Coriolus versicolor: a medicinal mushroom with promising immunotherapeutic values

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J. Clin. Pharmacol. 2002; 42; 976

Coriolus versicolor: A Medicinal Mushroom with Promising Immunotherapeutic Values

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Coriolus versicolor *(CV) is a medicinal mushroom widely prescribed for the prophylaxis and treatment of cancer and infection in China. In recent years, it has been extensively demonstrated both preclinically and clinically that aqueous extracts obtained from CV display a wide array of biological activities, including stimulatory effects on different immune cells and inhibition of cancer growth. The growing popularity of aqueous CV extracts as an adjunct medical modality to conventional cancer therapies has generated substantial commercial interest in developing these extracts into consistent and efficacious oral proprietary products. While very limited information is available on the physical, chemical, and pharmacodynamic properties of the active principles present in these extracts, there has been sufficient scientific evidence to support the feasibility of developing at least some of these constituents into an evidence-based immunodulatory agent. In this article, the background, traditional usage, pharmacological activities, clinical effects, adverse reactions, active constituents, and regulatory aspects of CV are reviewed. Presented also in this review are the current uses and administration, potential drug interactions, and contraindication of aqueous extracts prepared from CV.*

Journal of Clinical Pharmacology, 2002;42:976-984

Coriolus versicolor (CV) is the dried fruiting body or mycelia of *Coriolus versicolor* (L. er. Fr) Quel (alternative names: *Polyporus versicolor*, *Polysticutus versicolor* Fr., *Trametes Versicolor* [Fr.] Pil.) belonging to the Basidiomycetes class and Polyporaceae family.[1-3] In China, CV is named *Yun Zhi* (i.e., cloud-like mushroom), probably due to the fact that its wavy surface is covered with fluff (Figure 1). CV is called "turkey tail" in some European countries because it is fan shaped; is zoned with shades of brown, white, and gray in color on the upper surface; and grows in overlapping clusters on dead logs. In Japan, CV is known as *kawaratake*, which means "mushroom by the river bank."[1,2]

TRADITIONAL USES

More than 120 strains of CV were recorded in the *Compendium of Chinese Materia Medica*.[3] According to the theory of traditional Chinese medicine (TCM) practice, CV has a slightly sweet taste and cold property, exerting its effects via the liver and spleen in the body.[4] As a medicinal substance documented in some TCM classics, CV is considered useful for dispelling heat, removing toxins, strengthening physique, increasing energy and spirit, and enhancing the host's immune function.[2,4] In the clinical practice of TCM, CV is often indicated for various types of cancers, chronic hepatitis, and infections of the upper respiratory, urinary, and digestive tracts.[1,3,4]

PHARMACOLOGICAL ACTIONS

Effects on Immune System

The immunological activities of aqueous CV extracts have been extensively investigated both in vitro and in vivo over the past three decades.[5-10] In the in vitro situation, these extracts were found effective for activating T lymphocytes,[7,8,11-15] B lymphocytes,[7,12] monocytes/macrophages,[7,10-12,15] bone marrow cells,[7] natural killer cells, and lymphocyte-activated killer cells[11,12] as well as promoting the proliferation and/or production of antibodies and various cytokines such as interleukin (IL)-2 and IL-6, interferons, and tumor necrotic factor.[12] The immunomodulatory action of the extracts administered either orally or intraperitoneally was further substantiated by an augmentation of the ex vivo tumor

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Figure 1. Dried Coriolus versicolor *mushrooms. (Photograph by Albert H. L. Chow)*

cytotoxic activity of splenocytes and T-killer cells isolated from tumor-implanted mice.[12,15]

Numerous in vivo studies have revealed that aqueous CV extracts generally possess no significant immunological effect in the normal host but have the ability to restore certain depressed immunological responsiveness caused by tumor burden or chemotherapy back to the normal level.[8,16-18] Furthermore, the stimulatory effects of CV on the production of complement, interferon, and ILs have been observed in vivo.[16,17,19,20] The CV extract was also shown capable of enhancing the host's resistance to bacterial and fungal infections when administered intraperitoneally.[12]

Antitumor Effects

Several in vitro studies have suggested that CV extracts possess selective cytotoxic activity against certain tumor cells. Xu[21] reported that the growth of several human cancer cell lines—namely, gastric cancer (7907), lung cancer (SPC), leukemia (MCL), and lymphoma (SLY)—was markedly inhibited by a crude CV extract at 1 mg/ml after 72 hours of incubation. Similar findings were obtained by Yang and coworkers[2,18,22-24] for an acidic CV purified fraction, which inhibited the growth of the human leukemia cell line (HK-60), liver cancer cell line (SMMU-7721), and stomach cancer cell line (SCG-7901) at 100 μg/ml after 96 hours of incubation but exerted very little effect on normal cell lines such as human fetal liver and lung cells. Wan et al[25] attributed the antitumor activity of CV extracts to selective inhibitory actions against cellular DNA synthesis and division rather than apoptosis. However, this explanation cannot rationalize the observed contrasting effects of the extracts on the growth of tumor cells and of normal proliferative cells such as the lymphocytes and pluripotent stem cells. Thus, the cytotoxic mechanism of CV extracts still remains a subject of considerable debate.

The in vivo antitumor activities of CV extracts have also been extensively studied. A significant reduction of the tumor size after prolonged administration with CV extract was clearly shown in mice inoculated with leukemia cell (P388, HL-30, L1210),[9,10] nasopharyngeal carcinoma, lung adenocarcinoma (Lewis),[26,27] liver cancer (HEPG2, AH13, AH44, AH66, AH7974, AH66F),[28]

fibrosarcoma (MethA, SMT-2, SMT-5), mastocytoma (P815), mammary tumor, sarcoma (NH_2-resistant strain, Walker 256, MCS-8, MCS-1, MC-2, melanoma B16), or colon cancer. The extract also appeared to be effective for the prophylaxis against esophageal, colon, breast, liver, lung, and bladder cancers.[12]

Antimicrobial Effects

In some in vivo animal studies, CV extract was observed to display a broad spectrum of antibacterial and antifungal activities against common pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococus aureus*, *Candida albicans*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, and *Streptococus pneumoniae*. Intraperitoneal administration was more effective than oral administration, which required repeated administration for 2 weeks before significant therapeutic effect could be achieved.[16] The observed antimicrobial effects of the extract are possibly due to the activation of polymorphonuclear cells and an increased secretion of antimicrobial cytokines (e.g., tumor necrosis factor, IL-1). CV extracts have also been reported to show in vitro antiviral activities.[29,30]

Other Pharmacological Effects

Hepato-protective and analgesic activities have also been demonstrated with CV extracts.[31,32]

ACTIVE INGREDIENTS

The chemical composition of CV is understandably complex, based on consideration of its diverse biological activity profile. Various classes of compounds have been suggested to be responsible for the biological activities (immunostimulatory activity in particular) of aqueous CV extracts (Figure 2).[33] Of all these ingredients, polysaccharopeptide (PSP) is considered the major or representative category. Listed in Table I are the physicochemical properties of some of these compounds. Since PSP probably represents a homogeneous mixture of macromolecules with closely similar physicochemical characteristics, isolation of a single pure PSP for structural elucidation is technically difficult if not impossible. To date, only a few key structural features of PSP have been identified using a combination of less specific characterization techniques. These characterization studies suggested that PSP is a group of polysaccharides chemically linked to certain peptides. The polysaccharide strand is a β(1 → 3)-glucan

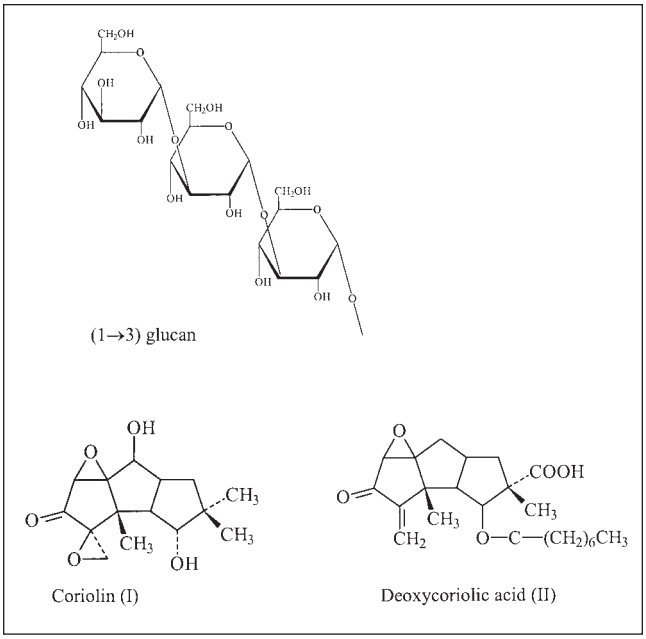

Figure 2. Chemical structures of some reported active constituents of Coriolus versicolor.[33]

branching at 4' and 6' positions. The peptide moiety is rich in aspartic and glutamic acids. Many other amino acids are also present but in a relatively small amount.[12] Aqueous extracts of CV usually contain PSP of widely different molecular weights. Only the ones of high molecular weight (i.e., > 10 kDa) are generally considered immunologically active.[5,34]

CLINICAL STUDIES

The therapeutic use of CV as an adjunct therapy in cancer treatment has been substantiated by numerous clinical trials employing PSP or PSK (Krestin), two of the most popular proprietary products manufactured from aqueous extracts of *Coriolus versicolor*. Table II summarizes the methodological parameters and the results of some of these trials. The methodological quality of these trials has been evaluated using the approach developed by Jadad et al with modification.[35] It is widely accepted that conventional cancer treatment provides palliative rather than curative therapy for many forms of cancers, which results in temporary clearing of the signs of cancer with the possibility of relapse right after stopping the cancer therapy.[36] Since a cure for cancer with conventional cancer therapies is normally not possible, these trials mainly focused on assessing

Table I Active Constituents Reported to Be Present in *Coriolus versicolor*

Chemical Class	Name	Source	Physicochemical Properties	Chemical Composition	Biological Properties	Reference
Polysaccharopeptides	PSK (Krestin)	Mycelia of *Coriolus versicolor* CM-101 strain	Brown in color; soluble in water; insoluble in organic solvents; stable to heat; mean MW = 100 kDa	18%-38% w/w protein (1 → 3)β-glucan branched at 4' and 6' positions	In vitro and in vivo immunorestorative and antitumor activities	16, 42
	PSP	Mycelia of *Coriolus versicolor* Cov-1 strain	Brown in color; soluble in water; insoluble in organic solvents; stable to heat; mean MW = 100 kDa	(1 → 3)β-glucan branched at 4' and 6' positions	In vitro and in vivo immunorestorative and antitumor activities	19
Polysaccharides	CVG (CV glucan)	Mycelia of *Coriolus versicolor* Iwade	White powder; soluble in water and DMSO; insoluble in organic solvents; heat stable; MW > 2000 kDa	Elemental analysis: C = 38%, H = 5.7%; glucose content = 98.4%-99.8%; (1 → 3)β-glucan	Enhance the antitumor effect of chemotherapy in vivo	55
	Coriolin I & II	Mycelia or fruiting body of *Coriolus versicolor*	MW: Coriolin I = 110 kDa; Coriolin II = 10 kDa	Monosaccharide units: glucose, fucose, mannose, galactose, galactose, and rhamnose; (1 → 3)β-glucan	In vivo antitumor and immunorestorative effect	33
Polypeptides	PCV (Peptide CV)	PSP	MW = 10 and 50 kDa		In vitro inhibitory effect on different human cancer cell lines; in vivo effects on proliferating white blood cells and increasing the weight of immune organs	18
	RNase-CV	PSP	Acidic; MW = 10-16 kDa	Partial amino acid sequence: Gly-Thr-Ala-Ala-Lys-Glu-Phe-Glu-Arg-Glu-His-Met	In vitro inhibitory effect on different human cancer cell lines; in vivo antitumor activities; in vivo immunostimulatory effects	22
Small molecules	Coriolin (I)	Mycelia of *Coriolus consors*	Colorless; needle shaped; melting point 175°C; soluble in polar organic solvents and water; MW = 280 Da	Elemental analysis: C = 63.6, H = 7.2, N = 0; sesquiterpene	In vitro inhibitory effect on the growth of gram +ve and –ve bacteria; little inhibitory effect on leukemia 1210 cell line	33
	Deoxycoriolic acid (II)	Mycelia of *Coriolus consors*	Colorless; oily; soluble in organic solvents; insoluble in water; MW = 404.2	Elemental analysis: C = 68.2, H = 8.2	Inhibitory effect on certain bacteria and tumor	33

Table II Assessment of Methodological Parameters on Clinical Trials of Some Aqueous Extracts of *Coriolus versicolor*

Reference	Jadad Score (maximum = 8)	Study Design	Sample Size (intervention/control)	Inclusion/Exclusion Criteria of the Studies	Treatment Schedule (intervention/control)	Results
37	1	Two parallel groups, follow-up study	185 stage I to III non-small-cell lung cancer patients treated with radical radiotherapy	Patients considered to be highly curable	One group of patients received PSK (3 g/day) for 2 weeks alternating with a 2-week rest period for 5 years.	PSK group showed significantly higher 2-year and 5-year survival rates ($p < 0.05$). Patients with better general health were more responsive to PSK treatment than those of poor performance status.
38	5	Randomization, follow-up study	540 estrogen receptor–positive breast cancer patients who underwent total mastectomy plus axillary dissection and received chemotherapy	Patients with bilateral breast cancer, patients with non-invasive carcinoma, males with breast cancer, patients with inflammatory breast cancer, pregnant or lactating patients, and patients with double cancers were excluded. Patients with leukocyte count > 3000/µl, platelet count > 100,000/µl, total protein level > 6.0 g/dl, and no other medical illness were included.	525/540 patients were randomly assigned to receive chemotherapy plus ftorafur (600 mg/day), chemotherapy plus PSK (3 g/day), or chemotherapy alone for 2 years.	Estrogen receptor +ve patients administered with PSK or ftorafur also showed significant improvement in 5-year survival rate and relapse-free period compared with the control ($p < 0.05$). No significant difference between the three patient groups in estrogen receptor –ve patients. Patients receiving PSK suffered fewer side effects than those receiving ftorafur.
39	4	Randomization, follow-up study	262 gastric cancer patients receiving surgery and chemotherapy	Patients with age > 75 years and having a positive purified protein derivative skin test and a primary tumor of T_2 or T_3 were included. Patients who underwent any radiotherapy, chemotherapy, or immunotherapy or having multiple cancers, severe complications, or any abnormal hematological findings were excluded.	245/262 patients were randomly assigned to control (chemotherapy) and treatment (chemotherapy plus PSK [3 g/day for 4 weeks alternating with a 4-week rest period]) groups.	PSK treatment group showed significantly higher 5-year disease-free survival ($p < 0.05$) and overall survival rate ($p < 0.05$). No difference in the side effect profile between two groups was found.
40	3	Randomization, follow-up study	65 patients with hepatocellular carcinoma receiving chemotherapy	Patients with life expectancy greater than 3 months, absence of any serious cardiac or renal problem, and absence of hypersensitivity to OK-432 were included; those with white blood cell count > 2000/µl, platelet count > 40,000/µl, and hemoglobin > 8 g/dl were included.	58/65 patients receiving chemotherapy were randomly assigned to one of the following four groups—namely, PSK (3 g/day every other week) group, lentinan (2 mg IV once a week) group, OK-432 (0.2-0.5 KE s.c. once a week) group, and control group.	No significant difference in survival rate in the four patient groups. No change in CD4+/CD8+ in all patients except those from PSK groups, which showed an unexpected decrease.

(continued)

Table II continued

Reference	Jadad Score (maximum = 8)	Study Design	Sample Size (intervention/control)	Inclusion/Exclusion Criteria of the Studies	Treatment Schedule (intervention/control)	Results
41	3	Randomization, follow-up study	359 patients with estrogen receptor–negative breast cancer	Women younger than 76 years of age with stage IIA, IIB, or IIIA primary breast cancer who had received any extended, standard, or modified radical mastectomy were included. Patients with bilateral cancer with non-invasive carcinoma, distant metastasis, nodal fixation, fixation to chest wall, and ulceration; patients who were pregnant or lactating; patients with a history of cancer in another organ; and patients who underwent prior therapy for breast cancer were excluded.	Patients received either standard chemotherapy or chemotherapy plus PSK (3 g/day) for 2 years.	No significant difference in the relapse-free survival or overall survival between the control and the PSK treatment group. No marked side effect due to PSK was found.
45	3	Double blind, randomization, placebo controlled	50 gastric cancer patients receiving surgery and chemotherapy		Patients received either PSP (3 g/day) or placebo for 3 months	Natural killer cells (NK) activity and CD4+/CD8+ increased significantly compared with control ($p < 0.05$).
46	4	Double blind, randomization, placebo controlled	151 inpatients with nonparvicellar lung cancer	Patients with high performance status; life expectancy > 3 months; no serious heart, liver, or kidney disease; normal hematological picture; and normal lung and liver functions were included.	Patients received either PSP (3 g/day) or placebo for 1 to 2 months.	Significant improvement of subjective assessment of some general symptoms. NK activity and IL-2 level increased significantly ($p < 0.05$).
47	4	Randomization, placebo controlled	82 gastric cancer patients receiving surgery and chemotherapy	Patients of age < 70, life expectancy > 3 months, and who had no major organ failure and received no chemotherapy or immunotherapy in the past 4 months	Patients received either chemotherapy plus PSP (3 g/day) for 2 months or chemotherapy alone.	NK activity, IL-2 level, and CD4+/CD8+ increased significantly compared with control ($p < 0.05$). No difference in toxicity (e.g., GI discomfort between treatment and control groups) was found.

the effects of the extract on the prolongation of the relapse-free period and improvement of prognosis in patients suffering from various kinds of cancer. With respect to these assessment parameters, the clinical usefulness of the extract appeared to be more evident for gastric and esophageal cancers than for breast, lung, and liver cancers.[37-42] Another clinical aspect of CV extracts that has been extensively studied is the immunopotentiating effect. Restoration of the immune status of cancer patients is important since development of leukopenia or thrombocyopenia, a common side effect of radiotherapy and chemotherapy, may necessitate not only dose reduction but also interruption of conventional cancer therapies.[36,43] In addition, immunocompromised patients are more exposed to the risk of opportunistic infections.[44] Based on the clinical data accrued to date, CV extracts appear highly effective for restoring depressed blood levels of lymphocytes and IL-2 and weakened antitumor activity of natural killer cells.[45-50] It is worth noting that patients with better immunocompetence and less severe forms of cancer show a better response to the administered CV extract. This suggests that the efficacy of the CV extract in the body is closely linked to the host's immune status.

DOSAGE

A dosage of 9 to 15 g CV decocted with water is recommended for oral daily dosing.[4] For dried CV extracts, 3 to 6 g is the daily oral dosage used in most clinical trials.

ADVERSE EFFECTS/TOXICITY

The LD_{50} of crude CV extract administered orally in mice was greater than 18 g/kg. No death, toxic symptoms, or obvious hematological and pathohistological changes were observed after a 3-month dosing period. No mutagenic and cytotoxic effects were detected with high doses of CV extract.[51-53]

DRUG INTERACTION

To date, no clearly defined drug interaction has been reported for CV. However, being an effective stimulant of various immunocompetent cells, CV can potentially counteract the effect of any coadministered immunosuppressant.

CONTRAINDICATION

CV is generally considered safe for human consumption, irrespective of age and gender. However, the use of CV may be contraindicated in patients suffering from autoimmune diseases or receiving bone marrow transplant.

REGULATORY STATUS

CV extracts are widely available as oral proprietary products on the market. These products are normally considered as health supplements and can be purchased without a prescription even though they are extensively used in cancer treatment for the relief of the side effects associated with radiation therapy and chemotherapy. However, in China and Japan, certain CV products are classified as drugs for specific therapeutic indications. The health authorities of Japan only regard CV extract useful as an adjunct therapeutic remedy and require it to be used in combination with other chemotherapeutic agents for the treatment of cancer.[54]

CONCLUSION

A substantial number of reports based on preclinical and clinical studies have clearly attested to the therapeutic values of aqueous CV extracts in the treatment of cancer. The clinical efficacy of the extracts after oral administration has been demonstrated in more than 30 clinical trials in which significant improvement in both survival rate and general health status was generally observed in cancer patients receiving chemotherapy and/or radiotherapy. Polysaccharopeptide (peptide-linked polysaccharide) with an average molecular weight in excess of 100 kDa is generally believed to be the principal component responsible for the immunomodulatory actions of CV. In conclusion, being an effective immunomodulant or immunostimulant with virtually no side effects, CV extract offers tremendous potential for development into an evidence-based oral immunotherapeutic agent.

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