response modifiers appear to act by activating, increasing, and/or restoring the reactivity of immunological effector mechanisms that are involved in resistance to tumor growth and metastasis. The inhibition of suppressor and other mechanisms that interfere with effective host resistance to tumors and help tumor cells to grow, develop, and metastasize are the targets for many biological response modifiers.

*G. lucidum* has been used extensively as a traditional herbal medicine in the treatment of many diseases such as chronic hepatopathy, hypertension, hyperglycemia, and cancer. Ikekawa *et al.* first reported on the anti-tumor effect of soluble extracts from *G. lucidum* in mice bearing transplanted sarcoma 180, and Sasaki *et al.* subsequently confirmed that the PS fractions of *G. lucidum* were responsible for the anti-tumor action of *G. lucidum*. In the past 3 decades, a number of *in vitro* and animal studies have demonstrated the anti-tumor activity of *G. lucidum* administered by different routes at different stages of tumor growth. In animal models, crude or partially purified PS of *G. lucidum* has effectively inhibited tumor metastasis. In addition, a crude *G. lucidum* PS fraction increased the lifespan when administered alone or in combination with conventional cytotoxic agents. Indeed, cancer patients in Asian countries often use *G. lucidum* products as an adjunct or as the sole therapy. However, like all other commonly used herbs, *G. lucidum* has not undergone rigorous clinical examinations. Thus, clinical data on the efficacy and safety of *G. lucidum* preparations are sparse.

Recently, a non-randomized clinical study by our group in 143 patients with advanced solid tumors indicated that treatment with *G. lucidum* PSs (Ganopoly) for 12 weeks resulted in stable disease in 26.6% patients for ≥12 weeks (range, 12–50 weeks). A further study found that treatment with *G. lucidum* PSs (Ganopoly) enhanced lymphocyte mitogenic reactivity to concanavalin A and phytohemagglutinin (PHA) and increased NK cell activity in advanced cancer patients. However, a recent study in healthy volunteers indicated that oral treatment with *G. lucidum* supplement at 1.44 g/day for 4 weeks had no effect on immune functions. Ganopoly is an aqueous PS fraction extracted from *G. lucidum* by a patented biochemical technique. It has been marketed as an over-the-counter product in New Zealand, Australia, Hong Kong, Singapore, China, and Taiwan, without the need for a doctor’s prescription. Cancer patients have used Ganopoly alone or in combination with chemotherapeutic agents.

The present study aimed to investigate the effects of Ganopoly, the water-soluble PS fractions extracted from *G. lucidum*, on the immune functions of patients with advanced lung cancer, which is one of the leading causes of death worldwide.

### MATERIALS AND METHODS

**Patient selection**

Patients were recruited into the study if they met the following eligibility criteria and did not meet any of the exclusion criteria: (1) advanced-stage (staged III–IV) lung cancer confirmed by pathological examination; (2) ≥4 weeks of interval between prior anti-cancer or radiation therapy and entry; (3) an Karnofsky performance status score ≥60; (4) a median survival of at least 12 weeks; (5) ≥18 years; (6) adequate bone marrow function, renal function, and liver function; and (7) informed consent for participation. Ethical approval was from the Research Ethics Committee at the Hospital of Fujian University of Traditional Chinese Medicine. Patients were excluded if they had severe concurrent conditions such as cardiovascular or liver diseases or had taken or were taking any *Ganoderma* preparations or any immunomodulating agents. Pregnant or lactating women were also excluded. Off-study criteria were (1) the patient’s desire to withdraw, (2) non-compliance, (3) unusual or unacceptable toxicity, or (4) emerging evidence that Ganopoly was of no benefit to patients with a similar tumor type.

As shown in Table 1, 36 patients with advanced lung cancer were included in this study. Thirty-five of 36 (97.2%) patients had two or more disease/organ sites affected, and 32 (88.9%) patients were treated with various modules including chemotherapeutic agents or radiation therapy. Thirty patients were assessable for immune function tests after 12 weeks. Six patients were not assessed because of non-compliance (*n* = 2), they were lost to follow-up (*n* = 3), or they died (*n* = 1). The death of one patient by week 10 was due to disease complication (respiratory failure). This patient stopped taking Ganopoly by week 8. There is no evidence indicating his death was due to a side effect of Ganopoly.

**Extraction and characterization of the *G. lucidum* PSs (Ganopoly)**

The fruiting bodies of *G. lucidum* collected from southern China were washed, disintegrated, and extracted twice with hot water at 70°C for 3 hours as described previously. All hot-water extracts were pooled, and the PS-enriched fractions were precipitated by the addition of 75% (vol/vol)
ethanol. The PS-enriched fraction was further purified by high-performance anion-exchange and gel filtration chromatography using a 1.6-× 100-cm column packed with Sephadex G-25 (Pharmacia, Uppsala, Sweden). The final PS products (Ganopoly) had an average molecular size of 4.85 × 10^5 Da, as determined by gel filtration chromatography and the phenol-sulfuric acid method. They consisted of glucose (61.2%), xylose (15.5%), fructose (14.4%), galactose (4.8%), and rhamnose (4.1%) linked together by 1→3 β-glycosidic linkages. The concentration of proteins was 0.35% as determined by the bicinchoninic acid method. Triterpenes were not detected in the final extracts by silica gel thin-layer chromatography or visualized by ultraviolet light shadowing. There was no detectable level of endotoxin (lipopolysaccharide) in the extracted PS fractions by using the chromogenic limulus amebocyte lysate assay.

Drug administration

Ganopoly was the only anti-cancer agent administered during the 12-week study period. Patients were treated with 1,800 mg, three times daily orally before meals for 12 weeks. Each capsule of Ganopoly contained 600 mg of extract of G. lucidum, with 25% (wt/wt) crude PSs. As the fruiting body of G. lucidum contains approximately 0.5% (wt/wt) PSs, a capsule of Ganopoly was equal to 9.0 g of fruiting body of G. lucidum, or a total dose of Ganopoly per day (5,400 mg) was equal to 81 g of fruiting body. The common dose of G. lucidum for folk use in China is 25-100 g per day, depending on the type and severity of diseases. As most herbs used for chronic diseases are administered for at least 1–4 months, we chose 12 weeks as the treatment regimen. Ganopoly was manufactured in accordance with Good Manufacturing Practice standards and provided by Encore International Corp.

Cell culture

Human peripheral mononuclear cells were grown in RPMI 1640 medium containing 10% (vol/vol) fetal bovine serum, 100 units/mL of penicillin, and 100 μg/mL of streptomycin (all from In Vitro Life Technologies, Auckland) in a water vapor-saturated atmosphere of 5% CO₂ at 37°C.

Cytotoxicity

The effect of Ganopoly on the growth of human peripheral mononuclear cells was investigated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as described. Briefly, a 200-mL (1 × 10^5 cells/mL) volume of an exponentially growing cell suspension was seeded into a Falcon 96-well plate (Becton Dickinson Co., Franklin Lakes, NJ), and 20 μL of Ganopoly (from a 0.05–1.0 mg/mL stock) was added. After incubation for 72 hours at 37°C, 20 μL of MTT solution (5 mg/mL in phosphate-buffered saline) was added to each well, and the plates were incubated for a further 4 hours at 37°C. The medium was then aspirated carefully from each well, and 180 μL of dimethyl sulfoxide was added to each well to dissolve the formazan crystals. Optical density was measured at 490 nm with an absorbance reader (Tecan Instruments Inc., Research Triangle Park, NC). Each experiment was performed in six to nine replicate wells for each drug concentration and carried out independently three times. The IC₅₀ value was defined as the concentration needed for a 50% reduction in the absorbance calculated based on the survival curves.

Determination of plasma cytokine concentrations

Plasma from patients before and after treatment was assayed for the determination of various cytokines including

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**Table 1. Demographic Profiles of Study Patients with Advanced Lung Cancer**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>36</td>
</tr>
<tr>
<td>Age (years) (mean ± SD) (range)</td>
<td>48.4 ± 7.0 (30–68)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
</tr>
<tr>
<td>Number of smokers</td>
<td>25</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
</tr>
<tr>
<td>Small cell</td>
<td>12</td>
</tr>
<tr>
<td>Non-small cell</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td>Number of patients with previous chemotherapy/radiation</td>
<td>32</td>
</tr>
<tr>
<td>Number of patients with ≥2 disease/organ sites affected</td>
<td>35</td>
</tr>
<tr>
<td>Patients not assessable after 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Non-compliance</td>
<td>2</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>3</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
</tr>
</tbody>
</table>

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IL-1, IL-2, IL-6, IFN-γ, and TNF-α using commercially available enzyme-linked immunosorbent assay kits (R & D Systems, Abingdon, UK). All determinations were performed at least in triplicate.

**PHA-stimulated lymphocyte proliferation**

The PHA-stimulated lymphocyte proliferation assay was performed using [3H]thymidine incorporation method as described.44 Mononuclear cells were separated from the heparinized blood of cancer patients by Ficoll-Hypaque gradients and maintained in RPMI 1640 medium. An aliquot of the harvested cells (5 x 10⁴ cells per well) was seeded using a 96-well plate in 0.2 mL of RPMI 1640/5% human AB serum and incubated with 10 mg/L of PHA (Sigma-Aldrich, St. Louis, MO). Cells were incubated at 37°C for 96 hours, 1 μCi of [3H]thymidine per well was added for the last 16 hours, and incorporated radioactivity was measured by a γ-counter. All assays were carried out at least in triplicate.

**Flow cytometry**

The lymphocyte subset analysis included CD3⁺ (T lymphocyte), CD4⁺ (T-helper cells), CD8⁺ (T-suppressor cells), and HNK-1 and CD56⁺ (NK cells). Peripheral blood samples (20 mL) were collected from each patient into heparinized tubes before the onset of treatment and after 12 weeks of treatment. Lymphocytes were separated by Ficoll-Hypaque centrifugation. Standard direct-labeling techniques were used as recommended by the manufacturers. Immunophenotyping was done by flow cytometry using conjugated antibodies able to detect specific epitopes. The antibodies for the identification of lymphocyte subsets were OKT4 (CD4⁺) and OKT8 (CD8⁺) from Ortho (Raritan, NJ). Immunofluorescence was examined with a FACScan analyzer (Becton Dickinson). The proportion of lymphocytes stained with each monoclonal antibody was converted to the absolute number per microliter by multiplying by the number of lymphocytes per microliter derived from the whole blood count.

**Determination of NK cell activity**

NK cell activity was tested in the total peripheral blood mononuclear cell population against the NK-sensitive K562 tumor cells by means of the ⁵¹Cr release assay as previously described.45 Briefly, effector peripheral blood mononuclear cells were freshly isolated and plated in 100-μL aliquots in 96-well microtiter plates. Tumor target cells (10⁷) were incubated with 100 μCi of sodium [⁵¹Cr]chromate (Amersham, Buckinghamshire, UK) for 90 minutes at 37°C and washed twice to remove excess isotope, and a quantity amounting to 5 x 10³ cells per well was added to the effector cells, to assess an effector to target ratio of 40 to 1. After an 18-hour incubation at 37°C in a CO₂ incubator, 100 μL of supernatant was removed from each well for radioactivity counting using a γ-counter. Spontaneous and maximum release values were established by incubating target cells in medium alone or with 5% Triton X-100, respectively. Spontaneous release did not exceed 15% of the maximum release. In all cases, cultures were set up in triplicate, and percent specific target cell lysis was calculated as follows:

\[
\% \text{ specific target cell lysis} = \frac{\text{Mean cpm}_{\text{experimental}} - \text{Mean cpm}_{\text{spontaneous}}}{\text{Mean cpm}_{\text{maximum}} - \text{Mean cpm}_{\text{spontaneous}}} \times 100
\]

**Statistical analysis**

Data were expressed as the mean ± standard deviation (SD). Correlation analysis was performed to determine the relationship between the immune variables measured (responses changed from the baseline values) in study patients. Comparisons of means of the immune variables at baseline and after 12 weeks of treatment were made using Student’s paired-samples t test. A value of P < .05 was considered statistically significant.

**RESULTS**

**Mitogenic reactivity to PHA**

Ganopoly at 0.05–1.0 mg/mL produced little or negligible cytotoxicity against peripheral mononuclear cells from lung cancer patients. There was an eightfold variability in the mitogenic reactivity to PHA as determined by [3H]thymidine incorporation by peripheral mononuclear cells among all patients. In all 30 assessable patients, administration of Ganopoly for 12 weeks resulted in an insignificant (P > .05) increase in mean lymphocyte mitogenic reactivity to concanavalin A (52.4 ± 11.5 vs. 54.9 ± 10.9). As shown in Figure 1, PHA responses after 12 weeks of treatment with Ganopoly were slightly enhanced in 16 patients (53.3%). However, the PHA

![FIG. 1. Mitotic response of peripheral blood lymphocytes to PHA at baseline and after a 12-week treatment with Ganopoly in advanced-stage lung cancer patients. Data points are from at least three determinations.](chart)
response remained unchanged in two patients or was decreased in 12 patients (29.3%).

**Effect of Ganopoly on plasma cytokine concentrations**

There was a three- to 10-fold variability in the plasma concentrations of IL-1, IL-2, IL-6, TNF-α, and IFN-γ in 36 advanced lung cancer patients. The mean values for plasma IL-1, IL-2, IL-6, TNF-α, and IFN-γ at baseline were 84.2 ± 19.1, 76.5 ± 17.7, 53.1 ± 15.9, 104.4 ± 32.4, and 62.1 ± 18.9 pg/mL, respectively, and the median values for these cytokines were 84.8, 84.2, 53.6, 107.2, and 63.3 pg/mL, respectively. Treatment with Ganopoly for 12 weeks resulted in an increase in the plasma concentrations of IL-2, IL-6, and IFN-γ in 17 (56.7%), 18 (60.0%) and 18 (60.0%) patients, respectively, whereas the concentrations of both IL-1 and TNF-α were decreased in 17 and 20 patients, respectively (Fig. 2).

**FIG. 2.** Changes in plasma concentrations of IL-1 (A), IL-2 (B), IL-6 (C), TNF-α (D), and IFN-γ (E) at baseline and after a 12-week treatment with Ganopoly in advanced-stage lung cancer patients. Data are mean ± SD values.
After a 12-week treatment with Ganopoly, the mean values for plasma IL-1, IL-2, IL-6, TNF-α, and IFN-γ were 79.1 ± 16.4, 82.3 ± 19.2, 57.1 ± 20.5, 96.9 ± 26.4, and 71.6 ± 19.6 pg/mL, respectively, and the median values for these cytokines were 75.3, 85.6, 55.8, 103.1, and 67.8 pg/mL, respectively. There was no statistical significance (P > .05) when a comparison was made between the values at baseline and those after 12 weeks of treatment with Ganopoly. Gender and smoking had insignificant effects on the changes of various cytokines tested.

Effects on the number and proportion of lymphocyte subsets

There was a remarkable variability (eight- to 11-fold) among the 36 cancer patients in the number of each lymphocyte subset at baseline. The mean numbers of CD3, CD4, CD8, and CD56 cells at baseline were 1,050.8 ± 472.5, 1,161.5 ± 446.2, 337.3 ± 162.4, and 286.1 ± 128.3, respectively, and the median values were 1,039.2, 1,210.8, 309.5, and 249.7, respectively. Ganopoly treatment produced an increase of CD3, CD4, CD8, and CD56 cells in 19 (63.3%), 20 (66.7%), 17 (56.7%), and 16 (53.3%) patients, respectively (Fig. 3).

The mean numbers of CD3, CD4, CD8, and CD56 cells after a 12-week treatment with Ganopoly were 1,107.2 ± 422.4, 1,183.4 ± 434.8, 344.2 ± 183.3, and 301.5 ± 126.3, respectively, and the median values were 1,121.5, 1,218.5, 321.8, and 279.4, respectively. However, Ganopoly treatment resulted in a slight decrease of CD4:CD8 ratio in 19 (63.3%) patients (baseline vs. 12 weeks: 4.174 ± 2.762 vs. 4.098 ± 2.806). There was no statistical significance (P > .05) when a comparison was conducted between the values at baseline and those after a 12-week treatment with Ganopoly. In addition, Ganopoly treatment had no or little effect on total peripheral blood lymphocyte counts and the CD4:CD8 T cell ratios.

Effect of Ganopoly on NK activity

Baseline NK cell activity against K562 cells was evaluated in all 41 lung cancer patients and compared with the cytotoxic activity after treatments. There was a marked interindividual variability among patients in NK cytotoxic activity against K562 target cells as demonstrated by a range of baseline killing varying from 9.5% to 63.5% at a 40:1 effector:target ratio, with a mean and median of 27.7 ± 8.6% and 27.2%, respectively. Ganopoly treatment resulted in an

![Fig. 3](image_url)  
**FIG. 3.** CD3⁺ (T lymphocyte; A), CD4⁺ (T-helper cells; B), CD8⁺ (T-suppressor cells; C), and CD56⁺ (NK cells; D) counts at baseline and after a 12-week treatment with Ganopoly in advanced-stage lung cancer patients. Data are mean ± SD values.
increase in the NK cell activity in 20 (66.7%) patients, and the mean and median values were 30.2 ± 9.4% and 30.4%, respectively (Fig. 4). However, a comparison between the values at baseline and those after a 12-week treatment with Ganopoly did not show any statistical significance (P > .05).

We also conducted a correlation study to identify the relationships between the changes of these immune functions following Ganopoly treatment for 12 weeks. The changes in IL-1 were correlated with those for IL-6, IFN-γ, CD3, CD4, CD8, and NK cell activity (P < .05), and IL-2 changes were correlated with those for IL-6, CD8, and NK cell activity. The changes in TNF-α were correlated with those for CD3, CD4, and CD56, and IFN-γ correlated with CD3 and CD4. Moreover, the CD3 changes were correlated with those for CD8 and CD56, whereas the CD4 changes were correlated with NK cell activity.

**DISCUSSION**

The present study indicated that treatment of advanced lung cancer patients with Ganopoly at 5.4 g/day for 12 weeks does not significantly alter the mean lymphocyte mitogenic reactivity to PHA, mean counts of CD3, CD4, CD8, and CD56, mean plasma levels of IL-1, IL-2, IL-6, IFN-γ, and TNF-α, and NK cell activity, as the differences between before and after treatment were statistically insignificant (P > .05). These results are consistent with those reported by Wachtel-Galar et al., where oral treatment with *G. lucidum* supplement at 1.44 g/day for 4 weeks did not affect the immune functions in healthy subjects. However, most preclinical studies using *in vitro* and animal models indicate that *G. lucidum* PSs are able to activate macrophages, T lymphocytes, and NK cells, and to induce the production of cytokines such as TNF-α, ILs, and IFNs *in vitro* with human immune cells and *in vivo* in mice. Such preclinical–clinical data inconsistencies may be due to differences in dose levels, immune status, and species differences in response to *G. lucidum* PSs. Minimal beneficial effects of the herbal medicine tested, advanced stage of lung cancer patients with low immune functions, limited sample size, and marked interindividual variability in the measured variables might contribute to the lack of drug response in lung cancer patients.

However, some marked biological responses were observed in some of the study lung cancer patients. For example, treatment with Ganopoly for 12 weeks increased the plasma concentrations of IL-2, IL-6, and IFN-γ in 56.7–60.0% patients, and the same treatment resulted in an increase in the NK cell activity in 20 (66.7%) patients. The mechanisms for such immune-stimulating effects of *G. lucidum* PSs are not fully identified, but the involvement of multiple immune effectors have been implicated, β-1,3-Glucans from medicinal mushrooms can bind to membrane complement receptor type 3 (CR3, αMβ2 integrin, or CD11b/CD18) on immune effector cells such as macrophages, releasing cytokines (*e.g.*, IL-1β, IL-6, IFN-γ, and TNF-α), nitric oxide, and other mediators.

Ganopoly treatment decreased plasma TNF-α concentrations in 20 advanced lung cancer patients. Most of these patients experienced less body weight loss, chronic nausea, fatigue, insomnia, and profuse sweating. Increased plasma TNF-α levels has been thought to contribute to cancer cachexia. Therefore, drugs that down-regulate TNF-α can result in improvements of cachexia with beneficial effects (*e.g.*, improved life quality) in advanced-stage cancer patients.

Ganopoly showed some stimulating effect on NK cells in some advanced lung cancer patients. NK cells together with cytotoxic T lymphocyte play an important role in immunologic surveillance in neoplasia and metastasis. Human NK cells, which make up approximately 15% of all circulating lymphocytes, can cause early production of cytokines and chemokines (*e.g.*, ILs), and lyse tumor cells without prior sensitization. In the late stage of cancer, NK cell activity is significantly decreased and associated with an impairment of cytokine production. Low NK cell activity has been associated with poor prognosis in advanced cancer patients. Therefore, a number of immunotherapeutic approaches to enhancing NK cell activity and production of cytokines such as IL-2 have been investigated in advanced-stage cancer patients, and beneficial effects have been observed in some patients. A recent study showed that various natural medicines such as Transfer Factor Plus and Agaricus Blazei Murill teas significantly increase NK cell activity, plasma TNF-α, and peripheral blood lymphocyte response to PHA.

Interestingly, our study demonstrated that the changes of the multiple immune variables monitored were correlated. For example, the changes of IL-1 were correlated with those for IL-6, IFN-γ, CD3, CD4, CD8, and NK cell activity (P < .05), and IL-2 changes were correlated with those for IL-6, CD8, and NK cell activity. This indicated that the immune variables monitored through this study were all important effector components that interplay in the network of
native defense. In a such defense network, macrophages play a key role as they are involved in all stages of the immune response. These cells act as a rapid protective mechanism by engulfing exogenous particles prior to T cell activation, take part in the initiation of T cell activation by processing and presenting antigen, and finally act as inflammatory, tumoricidal, and microbicidal cells in the effector phase of the cell-mediated responses following T cell-mediated activation.64 Both macrophages and T cells secrete a large number of cytokines that help to destroy tumor cells and pathogens. Additionally, B cells will be stimulated and consequently produce specific antibodies against tumor cell antigens. Because all these immune cells and components form a hierarchy and network structure that is governed by complicated feedback regulation mechanisms (probably mostly positive feedback when a immune stimulator is used), it is not a surprise that the observed changes in the monitored immune parameters were correlated.

The fate of the host–tumor interactions is considered to depend on the balance between the intrinsic aggressiveness (i.e., inherent metastatic potential) of the tumor and the strength of the host immune response. Evidence has indicated that immune function can be reduced or damaged in cancer patients receiving chemotherapy and radiotherapy, resulting in a decrease in cytotoxic T lymphocyte and NK cell activity.44,45,65 Therefore, standard chemotherapy and radiotherapy might negate or reduce the therapeutic benefits obtained by the increased tumor killing of the treatment. These negative effects may be particularly important in the treatment of immunogenic tumors where immune function of the host is a determining factor for the clinical outcome of treatment. Thus, immunotherapy may provide a strategy for overcoming the immunosuppressive effects of chemotherapy/radiotherapy. Recently, many biological response modifiers have been combined with cytotoxic chemotherapeutic agents/radiation, in attempt to enhance anti-cancer activity and reduce toxicity. The results of this study suggest the possibility that Ganopoly could reverse the immunosuppressive effects of traditional chemotherapy/radiotherapy in cancer patients, and it may represent a practical and promising adjunct approach for cancer treatment in combination with chemotherapy/radiotherapy. However, further studies are needed to identify unrevealed molecular targets and explore the optimum dosing, efficacy, and safety alone or in combination with chemotherapy/radiotherapy.

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REFERENCES


