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Coriolus versicolor mushroom for colorectal cancer treatment (Protocol)

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[Intervention Protocol]

Coriolus versicolor mushroom for colorectal cancer treatment

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

- To assess the effects of *Coriolus versicolor* and its extracts on adverse effects during cancer treatment (chemotherapy and radiotherapy).
- To assess effects due to *Coriolus versicolor* and its extracts on survival, recurrence, and disease progression.
- To evaluate the evidence in relation to the type of preparation of the mushroom (e.g. whole fresh, dried, or extract).

BACKGROUND

Description of the condition

Approximately 12.7 million new cases of cancer were diagnosed worldwide in 2008. Colorectal cancer is the third most common cancer, with an increasing incidence in the developing world (IARC and Cancer Research UK 2012). Colorectal cancer includes colon (large bowel) cancer and cancer of the rectum (the last portion of the gastro-intestinal tract before the anus). It may result in blood in the stools and gastro-intestinal symptoms including constipation, bloating and bowel obstruction. The treatment of colorectal cancer may involve surgery, chemotherapy, and possibly radiotherapy, or a strategy using monoclonal antibodies (antibodies designed to target specific types of cells) (NCI 2013; NICE 2011). Both the disease and its treatment may cause symptoms such as fatigue, anorexia, or depression, which adversely affect the quality of life of patients with colorectal cancer (Gray 2011). Chemotherapy regimens incorporating oxaliplatin or irinotecan, or both, may be more effective at preventing recurrence or delaying disease progression than those based solely on 5-fluorouracil/leucovorin, but serious adverse events and discontinuation of treatment due to toxicity are more frequent (Pandor 2006). Treatment-related adverse effects, including diarrhoea, neutropenia (low levels of neutrophils), stomatitis (inflammation of the mouth), nausea and vomiting, peripheral neuropathy (nerve damage), and hand-foot syndrome, are reported in about half of the patients treated (Schmoll 2007). Toxicity may be severe in 5% to 30% of patients,

requiring dose reduction or withdrawal of potentially life-saving or life-prolonging treatment. Thus, there is a need for adjuvant therapies that can support colorectal cancer patients through conventional cancer therapy by alleviating symptoms and side effects without adversely affecting overall survival.

Description of the intervention

Mushrooms have a long history of use to promote health in China and Japan and, as some mushroom preparations are orally bioavailable, they are relatively easy to administer (Lindequist 2005). Medicinal mushrooms appear to have low toxicity and useful immune-modulating and health-promoting properties that may combat fatigue and aid cellular repair. Numerous studies have been conducted in humans and several mushroom extracts are licensed as adjuvant treatments in oncology practice in Japan (Kidd 2000). There has been increasing interest in their use in western countries and they appear to be popular in the USA among cancer patients (Standish 2008), where they can be purchased without prescription. The four mushrooms commonly used clinically are *Coriolus versicolor* (also known as *Trametes versicolor*, Japanese and Chinese names Kawaratake and Yun Zhi, respectively), *Ganoderma lucidum* (Reishi or Ling Zhi), *Lentinula edodes* (Shiitake or Hua Gu/Xiang Gu) and *Grifola frondosa* (Maitake or Hui Shu Hua) (Smith 2000).

The *Coriolus versicolor* fungus, the focus of this review, has a colourful fruiting body with features that resemble a 'turkey tail'. It grows on dead logs in many countries worldwide and is not edible. Hot-water extracts of the whole fruiting body have been used in traditional Chinese medicine since historic times (Smith 2000). Today, two commercial extracts are used clinically in the Far East: polysaccharide-K (PSK) and polysaccharopeptide (polysaccharide-peptide or PSP). Both are orally bioavailable extracts from the cultured mycelium (the filamentous part of the mushroom that grows through the soil) of the *Coriolus versicolor* fungus. PSK (or Krestin®) was developed in Japan in the 1960s and is a soluble protein-bound polysaccharide derived from the CM-101 strain of the fungus. PSP was developed in China in the 1980s and is a polysaccharide-peptide derived from the COV-1 strain (Kidd 2000; Smith 2000). The molecular weights of the two preparations (about 100 kDa) and the biochemical compositions are similar but not identical. Commercial cultivation and production aims to ensure a steady supply of the fungus, control of the polysaccharide concentration (which varies considerably in the plant depending on growth phase and storage conditions) and purity of the final product. However, over-the-counter products may not be standardised (Memorial Sloan-Kettering 2012).

Coriolus extracts are used as adjuvant therapy for treating cancers, either combined with herbal mixtures in Asian cultures, or combined with conventional chemotherapy/radiotherapy, and they have been reported to have an effect by boosting suppressed immune function, extending the survival rate and improving quality of life (Eliza 2012).

Recommended doses vary according to the preparation. In the Chinese Pharmacopoeia, the recommended dose of *C. versicolor* is 9 g to 27 g daily (Chinese Pharmacopoeia 2005). The daily dose of the authorised PSK product (Krestin®), according to the manufacturer, is 3 g (Daiichi-Sankyo 2012). Doses of PSK most commonly used in clinical trials in cancer have been between 1 g and 3.6 g daily (Eliza 2012). Data available on pharmacokinetics are based mainly on studies in animal (small mammal) models. These indicate that PSK is rapidly absorbed and partly metabolised in the gastro-intestinal tract. Peak plasma levels occur between 0.5 to 2 hours for small molecules and 4 to 24 hours for large molecules (Memorial Sloan-Kettering 2012). Excretion is primarily through the lungs with 70% excreted in expired air after 24 hours (Daiichi-Sankyo 2012; Mitomi 1988). Radiolabelled PSK or its metabolites are also excreted in the urine and faeces with 86% excreted within 24 hours (Memorial Sloan-Kettering 2012; Mitomi 1988). Adverse interactions between *C. versicolor* mushroom and herbs or drugs have not been reported (Natural Database 2013). PSP has been shown to affect phase I metabolism and hepatic cytochrome P450 in animal models but the potential for clinically significant interactions in humans is low (Yeung 2012).

How the intervention might work

Coriolus versicolor has been used in traditional Chinese medicine as a general 'tonic' for anorexia, fatigue, and lack of strength, and is recorded in the Chinese Pharmacopoeia as an 'immune modulator' (Chinese Pharmacopoeia 2005). The pharmacological actions of mushrooms have been studied extensively in Japan and China in animal and human studies (Rowan 2003; Sullivan 2006). These studies support the idea that they are biological response modifiers that act by stimulating the non-specific immune system (Lindequist 2005; Ng 1998).

PSK has been shown to restore immune systems depressed by chemotherapy to normal levels in animal studies, and has been reported to improve survival in clinical studies (Sakamoto 2006). PSK is also reported to attenuate the adverse reactions induced by chemotherapy or radiotherapy, including neutropenia (Maehara 2012). Similar effects are reported for PSP: results of clinical trials in China indicated reduction in chemotherapy-induced adverse effects, including vomiting, and restoration of chemotherapy-induced immunosuppression when PSP was used in combination with cytotoxic agents (Chan 2006). Such findings suggest that these extracts have the potential to improve tolerance to chemotherapy and radiotherapy and to reduce adverse effects due to depressed immune function. Both products also appear to have anti-tumour properties, which may contribute to an overall effect on survival.

The mechanism of action is yet to be fully established. The immune-potentiating activity is attributed to mushroom proteogly-

cans: these proteoglycans comprise a central linear polypeptide chain with multiple side-branches of beta-D-glucans (Kidd 2000). Multiple potential actions have been reported including suppression of tumour cell growth, reversal of immune suppression, and an increase in white blood cell counts, mediated in part by scavenging of free radicals by PSK (Fisher 2002). A review of the biological effects of PSK suggested that it had beneficial effects on cytokines ('chemical messengers') including tumour necrosis factor-alpha (TNFα), interferon-gamma (IFNγ), and interleukin-2 (IL-2) (Standish 2008). Animal studies indicate that PSK does not affect the normally functioning immune response but can contribute to the restoration of a response depressed by tumour burden or chemotherapy. Specific mechanisms considered to be involved include production of antibodies and cytokines, and improved activity of natural killer cells, T cells, macrophages, and peripheral blood lymphocytes.

While immune-stimulatory actions may contribute to the apparent beneficial effects of these extracts, the mechanism of action underlying reports of reduced adverse effects when these extracts are used in combination with anticancer agents is as yet unclear. Effects on the pharmacokinetics of cytotoxic agents have been observed in some animal studies but results from human studies indicate that clinically significant effects are unlikely (Chan 2006).

Why it is important to do this review

For colorectal cancer patients in particular, radiotherapy and chemotherapy are used to prolong life and improve survival, but side effects can be a problem with significant numbers of patients suffering severe effects (Schmoll 2007), resulting in dose reduction or cessation of treatment, which have an impact on survival. Some of these side effects, such as fatigue and peripheral neuropathy, can persist into the survivorship period, and as more cancer patients survive, the prevalence of those with persistent side effects increases (Aziz 2007). This is particularly relevant as 50% of colorectal cancer patients in the UK currently survive more than 10 years (IARC and Cancer Research UK 2012). There is a need for adjuvant therapies that can support colorectal cancer patients through conventional cancer therapy by alleviating symptoms and side effects without adversely affecting survival.

A number of reviews of the effects of mushrooms in cancer have been conducted previously. Within the Cochrane Database of Systematic Reviews, a review of *Ganoderma lucidum* (Reishi mushroom) for cancer treatment concluded that there was insufficient evidence to support its use as a first-line treatment for cancer or long-term cancer survival, but that it could be considered for use as an alternative adjunct to conventional treatment due to its potential to enhance tumour response and stimulate host immunity while being generally well tolerated (Jin 2012). Several published systematic reviews have focused on *Coriolus versicolor* and its extracts. One meta-analysis published in 2012 focused on the effects of *Coriolus versicolor* on survival in cancer patients and concluded that there was strong evidence of a beneficial effect on survival, particularly in breast, gastric, and colorectal cancer patients (Eliza 2012). However, only research published up to 2003 was included. A second meta-analysis focused on the efficacy of PSK for survival of patients with curatively resected colorectal cancer; PSK used as an adjuvant to conventional chemotherapy improved overall and disease-free survival but risk of bias and adverse events were not addressed (Sakamoto 2006). The University of Texas MD Anderson Cancer Center also produced a detailed scientific review of studies published up to March 2005, summarising and categorising the research by study design (MD Anderson 2010). A review of safety data relating to medicinal mushrooms in cancer patients showed no evidence of cytotoxicity, mutagenicity, teratogenicity, effects on female ovulation, or reproduction at acute or chronic doses (Smith 2000). Adverse effects that have been reported include possible darkening of the fingernails and faeces (Kidd 2000). No systematic review has been performed to evaluate the strength of evidence on the effects of *Coriolus versicolor* and its extracts on both adverse effects during cytotoxic treatment and on survival in colorectal cancer. Thus, a review focusing on evaluating the evidence on the adjuvant effects of *Coriolus versicolor* and its extracts in colorectal cancer is warranted.

OBJECTIVES

- To assess the effects of *Coriolus versicolor* and its extracts on adverse effects during cancer treatment (chemotherapy and radiotherapy).
- To assess effects due to *Coriolus versicolor* and its extracts on survival, recurrence, and disease progression.
- To evaluate the evidence in relation to the type of preparation of the mushroom (e.g. whole fresh, dried, or extract).

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs) investigating the efficacy and safety of *Coriolus versicolor* and its extracts in participants with a confirmed diagnosis of colorectal cancer, in addition to conventional treatment. We will include trials regardless of language and publication status. We will consider all types of RCT design for inclusion, e.g. parallel-group and cluster-RCTs. We will only include trials including different types of cancer if data for colorectal cancer patients are reported separately.

Types of participants

Adult patients (minimum age 18 years) diagnosed with colorectal cancer regardless of tumour stage, age, or gender. Diagnosis must be confirmed by biopsy and will be stratified by tumour site and stage.

Types of interventions

Interventions will include any preparation of *Coriolus versicolor* (raw plant, decoction, capsule, tablet, tincture, extract, injection), any part of the mushroom (mycelium, stem, root, leave, spore, or whole), at any dose and regimen.

Trials will be included that compare:

- conventional treatment (chemotherapy with or without radiotherapy) plus *Coriolus versicolor* extract versus conventional treatment alone;
- conventional treatment and a complementary therapy plus *Coriolus versicolor* extract versus the same treatment without the extract;
- conventional treatment plus *Coriolus versicolor* extract versus conventional treatment plus placebo.

Types of outcome measures

Primary outcomes

- Overall survival at one year, three years, and five years.
- Adverse effect rates: the incidence of all reported adverse effects or toxicities, including modification of treatment or withdrawal from the trial due to adverse effects.

Secondary outcomes

- Disease progression at one year (plus three years and five years, if data are available) confirmed radiologically or biopsy proven.
- Disease recurrence at one year (plus three years and five years, if data are available) confirmed radiologically or biopsy proven.
- Response rates based on recommended criteria (World Health Organization (WHO) criteria or RECIST - Response Evaluation Criteria in Solid Tumors) for solid tumours (Therasse 2000).
- Quality of life evaluated using any validated assessment tool.

Search methods for identification of studies

We will impose no language restrictions and native speakers will translate studies if required.

Electronic searches

We will search the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (from inception to date);
- EMBASE (from inception to date);
- AMED (from inception to date);
- BIOSIS (from inception to date);
- CINAHL (from inception to date);
- The Cochrane Complementary Medicine Field Specialized Register.

International databases:

- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/trialsearch);
- Global Health Library (http://www.globalhealthlibrary.net/php/index.php).

Trial databases:

- ClinicalTrials.gov (http://clinicaltrials.gov/);
- US National Cancer Institute (http://www.cancer.gov/clinicaltrials);
- Current Controlled Trials (http://www.controlled-trials.com/).

Natural Medicines Comprehensive Database:

- http://naturaldatabase.therapeuticresearch.com.

Chinese databases:

- CQVIP, Chinese Scientific Journals Full-text Database (www.cqvip.com);
- CNKI database (www.cnki.net);
- Wanfang Data's Chinese Online Journals database (http://www.wanfangdata.com/);
- CBM (www.imicams.ac.cn).

Japanese databases:

- Ichushi Web (http://www.jamas.or.jp), web version of *Igaku Chuou Zasshi* (Japana centra revuo medicina);
- UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm);
- Japan Pharmaceutical Information Center (Japic-CTI) (http://www.clinicaltrials.jp/user/cte_main.jsp);
- Japan Medical Association-Center for Clinical Trials (JMACCT) (https://dbcentre3.jmacct.med.or.jp/jmactr/).

We will develop the MEDLINE search strategy and search strategies for databases other than MEDLINE in close collaboration with the Cochrane Colorectal Cancer Group Trials Search Coordinator. We will search all databases from their inception.

For comprehensive search strategies, see Appendix 1 (CENTRAL); Appendix 2 (MEDLINE); Appendix 3 (EMBASE).

Searching other resources

We will check the reference lists of all retrieved studies and relevant reviews for further relevant studies. We will screen the proceedings of the International Medicinal Mushroom Conference for studies. We will handsearch the specialist *International Journal of Medicinal Mushrooms*. We will contact manufacturers and authors to check for unpublished trials.

Data collection and analysis

Selection of studies

Two review authors will independently examine all titles and abstracts retrieved by the searches of Western databases (KP and JL) and the Chinese and Japanese databases (JPL and LT). If a record (title or abstract) cannot be rejected with certainty, we will obtain the full-text article for further evaluation. We will exclude duplicates. Disagreements will be resolved by discussion and if necessary by a third author. We will document the reasons for the exclusion of studies.

Data extraction and management

Two review authors will independently extract the following information on: patients (number randomised and analysed, age, sex, stage, treatment situation, setting), methods (design, observation period, analysis), interventions (type of preparation, application, dose and duration, control procedure, anticancer treatments), outcomes and results (reports of adverse effects, survival data, data on quality of life (QoL), number of dropouts, follow-up). We will use a pre-defined data extraction form for recording relevant data. Differences between review authors will be resolved by discussion or if necessary by consulting a third review author. If necessary, we will contact study authors for clarification of study methodology and results and, where relevant, for missing data.

Assessment of risk of bias in included studies

Two review authors will independently assess the trials using the Cochrane tool for assessing risk of bias (Higgins 2011). Differences will be resolved by discussion or, if necessary, by consulting another review author. Assessment of risk of bias (Appendix 6) will consider the following and we will assess this as per the criteria for judging risk of bias in the 'Risk of bias' assessment tool (Table 8.5.c) in the *Cochrane Handbook for Systematic Reviews of Interventions*.

- Sequence generation.
- Allocation concealment.
- Blinding of participants, personnel and outcomes assessors.
- Incomplete outcome data.
- Selective outcome reporting. This will follow the methods as per the Cochrane 'Risk of bias' assessment mentioned above. However, as a minimum we expect that trials should report adverse event data and survival or tumour response/disease progression.
- Other possible sources of bias: we will assess vested interests based on authorship and funding source for the trial and whether, if commercial funding was provided, this was stated to be unrestricted. If there is a clear statement on lack of a conflict of interest and no vested interest is apparent in the authorship or funding, we will judge the risk of bias to be low; where there is no statement we will judge the risk of bias to be unclear; and where a conflict of interest is apparent, we will judge the risk of bias to be high. We will also assess baseline differences between groups: if these are apparent and have not been addressed, we will judge the risk of bias to be high; if there are no significant baseline differences or these exist but the effect on results has been investigated and found not to be significant, we will judge the risk of bias to be low; in all other cases, we will judge risk of bias to be unclear.

Measures of treatment effect

We will extract the number of patients in each treatment arm who experienced the outcome of interest, in order to estimate a risk ratio (RR). If sufficient data are available, we will assess the severity of adverse events and categorise these according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), comparing rates of adverse events at each grade of severity (NCI 2010). If the data are available, we will also categorise adverse events as acute (during and up to six weeks after treatment) and late (after six weeks).

We will present dichotomous data as a risk ratio with corresponding 95% confidence interval (CI). We will present continuous data as a mean difference (MDs) for common measurement units or a standardised mean difference (SMD) for differing measurement units and different scales, along with corresponding 95% CI. We will calculate effect size and 95% CI for all primary and secondary outcomes. Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants are analysed in the groups to which they were assigned. We will also note the time points at which outcomes were collected and reported.

Unit of analysis issues

For individual trials, the unit of analysis will be the individual patient. In the case of including cluster-randomised study designs, the unit of analysis will be the cluster. We will extract data if the authors have adjusted for the sample size in each cluster, so that it is appropriately weighted in the following analysis. For studies in which control of clustering is not performed or reported adequately by the authors (after we have contacted them), and individual patient data are not available, we will correct for the intervention effects of cluster-RCTs by reducing the size of each

trial to its 'effective sample size', which is the number of the original sample size divided by the 'design effect'. We will calculate the design effect as 1 + (M-1)* ICC, where M is the average cluster size and ICC is the intracluster correlation coefficient, as described in chapter 16.3.4 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We will contact study authors to provide missing data. Where this proves unsuccessful, we will investigate the potential impact of the missing data. If trials reported the number of patients with data missing for the primary outcome, we will take a worst-case scenario approach to data analyses, that is, taking those with missing data in the treatment group as treatment failures, while taking those with missing data in the control group as treatment successes (Gamble 2005). We will compare per protocol analysis of available data with the analysis incorporating missing data. If the effect estimate is in the same direction and there is a significant difference between groups, we will be able to make a conclusion with more confidence. If the effect estimates from the two analyses are different, then we will need to interpret the findings with more caution and make a more conservative conclusion about the treatment effect.

Assessment of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by a formal statistical test of the significance of the heterogeneity (I^2) and, if possible, by subgroup analyses. If heterogeneity is detected ($I^2 \geq 50\%$), we will investigate possible reasons for this and consider whether it is appropriate to report a pooled estimate. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons.

Assessment of reporting biases

We will examine funnel plots to assess the potential for small study effects such as publication bias. We will check the symmetry of the funnel plot if a sufficient number of trials are included in a meta-analysis (more than 10 trials). If there is asymmetry of the funnel plot, it may suggest the existence of publication bias.

Data synthesis

If sufficient clinically similar studies are available, we will pool their results in meta-analyses.

For any dichotomous outcomes, we will calculate the RR for each study and then pool these.

For continuous outcomes, we will pool the MDs between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale, otherwise we will pool SMDs.

We will use random-effects models with inverse variance weighting for all primary analyses. We will perform all analyses using the Cochrane statistical software, Review Manager 5.3 (RevMan 2014). One author (JPL) will oversee all steps of data synthesis. We will summarise the results of included trials descriptively in tables.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis according to type of *Coriolus versicolor* preparation, dose, type of cancer (colon or rectal), stage of cancer and chemotherapy regimen.

Sensitivity analysis

We will perform sensitivity analysis excluding studies considered to be at high risk of bias.

Summary of findings

We will evaluate the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and present this in 'Summary of Findings' tables.

The GRADE system classifies the quality of evidence in one of four grades:

1. High: Further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate: Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate.
3. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low: Any estimate of effect is very uncertain.

The quality of evidence can be downgraded by one (serious concern) or two levels (very serious concern) for the following reasons: risk of bias, inconsistency (unexplained heterogeneity, inconsistency of results), indirectness (indirect population, intervention, control, outcomes) and imprecision (wide confidence interval, single trial).

The quality of evidence might be upgraded by one level due to a large summary effect.

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REFERENCES

Additional references

Aziz 2007
Aziz NM. Cancer survivorship research: state of knowledge, challenges and opportunities. *Acta Oncologica* 2007;**46**(4): 417–32.

Chan 2006
Chan SL, Yeung JH. Effects of polysaccharide peptide (PSP) from *Coriolus versicolor* on the pharmacokinetics of cyclophosphamide in the rat and cytotoxicity in HepG2 cells. *Food and Chemical Toxicology* 2006;**44**(5):689–94.

Chinese Pharmacopoeia 2005
Chinese Pharmacopoeia Commission. *Pharmacopoeia of the People's Republic of China*. Beijing: Chemical Industry Press, 2005.

Daiichi-Sankyo 2012
Daiichi-Sankyo. Krestin® (PSK). Package insert 2012.

Eliza 2012
Eliza WL, Fai CK, Chung LP. Efficacy of Yun Zhi (*Coriolus versicolor*) on survival in cancer patients: systematic review and meta-analysis. *Recent Patents on Inflammation and Allergy Drug Discovery* 2012;**6**(1):78–87.

Fisher 2002
Fisher M, Yang LX. Anticancer effects and mechanisms of polysaccharide-K (PSK): implications of cancer immunotherapy. *Anticancer Research* 2002;**22**(3):1737–54.

Gamble 2005
Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. *Journal of Clinical Epidemiology* 2005;**58**:579–88.

Gray 2011
Gray NM, Hall SJ, Browne S, Macleod U, Mitchell E, Lee AJ, et al. Modifiable and fixed factors predicting quality of life in people with colorectal cancer. *British Journal of Cancer* 2011;**104**(11):1697–703.

Higgins 2011
Higgins JPT, Green S (editors). Chapter 8: Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at www.cochrane-handbook.org.

IARC and Cancer Research UK 2012
International Agency for Research on Cancer and Cancer Research UK. World Cancer Factsheet. London: Cancer Research UK 2012.

Jin 2012
Jin X, Ruiz Beguerie J, Sze DM, Chan GC. *Ganoderma lucidum* (Reishi mushroom) for cancer treatment. *Cochrane Database of Systematic Reviews* 2012, Issue 6. [DOI: 10.1002/14651858.CD007731.pub2]

Kidd 2000
Kidd PM. The use of mushroom glucans and proteoglycans in cancer treatment. *Alternative Medicine Review* 2000;**5**(1): 4–27.

Lindequist 2005
Lindequist U, Niedermeyer TH, Julich WD. The pharmacological potential of mushrooms. *Evidence Based Complementary and Alternative Medicine* 2005;**2**(3):285–99.

Maehara 2012
Maehara Y, Tsujitani S, Saeki H, Oki E, Yoshinaga K, Emi Y, et al. Biological mechanism and clinical effect of protein-bound polysaccharide K (KRESTIN(®)): review of development and future perspectives. *Surgery Today* 2012; **42**(1):8–28.

MD Anderson 2010
MD Anderson Cancer Center. CIMER - Coriolus versicolor Detailed Scientific Review. University of Texas MD Anderson Cancer Center (original source): http://mushroomstudies.co/wp-content/uploads/2011/06/University-of-Texas-MD-Anderson-Cancer-Center-report.pdf (current source) Unknown (document downloaded April 2010).

Memorial Sloan-Kettering 2012
Memorial Sloan-Kettering Cancer Center. About herbs, botanicals and other products: *Coriolus versicolor*. http://www.mskcc.org/cancer-care/herb/coriolus-versicolor (accessed 9 July 2013).

Mitomi 1988
Ikuzawa M, Matsunaga K, Nishiyama S, Nakajima S, Kobayashi Y, Andoh T, et al. Fate and distribution of an antitumor protein-bound polysaccharide PSK (Krestin). *International Journal of Immunopharmacology* 1988;**10**(4): 415–23.

Natural Database 2013
Therapeutic Research Faculty. Natural Medicines Comprehensive Database. www.naturaldatabase.com (accessed 9 July 2013).

NCI 2010
National Cancer Institute. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4. http://evs.nci.nih.gov/ftp1/CTCAE/About.html Last updated 11 May 2010 (accessed 18 March 2013).

NCI 2013
National Cancer Institute. PDQ® Colon Cancer Treatment. http://www.cancer.gov/cancertopics/pdq/

treatment/colon/Patient/page1 Last updated: 8 February 2013 (accessed 18 March 2013).

Ng 1998

Ng TB. A review of research on the protein-bound polysaccharide (polysaccharopeptide, PSP) from the mushroom *Coriolus versicolor* (Basidiomycetes: Polyporaceae). *General Pharmacology* 1998;**30**(1):1–4.

NICE 2011

National Institute for Health and Clinical Excellence. Colorectal cancer: The diagnosis and management of colorectal cancer. CG131. London: National Institute for Health and Clinical Excellence 2011.

Pandor 2006

Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P. The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. Health Technology Assessment 2006; Vol. 10, issue 41:1–185.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rowan 2003

Rowan N, Sullivan R. Immunomodulatory activities of mushroom glucans and polysaccharide--Protein complexes in animals and humans (a review). *International Journal of Medicinal Mushrooms* 2003;**5**:95–110.

Sakamoto 2006

Sakamoto J, Morita S, Oba K, Matsui T, Kobayashi M, Nakazato H, et al. Meta-Analysis Group of the Japanese Society for Cancer of the Colon Rectum. Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curatively resected colorectal cancer: a meta-analysis of centrally randomized controlled clinical trials. *Cancer Immunology, Immunotherapy: CII* 2006;**55**(4): 404–11.

Schmoll 2007

Schmoll HJ, Cartwright T, Tabernero J, Nowacki MP, Figer A, Maroun J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *Journal of Clinical Oncology* 2007;**25**(1):102–9.

Smith 2000

Smith JE, Rowan NJ, Sullivan R. *Medicinal Mushrooms and Cancer: Their Therapeutic Properties and Current Medical Usage with Special Emphasis on Cancer Treatments*. London: Cancer Research UK, 2000.

Standish 2008

Standish LJ, Wenner CA, Sweet ES, Bridge C, Nelson A, Martzen M, et al. *Trametes versicolor* mushroom immune therapy in breast cancer. *Journal of the Society of Integrative Oncology* 2008;**6**(3):122–8.

Sullivan 2006

Sullivan R, Smith JE, Rowan NJ. Medicinal mushrooms and cancer therapy: translating a traditional practice into Western medicine. *Perspectives in Biology and Medicine* 2006;**49**(2):159–70.

Therasse 2000

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute* 2000;**92**(3):205–16.

Yeung 2012

Yeung JH, Or PM. Polysaccharide peptides from *Coriolus versicolor* competitively inhibit model cytochrome P450 enzyme probe substrates metabolism in human liver microsomes. *Phytomedicine* 2012;**19**(5):457–63.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. *The Cochrane Library* search strategy

#1 MeSH descriptor: [Trametes] explode all trees
#2 (Coriolus versicolor or Trametes versicolor or Polyporus versicolor or Polystictus versicolor or Kawaratake or Yun Zhi or polysaccharide-K or PSK or Krestin or polysaccharopeptide or polysaccharide-peptide or PSP or VPS or Turkey Tail or cloud mushroom or unji mushroom):ti,ab,kw
#3 (#1 or #2)
#4 MeSH descriptor: [Colorectal Neoplasms] explode all trees
#5 ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) near/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)):ti,ab,kw
#6 (#4 or #5)
#7 (#3 and #6)

Appendix 2. MEDLINE search strategy

1. exp Trametes/
2. (Coriolus versicolor or Trametes versicolor or Polyporus versicolor or Polystictus versicolor or Kawaratake or Yun Zhi or polysaccharide-K or PSK or Krestin or polysaccharopeptide or polysaccharide-peptide or PSP or VPS or Turkey Tail or cloud mushroom or unji mushroom).mp.
3. 1 or 2
4. exp Colorectal Neoplasms/
5. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.
6. 4 or 5
7. 3 and 6

Appendix 3. EMBASE search strategy

1. exp trametes versicolor/
2. (Coriolus versicolor or Trametes versicolor or Polyporus versicolor or Polystictus versicolor or Kawaratake or Yun Zhi or polysaccharide-K or PSK or Krestin or polysaccharopeptide or polysaccharide-peptide or PSP or VPS or Turkey Tail or cloud mushroom or unji mushroom).mp.
3. 1 or 2
4. exp colon cancer/
5. exp rectum cancer/
6. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.
7. 4 or 5 or 6
8. 3 and 7

Appendix 4. Search strategies for other databases

AMED

1. (Coriolus versicolor or Trametes versicolor or Polyporus versicolor or Polystictus versicolor or Kawaratake or Yun Zhi or polysaccharide-K or PSK or Krestin or polysaccharopeptide or polysaccharide-peptide or PSP or VPS or Turkey Tail or cloud mushroom or unji mushroom).mp.
2. exp Intestinal Neoplasms/
3. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.
4. 2 or 3
5. 1 and 4

BIOSIS

1. (Coriolus versicolor or Trametes versicolor or Polyporus versicolor or Polystictus versicolor or Kawaratake or Yun Zhi or polysaccharide-K or PSK or Krestin or polysaccharopeptide or polysaccharide-peptide or PSP or VPS or Turkey Tail or cloud mushroom or unji mushroom).mp.
2. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.
3. 1 and 2

CINAHL

As per MEDLINE

Appendix 5. Additional search terms for Chinese databases

Cai rong ge ai jun + hui zhi + wa jun + cai yun ge gai jun + duo se niu gan jun + hong jian shou + qian ceng gu (云芝+彩绒革盖菌+灰芝+瓦菌+彩云革盖菌+多色牛肝菌+红见手+千层蘑)

Appendix 6. Assessment of risk of bias

Risk of bias in randomised trials

Extracted from the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org/).
Table 8.5.d: Criteria for judging risk of bias in the 'Risk of bias' assessment tool

RANDOM SEQUENCE GENERATION Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	
Criteria for a judgement of 'low risk' of bias	The investigators describe a random component in the sequence generation process such as: · referring to a random number table; · using a computer random number generator; · coin tossing;

(*Continued*)

	· shuffling cards or envelopes; · throwing dice; · drawing of lots; · minimisation*. *Minimisation may be implemented without a random element, and this is considered to be equivalent to being random
Criteria for the judgement of 'high risk' of bias	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: · sequence generated by odd or even date of birth; · sequence generated by some rule based on date (or day) of admission; · sequence generated by some rule based on hospital or clinic record number · other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, for example: · allocation by judgement of the clinician; · allocation by preference of the participant; · allocation based on the results of a laboratory test or a series of tests; · allocation by availability of the intervention.
Criteria for the judgement of 'unclear risk' of bias	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
ALLOCATION CONCEALMENT Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	
Criteria for a judgement of 'low risk' of bias	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: · central allocation (including telephone, web-based and pharmacy-controlled randomisation); · sequentially numbered drug containers of identical appearance; · sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'high risk' of bias	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: · using an open random allocation schedule (e.g. a list of random numbers); · assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); · alternation or rotation; · date of birth;

(*Continued*)

	· case record number; · any other explicitly unconcealed procedure.
Criteria for the judgement of 'unclear risk' of bias	Insufficient information to permit judgement of 'low risk' or 'high risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement - for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed
BLINDING OF PARTICIPANTS AND PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	
Criteria for a judgement of 'low risk' of bias	Any one of the following: · no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; · blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Criteria for the judgement of 'high risk' of bias	Any one of the following: · no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; · blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
Criteria for the judgement of 'unclear risk' of bias	Any one of the following: · insufficient information to permit judgement of 'low risk' or 'high risk'; · the study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT Detection bias due to knowledge of the allocated interventions by outcome assessors	
Criteria for a judgement of 'low risk' of bias	Any one of the following: · no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; · blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
Criteria for the judgement of 'high risk' of bias	Any one of the following: · no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; · blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding

(*Continued*)

Criteria for the judgement of 'unclear risk' of bias	Any one of the following: · insufficient information to permit judgement of 'low risk' or 'high risk'; · the study did not address this outcome.
INCOMPLETE OUTCOME DATA Attrition bias due to amount, nature or handling of incomplete outcome data	
Criteria for a judgement of 'low risk' of bias	Any one of the following: · no missing outcome data; · reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); · missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; · for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate; · for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; · missing data have been imputed using appropriate methods.
Criteria for the judgement of 'high risk' of bias	Any one of the following: · reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; · for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; · for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; · 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; · potentially inappropriate application of simple imputation
Criteria for the judgement of 'unclear risk' of bias	Any one of the following: · insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided); · the study did not address this outcome.
SELECTIVE REPORTING Reporting bias due to selective outcome reporting.	

(*Continued*)

Criteria for a judgement of 'low risk' of bias	Any of the following: · the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; · the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Criteria for the judgement of 'high risk' of bias	Any one of the following: · not all of the study's pre-specified primary outcomes have been reported; · one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; · one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); · one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; · the study report fails to include results for a key outcome that would be expected to have been reported for such a study
Criteria for the judgement of 'unclear risk' of bias	Insufficient information to permit judgement of 'low risk' or 'high risk'. It is likely that the majority of studies will fall into this category
OTHER BIAS Bias due to problems not covered elsewhere in the table.	
Criteria for a judgement of 'low risk' of bias	The study appears to be free of other sources of bias.
Criteria for the judgement of 'high risk' of bias	There is at least one important risk of bias. For example, the study: · had a potential source of bias related to the specific study design used; or · has been claimed to have been fraudulent; or · had some other problem.
Criteria for the judgement of 'unclear risk' of bias	There may be a risk of bias, but there is either: · insufficient information to assess whether an important risk of bias exists; or · insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

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DECLARATIONS OF INTEREST

None known.

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