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Professional Resource: Coriolus Versicolor

Brief Background

Medicinal mushrooms have been used in traditional oriental therapy throughout history, with polysaccharopeptides being one of the most highly studied constituents (1). One of the most common mushrooms is *Coriolus versicolor (Coriolus)*, a fungus that grows in wooded temperate zones year round on tree trunks, stumps, dead logs, and branches. In traditional oriental medicine, *Coriolus* was dried and ground into a tea where the observed healing properties prompted Chinese and Japanese scientists to begin clinical research on the use of this mushroom in clinical practice. The most common commercial extracts include polysaccharopeptide Krestin (PSK), the Japanese version, and polysaccharopeptide PSP, the Chinese version. Both are extracted from *Coriolus* mycelia. Numerous other neutraceutical extract preparations are available worldwide in forms such as tablets, syrups, capsules, food additives, and traditional forms such as teas.

Proper Name

Coriolus versicolor

Common Names

Agaricus versicolor; Boletus versicolor; Polyporus versicolor; Polystictus versicolor; Poria Versicolor; Trametes versicolor; Yun-Zhi (Chinese); Kawaratake (Japanese); PSP; PSK; Turkey Tail

Common Uses in Cancer Care

Coriolus is most commonly prescribed in cancer care to:

- Stimulate the immune system
- Inhibit the growth of cancer cells
- Reduce side effects from chemotherapy and/or radiotherapy
- Improve cancer related symptoms
- Slow disease progression
- Improve quality of life

Route of Administration

Coriolus extracts are most commonly administered orally in capsule form.

Mechanism of Action

Coriolus polysaccharopeptides have a broad range of physiological activity including immune system enhancement, antitumor and anticancer effects, antimicrobial effects, and various other effects contributing to increased quality of life (2). These extracts are classified as biological response modifiers and are accepted as beneficial adjuncts to conventional therapies in many countries around the world.

Coriolus extracts have been studied both in vivo and in vitro for their immunological activities, although the exact mechanism of these actions remains to be fully understood. Immunopotentiation is said to occur by activation of B lymphocytes, T lymphocytes, macrophages and monocytes, bone marrow cells, natural killer cells, and lymphocyte-activation killer cells (1–5). *Coriolus* extracts are also known to induce production/proliferation of various antibodies and cytokines such as interferons, interleukin-2 and interleukin-6, tumor necrosis factor, and immunoglobulin-G (1–3). In vivo, *Coriolus* extracts have also demonstrated the ability to restore immunosuppression resulting from cancer as well as treatments such as chemotherapy, radiation and blood transfusions (1,2,6). It is this ability to counteract some of the negative effects of chemotherapy on immune function and the induction of leukopenia that makes *Coriolus* a beneficial therapy in combination with various chemotherapeutic agents (6).

In vivo and in vitro, *Coriolus* extracts display cytotoxic, antitumor activities against multiple tumor cell lines and cancer types including leukemia, lymphoma, esophageal, colon, breast, gastric, liver, lung, bladder, gastric, and various other types of cancer (2,5). These extracts are thought to induce apoptosis and prohibit angiogenesis via the production of glutathione peroxidase and superoxide dismutase, anti-inflammatory action, and overall immune system enhancement (1,2,6).

In numerous studies, *Coriolus* extracts have demonstrated antiviral, antifungal, and antibacterial activities against a wide range of common pathogens including *Pseudomonas aeruginosa, Candida albicans, Escherichia coli, Staphylococcus aureus, Streptococus pneumoniae, Listeria monocytogenes, and Klebsiella pneumonia* (2). These effects are most likely due to an increased secretion of antimicrobial cytokines as well as through the stimulation of polymorphonuclear cells.

Coriolus is said to improve quality of life through multiple actions including analgesic properties, hepato-protection, appetite improvement, reduction in intestinal disorders and a general calming of the central nervous system (1,2,6).

Clinical Evidence related to Effectiveness

There have been numerous clinical studies conducted over the past several decades to assess the effectiveness of *Coriolus* as a treatment in cancer care. Human level evidence varies in quality and ranges from individual case reports, to randomized controlled trials (RCTs). The evidence has also been reviewed and pooled in systematic reviews and meta-analyses. Overall, *Coriolus* extracts appear to be effective in particular for improving survival, immune response, quality of life and symptom management.

Survival

A recent systematic review and meta-analysis included data from 13 randomized control trials (RCT) including 2,587 cancer patients randomized to receive doses of *Coriolus* ranging from 1-3.6 g daily, or

placebo, plus standard care for the duration of 1-36 months (7). Results indicated a significant survival advantage for people treated with *Coriolus* plus standard care over people treated with standard care alone. Overall, for people randomized to a *Coriolus* group, there was a 9% reduction in 5-year mortality (95% CI: 1.07-1.16; p<0.001), an effect that was observed among people diagnosed with breast, gastric and colorectal cancer but not esophageal cancer or nasopharyngeal carcinoma.

A separate meta-analysis specific to curatively resected colon cancer calculated overall survival and disease-free survival using data from three RCTs including 1,094 patients (8). Results were analyzed using the weighted average of the individual log hazard ratios, with the overall survival risk ratio for all eligible patients calculated as 0.71 (95% confidence interval (CI): 0.55–0.90; P=0.006), and the disease-free survival ratio as 0.72 (95% CI: 0.58–0.90; P=0.003). According to these results, the addition of *Coriolus* extract to the standard oral fluorinated pyrimidine based chemotherapy may offer a significant advantage in terms of both survival and disease-free survival over chemotherapy alone in patients with curatively resected colorectal cancer.

Similarly, a meta-analysis specific to curatively resected gastric cancer evaluated the effects of *Coriolus* extracts on survival in 8,009 patients enrolled in eight RCTs, with a range of quality scores (10). Data from these eight trials combined resulted in a hazard ratio of 0.88 (95% CI, 0.79–0.98; p = 0.018) indicating a statistically and clinically significant improvement in survival for people treated with a combination of *Coriolus* with chemotherapy over chemotherapy alone. These results were confirmed in a sensitivity analysis including only the three trials with the highest methodological quality (HR = 0.78; 95% CI, 0.64–0.97; P = 0.027).

The positive impact of *Coriolus* on survival has also been documented in non-randomized trials, observational studies and case reports not included in the above reviews. For example, a broad systematic review summarized the effect of the use of a variety of immunomodulatory dietary polysaccharides in both humans and animals, and concludes that in all reviewed studies *Coriolus* contributed to increased overall survival for people diagnosed with advanced stage gastric, colon and colorectal cancer (9). Methodological quality of included studies was not addressed in this review.

Several non-RCTs examined the effects of *Coriolus* on survival in gastric cancer patients with mixed results. In one retrospective study investigating the use of *Coriolus* after non-curative resection in stage IV gastric cancer patients, the 5 and 10-year survival rates in the *Coriolus* groups were significantly higher than in the non-*Coriolus* groups, with the rate being the highest in those patients with severe lymph node metastases (14); yet another retrospective study found no significant improvement, except when adjusted for disease stage when people diagnosed as stage III did seem to have a more favourable response (15). One observational study found that a combination chemotherapy including *Coriolus* improved the 15-year survival rate in patients with advanced gastric cancer after curative resection (16). In a single case study report of a 45-year-old male with gastric cancer, long-term survival of 5 years and 10 months was achieved after postoperative treatment comprised of UFT with *Coriolus* (17).

Among non-RCTs for patients with colon cancer, one retrospective study involving patients with primary colorectal cancer found a significant difference in 5-year survival rates (92.2%) in those treated with a combination of chemotherapy and *Coriolus* versus those treated with chemotherapy alone (83.5%) or without any chemotherapy (66.5%) following resection (24). In a retrospective analysis of 101 primary colorectal cancer patients assigned to receive either oral fluoropyrimidines alone or with the addition of *Coriolus* post-surgically, the 10-year survival rates for the *Coriolus* group were significantly higher (81.9%) than the control group (50.6%) (25). In another retrospective analysis of 63 elderly patients with

resected colorectal cancer, patients receiving UFT plus *Coriolus* demonstrated significantly better 3-year relapse-free and overall survival rates than those treated with UFT alone (26).

Immune System Response

A number of RCTs have investigated the effects of *Coriolus* extracts on immune system response in healthy individuals as well as people with a cancer diagnosis. Overall, the body of evidence indicates a positive impact of *Coriolus* use on the immune system.

One RCT sought to determine the immunological effects of *Coriolus* on 100 healthy subjects and found that regular oral consumption of *Coriolus* could significantly elevate PBMC gene expression of interleukin (IL)-2 receptor, increase the percentage and absolute counts of T helper cell and the ratio of CD4+ (T helper)/CD8+ (T suppressor and cytotoxic T) cells, as well as significantly enhance the ex vivo production of typical Th1 cytokine interferon-g from PBMC activated by phytohemaglutinin and lipopolysaccharide (all $p < 0.005$) (31).

One RCT involving patients with gastric cancer receiving either UFT alone or UFT in combination with *Coriolus* documented a significant reduction in the proportion of CD57 T cells in patients receiving the combination treatment but no significant difference in any other immune cells (3). Another RCT comprised of gastric cancer patients elucidated that a change in stimulation index (SI) seen in those patients receiving *Coriolus* may be associated with an inhibition of immunosuppressive activity in cancer patients, with higher SI group achieving a much higher overall survival rate than in the low SI group (11). In an RCT involving stage III gastric cancer patients, those patients receiving a combination of the chemotherapy drug S-1 with *Coriolus* demonstrated a significantly lower T-cell apoptosis than those receiving S-1 alone, thus it was concluded that *Coriolus* was able to partially prevent apoptosis of peripheral blood T cells that commonly occurs in patients receiving chemotherapies such as S-1 (32). Another RCT assessed the immunological effects of *Coriolus* in patients with gastrointestinal cancer by duration and frequency of administration and found that the effects of *Coriolus* were significantly influenced by duration, but not by frequency of administration (33). In those patients receiving *Coriolus* longer than 14 days, there were an increased number of cytotoxic effecter cells in the peripheral blood lymphocytes as well as an increase in helper T cells and a decrease in suppressor cells in the regional node lymphocytes.

One RCT elucidated which immunological markers could indicate *Coriolus* effectiveness in terms of disease-free survival in stage II and III colorectal cancer patients and found that *Coriolus* decreased the mean serum immunosuppressive acidic protein level, and increased the mean population of natural killer cells compared with the controls, and both changes were associated with greater overall disease-free survival (34). In an RCT of 87 patients with colorectal cancer, it was determined that preoperative carcinoembryonic antigen levels and purified protein derivative reaction values were predicative markers of increased 7-year survival (overall, cancer-death, and disease-free) in the *Coriolus* group as compared to the control group (35). In another RCT, 111 patients with colorectal cancer were randomized to receive either *Coriolus* or a placebo post-surgically and increased survival was already mentioned above; the *Coriolus* group also demonstrated enhancement in the activities of polymorphonuclear leukocytes over those in the control group (23).

In an RCT involving 58 patients with hepatocellular carcinoma, patients were randomized to one of four groups receiving either 5-FU alone or in combination with lentinan, OK-432, or *Coriolus* (36). In the *Coriolus* group alone, the T4/T8 ratio of lymphocytes was reduced after therapy, however there was no

significant difference among the groups in terms of mean survival time, mortality rate, or time to progression.

In a phase-II double blind RCT involving 34 patients with non-small cell lung cancer, all patients received paclitaxol and carboplatin plus either *Coriolus* or a placebo (37). After just 28 days of treatment, those patients in the *Coriolus* group significant improvement in blood leukocyte and neutrophil counts, serum IgG and IgM, and percent of body fat over the control group.

In a non-randomized, control trial involving patients with primary colorectal or gastric cancer, those patients who received *Coriolus* demonstrated a shift of the Th1/Th2 and DC1/DC2 balance from Th2 and DC2 dominance which are typical in cancer patients towards Th1 and DC1 dominance, generally associated with healthy, non-cancer patients as well as a significant decrease in IL-10 production (38). One interventional study comprised of ten patients with metastatic colorectal cancer found that a combination of cisplatin with UFT and *Coriolus* reduced serum concentration of interleukin-2 and tumor necrosis factor ($p < 0.05$) after two months of treatment, suggesting that this combination has immunomodulative potential in this group of patients (39).

Adverse Events and Side Effects

In the majority of studies involving *Coriolus*, no adverse reactions or side effects are reported. In those studies in which side effects are reported, they are usually mild and limited to gastrointestinal symptoms and cannot be distinguished from concurrent treatment with chemotherapeutics or the disease process itself. In one systematic review and meta-analysis including 2,587 patients, adverse effects were reported in both the *Coriolus* groups and control groups, including mild nausea and/or vomiting, diarrhea, liver dysfunction and leucopenia (7). In an RCT involving gastric cancer patients randomized to receive either standard chemotherapy alone or with the addition of *Coriolus*, side effects consisted of nausea, leucopenia, and liver function impairment, although there were no significant differences between the groups (12). In another RCT comprised of colorectal cancer patients receiving either *Coriolus* or a placebo, pigmentation of nails and coughing were both increased in the *Coriolus* group, although it was noted that the coughing may be due to the powder form that the *Coriolus* was administered in; although diarrhea and constipation were also noted symptoms, there were no significant differences between the *Coriolus* and the control group (23). One RCT involving 100 healthy subjects given 50mg/kg of body weight *Coriolus* over a period of time found no adverse effects on liver or renal function nor on biochemical bone profile (31).

It has been reported that the LD_{50} of *Coriolus* extract administered to mice is greater than 18 g/kg with no death, toxicity, or obvious hematological and pathohistological changes seen after a 3-month period (2). Further, no mutagenic or cytotoxic effects were observed in high dose administration of *Coriolus*. Toxicological assessments have concluded a low toxicity with a high median lethal dose, and no abnormalities were observed in animals or humans following acute and chronic toxicity tests (5).

Interactions with other Therapies, including Drugs and Natural Health Products

Numerous studies have demonstrated the safety of *Coriolus* combined with various forms of chemotherapy (3, 11, 13-22, 24-30, 32, 36-37, 39). One study specifically examined the effects of *Coriolus* on the metabolism of tegafur to 5-FU and found no potential negative interaction (40).

Due to the stimulatory effects of *Coriolus* on immunocompetent cells, there is the potential for counteraction when administered with immunosuppressants (2). Therefore, caution should be exercised when administering *Coriolus* alongside immunosuppressants, or this combination should be avoid altogether.

Thrombocytopenia has been observed in patients receiving co-therapy with *Coriolus* and chemotherapy, and while it cannot be determined if this was attributable to the chemotherapy or the *Coriolus*, caution should be used when administering these therapies together (12,41).

Cautions and Contraindications

Coriolus is considered safe for human consumption regardless of age or gender; however use may be contraindicated in patients receiving a bone marrow transplant or those suffering from autoimmune diseases (2). Further, *Coriolus* has been known to cause leukopenia, therefore caution should be used in those with suppressed immune systems (20,41). The use of *Coriolus* should be completely avoided in anyone with known allergies or hypersensitivities to *Coriolus* or any of its constituents.

Coriolus should be used cautiously in patients with known bleeding or clotting disorders and in those using anticoagulant or antiplatelet agents, as *Coriolus* has been associated with thrombocytopenia (20).

Coriolus has been reported to cause liver damage, therefore liver enzymes should be monitored closely in all people treated with *Coriolus* (20,41).

Coriolus is not recommended during pregnancy or lactation due to a lack of sufficient data.

Dosing, frequency and length of treatment

Recommended oral doses of *Coriolus* extract decocted with water are 9-15 g daily while the dose for dried *Coriolus* extracts is 3-6 grams daily (2).

Disclaimer

The OICC has prepared this monograph, as part of a series, to share results of a review of the scientific literature related to common therapies and products used within patient care at our centre. It therefore reflects therapies and products used within the defined scope of practice for our practitioners in Ontario, Canada. The information in this monograph should not be interpreted as medical advice nor should replace the advice of a qualified healthcare provider.

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