BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005016
Article Type:	Protocol
Date Submitted by the Author:	07-Feb-2014
Complete List of Authors:	Park, Bongki; Korea Institute of Oriental Medicine, Medical Research Division Jun, Ji Hee; Korea Institute of Oriental Medicine, Medical Research Division Jung, Jeeyoun; Korea Institute of Oriental Medicine, Medical Research Division You, Sooseong; Korea Institute of Oriental Medicine, Medical Research Division Lee, Myeong Soo; Korea Institute of Oriental Medicine, Medical Research Division
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Oncology
Keywords:	COMPLEMENTARY MEDICINE, Adult oncology < ONCOLOGY, Herbal medicine < THERAPEUTICS

Herbal medicines for cancer cachexia : Protocol for a systematic review

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Running title: Protocol of systematic review of herbal medicine for cancer cachexia

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Abstract

Introduction: To assess the efficacy of herbal medicines as a treatment of cancer cachexia.

Methods and analysis: We will search the following thirteen electronic databases from their inception. MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Allied and Complementary Medicine Database (AMED), China National Knowledge Infrastructure (CNKI), Wanfang, Journal Integration Platform (VIP) and six Korean Medical Databases (Korean Studies Information, DBPIA, Korea Institute of Science Technology Information, Research Information Center for Health Database, Korean Medline, and National Assembly Library) without restrictions on time or language. The data will be extracted independently by two authors using pre-defined criteria. Disagreements will be resolved by discussion between the authors. The risk of bias will be assessed using the Cochrane of risk of bias tool.

Dissemination: The review will be published in a journal. The review will also be disseminated electronically and in print. An updated of the review will be conducted to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2013:CRD42013006612

Keywords: Cancer, cachexia, herbal medicine, traditional East Asian medicine, randomised clinical trials, systematic review

Article focus

- *This systematic review aims to evaluate randomized controlled trials and quasi-randomised trials and to present the efficacy of herbal medicines for cancer cachexia.*

Key messages

- *This systematic review will be performed with a comprehensive search strategy and will establish the current state of the evidence using unbiased methods.*

Strengths and limitations of this study

- *The strength of this review is its extensive, unbiased search of various databases without language restriction.*
- *The trial screening and data extraction will be conducted independently by two authors.*
- *The review team is consists of experts from each field: traditional Korean medicine (Park BK, Jung JY), traditional Chinese medicine (Jun JH), conventional medicine (You SS) and methodology (Lee MS).*

Introduction

Description of the condition

Cancer cachexia is a common syndrome among cancer patients, especially in advanced cancer. More than 70~80% of advanced cancer patients suffer from cachexia.[1]

Generally, cachexia is characterised by loss of weight, muscle atrophy, anorexia and fatigue. The definition of cancer cachexia differs slightly according to the research study,[2-5] but the recent international consensus has defined cancer cachexia as a multifactorial syndrome characterised by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[4] The pathophysiology of cancer cachexia is a negative energy balance caused by a variable combination of reduced food intake and abnormal metabolism.4 6 The metabolic mechanisms of adipose mass reduction, loss of skeletal muscle and protein degradation are known to be mediated by pro-inflammatory cytokines, neuropeptides, hormones, catabolic factors and digestive factors.[1 6-8]

Cancer cachexia causes numerous clinical problems. Cancer cachexia reduces activity or quality of life9 and restricts conventional therapy such as chemotherapy.[10] Above all, Cancer cachexia is associated with a poor survival rate.[11 12] In various cancer types, the survival of patients with cachexia is shorter than that of other patients.[1]

Description of the intervention

There are several agents for managing cancer cachexia. Megestrol acetate, cannabinoids, corticosteroids and ghrelin are known to affect appetite. EPA, HMB, thalidomide, corticosteroids and non-steroidal anti-inflammatory drugs are known to affect cachectic mediators or signal pathways.[1 6 13] Some drugs, such as megestrol acetate and corticosteroids exhibit confirmed effectiveness in combatting cancer cachexia by randomised controlled

trials and systematic reviews.1 However, to date, there is no identified standard treatment for cancer cachexia.

Herbal medicines have been used widely to treat diverse diseases for thousands of years. Especially in East Asia, herbal medicines have been developed on a basis of unique theories: Yin and Yang, the five elements and visceral manifestation theory. The major principle of treating diseases is reinforcing the healthy qi and eliminating the pathogenic factors. Many herbal medicines are prescribed according to this principle.

Recently, herbal medicines have been used to alleviate the adverse effects of conventional therapies or to improve a quality of life. A survey demonstrated that 75% of colorectal cancer patients used at least one type of complementary alternative medicine (CAM) during their lifetimes.[14] Another survey reported that 39% of breast cancer patients used herbs or medical herbal teas.[15]

How the intervention might work

Some herbs, such as ginseng radix, astragali radix or some herbal prescriptions, are known to increase appetite, facilitate physical function and boost immune function.[16-20] Other herbs, such as coptidis rhizoma, exhibit anti-inflammatory functions.[21-23] Many herbs are associated with anti-cancer properties including cancer cell - cytotoxicity, cell-apoptosis and invasion and metastasis prevention.[24-26]

Many practitioners and researchers have attempted to explore herbal medicines for the treatment of cancer cachexia. The oral administration of Rikkunshito is known to stimulate ghrelin secretion.[27] One research study reported that coptidis rhizoma might exhibit an anti-cachectic effect and that berberine, the major component, might prevent cancer-induced cachexia.[28]

Why it is important to do this review

To our knowledge, no systematic reviews assessing herbal medicines in cancer cachexia have been conducted. There is no identified standard treatment for cancer cachexia, and a comprehensive evaluation of the efficacy and the safety of herbal medicines will inform the recommendation for treatment of cancer cachexia.

Objectives

To assess the efficacy of herbal medicines for cancer cachexia.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials (quasi-RCTs) will be included in this systematic review without restrictions on time or language.

Types of participants

The participants will include cancer patients diagnosed by histological or clinical diagnosis who meet the international consensus of cancer cachexia[4]. The diagnostic criteria for cancer cachexia are as follows :

1. Weight loss > 5% over the past 6 months (in absence of simple starvation); or
2. Body Mass Index (BMI) < 20 and any degree of weight loss > 2%; or
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All types of herbal medicines will be included. There is no limitation on the number of herbs, administration methods, dosage or duration of treatment. The comparisons will be either with other therapeutic agents such as megestrol acetate or corticosteroids or with no other treatment.

Types of outcome measures

Primary outcomes

1. Weight gain.

2. Body composition.

Secondary outcomes

1. Improvement in quality of life by means of a validated instrument.

2. Increase of appetite.

3. Reduction in fatigue.

4. Serum levels of inflammatory markers, including ESR and CRP as well as TNF-alpha, IL-1, IL-6, and IFN-gamma.

5. Adverse effects.

Search methods for the identification of studies

Electronic searches

We will search the following electronic databases regardless of publication date or language:

- MEDLINE (PubMed),
- The Cochrane Central Register of Controlled Trials (CENTRAL),
- EMBASE,
- Allied and Complementary Medicine Database (AMED),
- China National Knowledge Infrastructure (CNKI),

- Wanfang Database.
- VIP (Journal Integration Platform)
- Six Korean Medical Databases (Korean Studies Information, DBPIA, Korea Institute of Science Technology Information, Research Information Center for Health Database, Korean Medline, and National Assembly Library)

Other sources

We will scan the reference lists of reviews and retrieve articles for additional studies. In addition, we will search the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/mrct), clinical trials.gov (www. Clinicaltrials.gov) and Google scholar (http://scholar.google.co.kr/).

Search strategy

We will model subject strategies for databases on the search strategy designed for MEDLINE (PubMed; see Appendix 1) and CNKI (see Appendix 2) and modify it for use in the other databases.

Data collection and analysis

Selection of studies

Two review authors (Park BK and Jun JH) will independently assess the titles and abstracts of articles searched by electronic databases and determine their eligibility for inclusion. Hard copies of the relevant articles will be retrieved. Disagreements will be resolved by discussion, if necessary, by the arbiter (Lee MS).

Data extraction and management

Two review authors (Park BK and Jun JH) will read all the articles and independently extract the data using a standard data extraction form. The form includes methodology, participants, interventions, duration of treatment, outcomes and conclusions. Consensus will be reached by discussion in the case of discrepancy. When disagreements are not resolved by discussion, they will be arbitrated by another author (Lee MS).

Assessment of the risk of bias in the included studies

Three authors (Park BK, You SS and Jung JY) will assess the risk of bias using the Cochrane tool of risk of bias (version 5.1.0).[29] The following items will be assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias. The evaluated domains will be assessed as Yes, No or Unclear according to the criteria. We will resolve any disagreements by discussion or arbitration (Lee MS).

Measurement of the treatment effect

We will use the mean difference (MD) with 95% confidence intervals (CI) for continuous outcomes or risk ratios (RR) with 95% CI for binary outcomes. In the case of the use of different measurement scales, standardised mean difference (SMD) analysis with 95% CI will be performed.

Units of analysis issues

We will include data from parallel-group studies for the meta-analysis. If we include cross-over trials, only the first treatment period data will be analysed. When the trial has more than

one control group, the unit of analysis will be applied to each group.

Dealing with missing data

We will try to contact the corresponding authors by e-mail if there is any missing or insufficient data from the trial as much as possible. The intent-to-treat (ITT) principle will be applied for statistical analysis. The individual patient data will be sought from the original source or from the published trial reports when the individual patient data are unavailable.

Assessment of heterogeneity

We will use the random effects model for the meta-analysis. Heterogeneity will be assessed by inspecting the forest plots. In addition, heterogeneity will be tested by the I^2 test for quantifying inconsistencies among the included studies. A result higher than 50% would represent substantial heterogeneity. If heterogeneity exits, we will conduct a subgroup analysis to examine the possible cause.[30]

Assessment of reporting biases

If more than 10 trials are included in the meta-analysis, we will conduct funnel plots to assess the potential for publication bias and small study effects.[31] Asymmetry in funnel plots implied possible small study effects, such as publication bias. We will include all eligible trials, regardless of their methodological quality.

Data synthesis

If there are sufficient studies and comparable outcomes, we will perform a meta-analysis using random effect modelling.

1. Herbal medicine versus conventional medical treatments

2. Herbal medicine versus no treatment

3. Herbal medicine versus placebo

4. Herbal medicine plus conventional medical treatment versus conventional medical treatment only

Subgroup analysis and investigation of heterogeneity

If there are sufficient data, subgroup analyses will be conducted to explore the differences in the effect sizes, type of cancer, stage of cachexia4 and types of herbal medicine.

Sensitivity analysis

For sensitivity analysis, the meta-analysis will be repeated, substituting decisions alternatively to test the robustness of the primary decisions of the review process. The principal decision nodes are as follows:

1. Methodological quality (sequence generation, allocation concealment or blinding in the assessment of outcomes and symptom severity);

2. Sample size (small sample size studies, e.g., over 30 in each group)

Ethics and dissemination

Ethical approval is not required, given that this protocol is for a systematic review. The review will be disseminated widely through peer-reviewed publications and conference presentations.

Discussion

This is the protocol for a review and there is no primary data collection. The systematic review will be published in a peer-reviewed journal and disseminated electronically or in

print. Updates of the review will be conducted to inform and guide healthcare practice and policy.

Contribution of authors

All authors (Park BK, Jun JH, Jung JY, You SS and Lee MS) contributed to the drafting of the protocol. The protocol was revised, and the final version was approved by all authors. The search strategy was developed and will be run by Park BK and Jun JH. Copies of studies will be obtained by Park BK and Jun JH. Selection of the studies to include will be done by Park BK and Jun JH. Lee MS will act as an arbiter in the study selection stage. Extraction of data from studies will be conducted by Park BK, Jun JH, Jung JY and You SS. Entering data into RevMan will be conducted by Park BK, Jung JY. Carrying out the analysis will be done by Park BK, Jung JY and Lee MS. Interpretation of the analysis will be done by all authors. The final review will be drafted by all authors. The review will be updated by Park BK and Lee MS.

Competing interests

None declared

Funding

The authors were supported by Korea Institute of Oriental Medicine (K13400, K13281).

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APPENDICES

Appendix 1. MEDLINE (Pubmed) search strategy

#1. exp Neoplasms/

#2. (cancer or oncolog* or neoplasm* or malignan* or tumor or tumour or carcinoma* or adenocarcinoma* or osteosarcoma* or sarcoma* or leukemi* or lymphoma* or teratoma* or metastat*).mp.

#3. #1 or #2

#4. exp Weight loss/

#5. exp Malnutrition/

#6. (cachexia* or cachectic* or weight loss or loss of weight or underweight or malnutrition or wasting syndrome or anorexia* or muscle atrophy or sarcopenia).mp.

#7. or/#4-#6

#8. exp Medicine, East Asian Traditional/

#9. exp Drugs, Chinese herbal/

#10. exp Herbal Medicine/

#11. exp Plants, Medicinal/

#12. (traditional Korean medicine or traditional Chinese medicine or Traditional oriental medicine or Kampo medicine or alternative medicine or complementary medicine or herb or herbal or herbs or decoction* or botanic*).mp.

#13. or/#8-#12

#14. exp Randomized Controlled Trials as Topic/

#15. exp Clinical Trials as Topic/

#16. exp controlled clinical trials as topic/

#17. (randomized controlled trial* or controlled clinical trial* or randomized* or randomly* or placebo or clinical trial* or controlled trial*).mp.

#18. or/#14 - #17

#19. #3 and #7 and #13 and #18

Appendix 2. CNKI search strategy

(恶病质 or 恶液质 or 癌症恶病质 or 癌恶病质 or 肿瘤恶病质 or 癌性恶病质) and (中医药 or 中医 or 中西医结合 or 中药 or 中草药 or 中药制剂 or 汤 or 丸 or 散 or 注射液 or 口服液 or 中成药 or 饮) and (随机 or 对照)

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Date Submitted by the Author:	10-May-2014
Complete List of Authors:	Park, Bongki; Korea Institute of Oriental Medicine, Medical Research Division Jun, Ji Hee; Korea Institute of Oriental Medicine, Medical Research Division Jung, Jeeyoun; Korea Institute of Oriental Medicine, Medical Research Division You, Sooseong; Korea Institute of Oriental Medicine, Medical Research Division Lee, Myeong Soo; Korea Institute of Oriental Medicine, Medical Research Division
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5. Survival rate

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- Six Korean Medical Databases (Korean Studies Information, DBPIA, Korea Institute of Science Technology Information, Research Information Center for Health Database, Korean Medline, and National Assembly Library)

Other sources

We will scan the reference lists of reviews and retrieve articles for additional studies. In addition, we will search the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) and Google scholar (http://scholar.google.co.kr/).

Search strategy

We will model subject strategies for databases on the search strategy designed for MEDLINE (PubMed; see Appendix 1) and CNKI (see Appendix 2) and modify it for use in the other databases.

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Two review authors (Park BK and Jun JH) will independently assess the titles and abstracts of articles searched by electronic databases and determine their eligibility for inclusion. Hard copies of the relevant articles will be retrieved. Disagreements will be resolved by discussion, if necessary, by the arbiter (Lee MS).

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We will use the mean difference (MD) with 95% confidence intervals (CI) for continuous outcomes or risk ratios (RR) or odds ratio (OR) with 95% CI for binary outcomes. If the event rate lower than 1%, Peto Odds ratio (OR) with 95% CI will be used, lower than 20%, OR with 95% CI and more than 20%, RR will be used. In the case of the use of different measurement scales, standardised mean difference (SMD) analysis with 95% CI will be performed.

Units of analysis issues

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1. Herbal medicine versus conventional medical treatments

2. Herbal medicine versus no treatment

3. Herbal medicine versus placebo

4. Herbal medicine plus conventional medical treatment versus conventional medical treatment only

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1. Methodological quality (sequence generation, allocation concealment or blinding in the assessment of outcomes and symptom severity);

2. Sample size (small sample size studies, e.g., over 30 in each group)

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Ethical approval is not required, given that this protocol is for a systematic review. The review will be disseminated widely through peer-reviewed publications and conference presentations.

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This is the protocol for a review and there is no primary data collection. The systematic review will be published in a peer-reviewed journal and disseminated electronically or in print. Updates of the review will be conducted to inform and guide healthcare practice and policy.

Funding

The authors were supported by Korea Institute of Oriental Medicine (K13400, K13281).

Contribution of authors

All authors (Park BK, Jun JH, Jung JY, You SS and Lee MS) contributed to the drafting of the protocol. The protocol was revised, and the final version was approved by all authors. The search strategy was developed and will be run by Park BK and Jun JH. Copies of studies will be obtained by Park BK and Jun JH. Selection of the studies to include will be done by Park BK and Jun JH. Lee MS will act as an arbiter in the study selection stage. Extraction of data from studies will be conducted by Park BK, Jun JH, Jung JY and You SS. Entering data into RevMan will be conducted by Park BK, Jung JY. Carrying out the analysis will be done by Park BK, Jung JY and Lee MS. Interpretation of the analysis will be done by all authors. The final review will be drafted by all authors. The review will be updated by Park BK and Lee MS.

Competing interests

None declared

Data Sharing Statement

No additional data available

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Herbal medicines for cancer cachexia : Protocol for a systematic review

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Medical Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea

Running title: Protocol of systematic review of herbal medicine for cancer cachexia

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Article focus

- *This systematic review aims to evaluate randomized controlled trials and quasi-randomised trials and to present the efficacy of herbal medicines for cancer cachexia.*

Key messages

- *This systematic review will be performed with a comprehensive search strategy and will establish the current state of the evidence using unbiased methods.*

Strengths and limitations of this study

- *The strength of this review is its extensive, unbiased search of various databases without language restriction.*
- *The trial screening and data extraction will be conducted independently by two authors.*
- *The review team is consists of experts from each field: traditional Korean medicine (Park BK, Jung JY), traditional Chinese medicine (Jun JH), conventional medicine (You SS) and methodology (Lee MS).*

Abstract

Introduction: To assess the efficacy of herbal medicines as a treatment of cancer cachexia.

Methods and analysis: We will search the following thirteen electronic databases from their inception. MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Allied and Complementary Medicine Database (AMED), China National Knowledge Infrastructure (CNKI), Wanfang, Journal Integration Platform (VIP) and six Korean Medical Databases (Korean Studies Information, DBPIA, Korea Institute of Science Technology Information, Research Information Center for Health Database, Korean Medline, and National Assembly Library) without restrictions on time or language. The data will be extracted independently by two authors using pre-defined criteria. Disagreements will be resolved by discussion between the authors. The risk of bias will be assessed using the Cochrane of risk of bias tool.

Dissemination: The review will be published in a journal. The review will also be disseminated electronically and in print. An updated of the review will be conducted to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2013:CRD42013006612

Keywords: Cancer, cachexia, herbal medicine, traditional East Asian medicine, randomised clinical trials, systematic review

Introduction

Description of the condition

Cancer cachexia is a common syndrome among cancer patients, especially in advanced cancer. More than 70~80% of advanced cancer patients suffer from cachexia.[1]

Generally, cachexia is characterised by loss of weight, muscle atrophy, anorexia and fatigue. The definition of cancer cachexia differs slightly according to the research study,[2-5] but the recent international consensus has defined cancer cachexia as a multifactorial syndrome characterised by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[4] The pathophysiology of cancer cachexia is a negative energy balance caused by a variable combination of reduced food intake and abnormal metabolism.4 6 The metabolic mechanisms of adipose mass reduction, loss of skeletal muscle and protein degradation are known to be mediated by pro-inflammatory cytokines, neuropeptides, hormones, catabolic factors and digestive factors.[1 6-8]

Cancer cachexia causes numerous clinical problems. Cancer cachexia reduces activity or quality of life9 and restricts conventional therapy such as chemotherapy.[10] Above all, Cancer cachexia is associated with a poor survival rate.[11 12] In various cancer types, the survival of patients with cachexia is shorter than that of other patients.[1]

Description of the intervention

There are several agents for managing cancer cachexia. Megestrol acetate, cannabinoids, corticosteroids and ghrelin are known to affect appetite. EPA, HMB, thalidomide, corticosteroids and non-steroidal anti-inflammatory drugs are known to affect cachectic mediators or signal pathways.[1 6 13] Some drugs, such as megestrol acetate and corticosteroids exhibit confirmed effectiveness in combatting cancer cachexia by randomised controlled

trials and systematic reviews.1 However, to date, there is no identified standard treatment for cancer cachexia.

Herbal medicines have been used widely to treat diverse diseases for thousands of years. Especially in East Asia, herbal medicines have been developed on a basis of unique theories: Yin and Yang, the five elements and visceral manifestation theory. The major principle of treating diseases is reinforcing the healthy qi and eliminating the pathogenic factors. Many herbal medicines are prescribed according to this principle.

Recently, herbal medicines have been used to alleviate the adverse effects of conventional therapies or to improve a quality of life. A survey demonstrated that 75% of colorectal cancer patients used at least one type of complementary alternative medicine (CAM) during their lifetimes.[14] Another survey reported that 39% of breast cancer patients used herbs or medical herbal teas.[15]

How the intervention might work

Some herbs, such as ginseng radix, astragali radix or some herbal prescriptions, are known to increase appetite, facilitate physical function and boost immune function.[16-20] Other herbs, such as coptidis rhizoma, exhibit anti-inflammatory functions.[21-23] Many herbs are associated with anti-cancer properties including cancer cell - cytotoxicity, cell-apoptosis and invasion and metastasis prevention.[24-26]

Many practitioners and researchers have attempted to explore herbal medicines for the treatment of cancer cachexia. The oral administration of Rikkunshito is known to stimulate ghrelin secretion.[27] One research study reported that coptidis rhizoma might exhibit an anti-cachectic effect and that berberine, the major component, might prevent cancer-induced cachexia.[28]

Why it is important to do this review

To our knowledge, no systematic reviews assessing herbal medicines in cancer cachexia have been conducted. There is no identified standard treatment for cancer cachexia, and a comprehensive evaluation of the efficacy and the safety of herbal medicines will inform the recommendation for treatment of cancer cachexia.

Objectives

To assess the efficacy of herbal medicines for cancer cachexia.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials (quasi-RCTs) will be included in this systematic review without restrictions on time or language.

Types of participants

The participants will include cancer patients diagnosed by histological or clinical diagnosis who meet the international consensus of cancer cachexia[4]. The diagnostic criteria for cancer cachexia are as follows :

1. Weight loss > 5% over the past 6 months (in absence of simple starvation); or
2. Body Mass Index (BMI) < 20 and any degree of weight loss > 2%; or
3. Appendicular skeletal muscle index consistent with sarcopenia (males<7.26 kg/m; females<5.45 kg/m) and any degree of weight loss >2%

Types of interventions

All types of herbal medicines will be included. There is no limitation on the number of herbs, administration methods, dosage or duration of treatment. The comparisons will be either with other therapeutic agents such as megestrol acetate or corticosteroids or with no other treatment.

Types of outcome measures

Primary outcomes

1. Weight gain.

2. Body composition.

Secondary outcomes

1. Improvement in quality of life by means of a validated instrument.

2. Increase of appetite.

3. Reduction in fatigue.

4. Serum levels of inflammatory markers, including ESR and CRP as well as TNF-alpha, IL-1, IL-6, and IFN-gamma.

5. Survival rate

6~~5~~. Adverse effects.

Search methods for the identification of studies

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We will search the following electronic databases regardless of publication date or language:

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APPENDICES

Appendix 1. MEDLINE (Pubmed) search strategy

#1. exp Neoplasms/

#2. (cancer or oncolog* or neoplasm* or malignan* or tumor or tumour or carcinoma* or adenocarcinoma* or osteosarcoma* or sarcoma* or leukemi* or lymphoma* or teratoma* or metastat*).mp.

#3. #1 or #2

#4. exp Weight loss/

#5. exp Malnutrition/

#6. (cachexia* or cachectic* or weight loss or loss of weight or underweight or malnutrition or wasting syndrome or anorexia* or muscle atrophy or sarcopenia).mp.

#7. or/#4-#6

#8. exp Medicine, East Asian Traditional/

#9. exp Drugs, Chinese herbal/

#10. exp Herbal Medicine/

#11. exp Plants, Medicinal/

#12. (traditional Korean medicine or traditional Chinese medicine or Traditional oriental medicine or Kampo medicine or alternative medicine or complementary medicine or herb or herbal or herbs or decoction* or botanic*).mp.

#13. or/#8-#12

#14. exp Randomized Controlled Trials as Topic/

#15. exp Clinical Trials as Topic/

#16. exp controlled clinical trials as topic/

#17. (randomized controlled trial* or controlled clinical trial* or randomized* or randomly* or placebo or clinical trial* or controlled trial*).mp.

#18. or/#14 - #17

#19. #3 and #7 and #13 and #18

Appendix 2. CNKI search strategy

(恶病质 or 恶液质 or 癌症恶病质 or 癌恶病质 or 肿瘤恶病质 or 癌性恶病质) and (中医药 or 中医 or 中西医结合 or 汉方 or 汉方医学 or 东洋医学 or 中药 or 中草药 or 中药制剂 or 汤 or 丸 or 散 or 注射液 or 口服液 or 中成药 or 饮) and (随机 or 对照)

APPENDICES

Appendix 1. MEDLINE (Pubmed) search strategy

#1. exp Neoplasms/

#2. (cancer or oncolog* or neoplasm* or malignan* or tumor or tumour or carcinoma* or adenocarcinoma* or osteosarcoma* or sarcoma* or leukemi* or lymphoma* or teratoma* or metastat*).mp.

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#8. exp Medicine, East Asian Traditional/

#9. exp Drugs, Chinese herbal/

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#12. (traditional Korean medicine or traditional Chinese medicine or Traditional oriental medicine or Kampo medicine or alternative medicine or complementary medicine or herb or herbal or herbs or decoction* or botanic*).mp.

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Appendix 2. CNKI search strategy

(恶病质 or 恶液质 or 癌症恶病质 or 癌恶病质 or 肿瘤恶病质 or 癌性恶病质) and (中医药 or 中医 or 中西医结合 or 汉方 or 汉方医学 or 东洋医学 or 中药 or 中草药 or 中药制剂 or 汤 or 丸 or 散 or 注射液 or 口服液 or 中成药 or 饮) and (随机 or 对照)