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Review:

A systematic review of herbal medicines for the treatment of cancer cachexia in animal models*

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Abstract: Objective: The aim of this study is to summarize preclinical studies on herbal medicines used to treat cancer cachexia and its underlying mechanisms. Methods: We searched four representing databases, including PubMed, EMBASE, the Allied and Complementary Medicine Database, and the Web of Science up to December 2016. Randomized animal studies were included if the effects of any herbal medicine were tested on cancer cachexia. The methodological quality was evaluated by the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADE) checklist. Results: A total of fourteen herbal medicines and their compounds were identified, including Coptidis Rhizoma, berberine, Bing De Ling, curcumin, Qing-Shu-Yi-Qi-Tang, *Scutellaria baicalensis*, Hochuekkito, Rikkunshito, hesperidin, atractylodin, Sipjeondaebo-tang, Sosiho-tang, Anemarrhena Rhizoma, and Phellodendri Cortex. All the herbal medicines, except curcumin, have been shown to ameliorate the symptoms of cancer cachexia through anti-inflammation, regulation of the neuroendocrine pathway, and modulation of the ubiquitin proteasome system or protein synthesis. Conclusions: This study showed that herbal medicines might be a useful approach for treating cancer cachexia. However, more detailed experimental studies on the molecular mechanisms and active compounds are needed.

Key words: Cancer; Cachexia; Herbal medicine; Traditional East Asian medicine systematic review
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1 Introduction

Cachexia is a complex syndrome that frequently occurs in advanced cancer patients. The incidence of cancer cachexia depends on the cancer type, with approximately 30% to 80% of advanced cancer patients suffering from cachexia (Mantovani et al., 2001; Teunissen et al., 2007). Anorexia, weight loss, and the loss of adipose tissue and skeletal muscle are the main symptoms of cancer cachexia. Various definitions of cancer cachexia have been proposed (Evans et al., 2008; Muscaritoli et al., 2010; Fearon et al., 2011; Blum et al., 2014), but the present consensus defines "cancer cachexia as a multifactorial syndrome characterized by the ongoing loss of skeletal muscle mass with or without the loss of fat mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (Muscaritoli et al., 2010; Fearon et al., 2011). Although the underlying mechanisms have not been fully determined, cancer cachexia occurs because of a protein and

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energy imbalance induced by an abnormal metabolism and reduced food intake (Fearon et al., 2011; Mendes et al., 2015; Penet and Bhujwalla, 2015).

Cancer cachexia causes many clinical problems including lowered activity, quality of life, and response to chemotherapy (Brown, 2002). Additionally, it is associated with a poor survival rate and accounts for approximately 20% of cancer deaths (Tisdale, 1997). Therefore, the management of cancer cachexia is an important issue. Many therapeutic approaches for cancer cachexia have been investigated in preclinical studies and clinical trials and include appetite stimulants, anti-inflammatory agents, ghrelin, nutritional support, and anabolics (Penet and Bhujwalla, 2015; von Haehling and Anker, 2015). Megestrol acetate (MA), known to improve the appetite through neuropeptide Y (NPY) and to down-regulate pro-inflammatory cytokines, is an approved drug for cancer cachexia in the United States and several European nations (Argilés et al., 2013). Recent randomized controlled trials and a systematic review showed significant improvements in appetite and weight gain with this treatment (Pascual López et al., 2004; Lesniak et al., 2008; Wen et al., 2012). In addition, L-carnitine and melatonin have been shown to improve anorexia both in vivo and in randomized controlled trials (Raghavendra and Kulkarni, 2000; Del Fabbro et al., 2013a; von Haehling and Anker, 2015). For anti-inflammatory agents, thalidomide and pentoxyphylline have been reported to have anti-inflammatory properties (Davis et al., 2012; Yennurajalingam et al., 2012; Rattanasompattikul et al., 2013). Recently, a monoclonal antibody that targets interleukin-α was investigated in phase I clinical trials (Hong et al., 2014). The administration of ghrelin or its agonist, anamorelin, has been shown to increase food intake and prevent weight loss (Neary et al., 2004; Strasser et al., 2008; Lenk et al., 2013). In addition, anabolics such as enbosarm and testosterone have been shown to have therapeutic effects on cachexia (Del Fabbro et al., 2013b; Dobs et al., 2013; Crawford et al., 2016).

Oriential medicine uses herbal medicines for treating a variety of diseases. Therefore, many studies have been conducted to explore the use of herbal medicines for treating diseases, including cancer cachexia. The therapeutic mechanisms of herbal medicines and their active compounds have been gradually uncovered and interpreted through in vivo studies. The aim of this study is to summarize such preclinical studies for the treatment of cancer cachexia and the underlying mechanisms.

2 Methods

2.1 Search strategy

Four electronic databases (PubMed, EMBASE, the Allied and Complementary Medicine Database (AMED), and the Web of Science) were searched with the following search terms (established by discussion with oncologists and experts in this field): ((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*) and (cachexia* or cachectic* or weight loss or loss of weight or underweight or malnutrition or wasting syndrome or anorexia* or muscle atrophy or sarcopenia)) and (traditional Korean medicine or traditional Chinese medicine or traditional oriental medicine or Kampo medicine or herb or herbal or herbs or decoction* or botanic*).

2.2 Eligibility criteria

We included in vivo experimental studies using cachectic animal models induced by cancer cell implementation that administered interventions including herbal medicines or their compounds. There was no limitation on the number, administration method, dosage, or duration of treatment. We also included articles with the full text written in English. We excluded experimental studies using in vitro models only or cachectic animal models not induced with cancer cells. We also excluded studies without appropriate control groups.

2.3 Data extraction

We extracted the following information from the articles: the authors, year of publication, herbal medicines including their compositions or active compounds, drug dosage, animal species and number, the type of implanted cancer cells, and outcome measurements. The primary outcomes were biomarkers associated with cancer cachexia. The secondary outcomes were changes in the cachectic symptoms such as weight loss, muscle atrophy, fat depletion,

and poor intake. The third outcomes were changes in the tumor size and survival.

2.4 Assessment of methodological quality and data analyses

The methodological quality of the included studies was evaluated by seven items based on the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADE) checklist and the assessment tool of other systematic reviews in animal models. The seven items consisted of: (1) the randomized allocation of animals to the experimental group; (2) intervention allocation concealment; (3) blinded assessment of the outcome; (4) a statement of sample size calculation; (5) a statement of the number of excluded animals and the reason; (6) a statement of compliance with regulatory requirements; and (7) a statement of possible conflicts of interest. The evaluated domains were assessed as "yes" or "no" according to the criteria.

3 Results

3.1 Characteristics of the included studies

We identified 518 articles from the four electronic databases. After excluding duplicate studies and articles that did not meet the inclusion criteria on the basis of reading the title and abstract, the full texts of 25 articles were retrieved and evaluated. Of the 25 articles, 12 were excluded because they did not report in vivo research and/or were duplicates. As a result, we selected 13 in vivo studies for this study (Iizuka et al., 2000, 2002; Xu et al., 2005; Beckett et al., 2008; Fujitsuka et al., 2011; Chou et al., 2012; Wang et al., 2012; Yae et al., 2012; Choi et al., 2014; Terawaki et al., 2014; Ohbuchi et al., 2015; Kim et al., 2016; Zhuang et al., 2016) (Fig. 1).

The characteristics of the included studies are summarized in Table 1. Nine studies were performed with mice and four studies used rats. A total of eight techniques were used for cancer cachectic models.

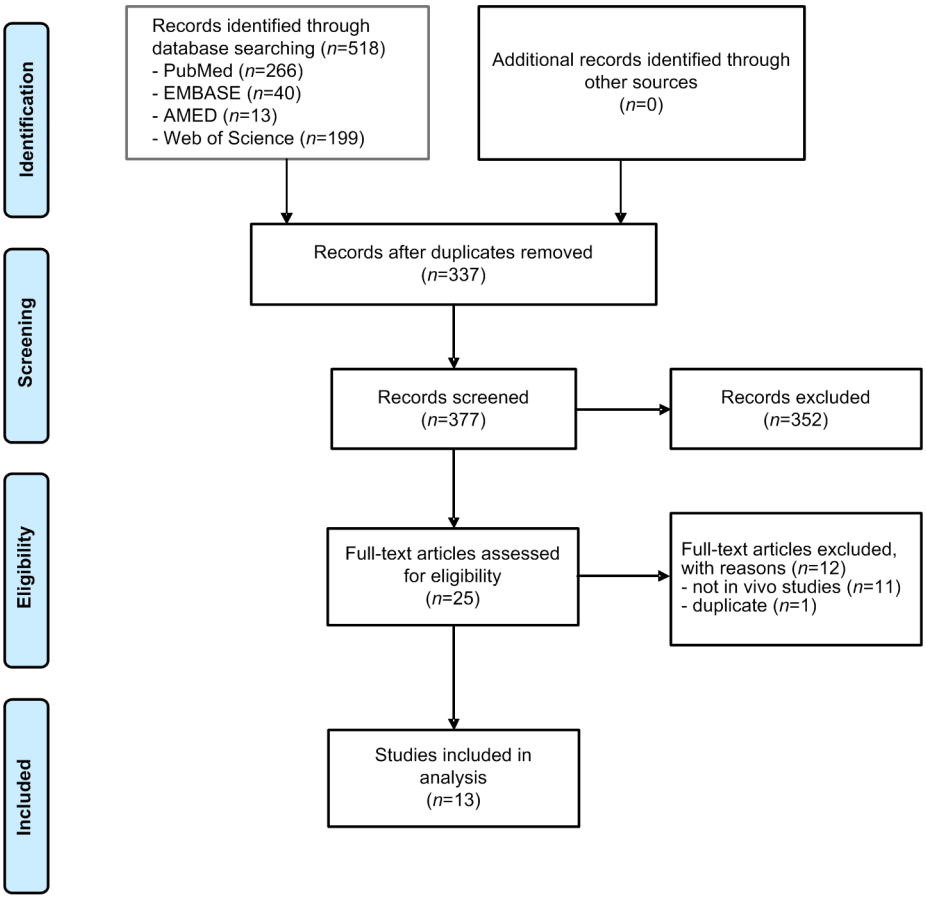

Fig. 1 Flow diagram of selection of studies

Table 1 Characteristics of the included studies

Author (year)	Animal model, implanted cancer cell	Interventions (dose)	Control	Outcome measurements and results
Iizuka et al. (2000)	BALB/c nude mice, YES-2 cell	Coptidis Rhizoma (water extraction, 10 mg/g in diet)	Untreated	IL-6 in tumor (↓) Weight loss (↓), food intake (n.s.) Tumor size (n.s.)
Iizuka et al. (2002)	BALB/c mice, colon 26/clone 20 cell	Coptidis Rhizoma (water extraction, 10 or 20 mg/g in diet)	Untreated	IL-6 in serum and tumor (↓), IL-6 in liver and spleen (n.s.) Weight loss (↓), loss of gastrocnemius muscle (↓), loss of epididymal adipose tissue (↓), food intake (n.s.) Tumor size (n.s.)
		Berberine (1, 2, and 4 mg/g in diet)	Untreated	IL-6 in serum and tumor (↓), IL-6 in liver and spleen (n.s.) Weight loss (↓), loss of gastrocnemius muscle (↓), loss of epididymal adipose tissue (↓), food intake (n.s.) Tumor size (n.s.)
Xu et al. (2005)	BALB/c mice, CT26 cell	5-FU plus Bing De Ling* (water extraction, 0.121 g/mL of water)	5-FU	Weight loss (↓) Tumor size (↓), survival rates (↑)
Beckett et al. (2008)	C57BL/6 mice, Lewis lung carcinoma	Curcumin (powder, 150 mg/kg in diet)	Untreated	Weight loss (n.s.), loss of muscle weight (n.s.), food intake (n.s.) Tumor size (n.s.)
	C57BL/6 mice, B16 melanoma tumor cell	Curcumin (powder, 150 mg/kg in diet)	Untreated	Weight loss (n.s.), loss of muscle weight (n.s.), food intake (n.s.) Tumor size (↓)
Chou et al. (2012)	C57BL/6 mice, Lewis lung carcinoma cell	QSYQT* (water extraction, 10 mL/kg in water)	Untreated	IL-1β (↓), IL-6 (↓), and TNF-α (↓) in serum, NF-κB mRNA (↓) in spleen Weight loss (↓), food intake (n.s.) Tumor size (n.s.)
Wang et al. (2012)	C57BL/6 mice, Lewis lung carcinoma cell	5-FU plus QSYQT* with *Scutellaria baicalensis* (1.5 and 3.0 mg/g)	5-FU	IL-6 (n.s.), TNF-α (n.s.), and MCP-1 (↓) in serum, NF-κB mRNA (n.s.), and MuRF-1 mRNA (↓) in gastrocnemius muscle Weight loss (↓), loss of the gastrocnemius muscle (↓) Tumor size (↓)
Yae et al. (2012)	BALB/c mice, colon 26/clone 20 cell	Hochuekkito* (water extraction, 1.2 g/kg in diet)	Untreated	IL-6 (↓) in serum and marcrophage surrounding tumor, IL-6 (n.s.) in tumor cells, TNF-α (n.s.) in serum Weight loss (carcass weight) (↓), loss of the gastrocnemius muscle and fat tissue (↓), food intake (↑) Tumor size (n.s.)
Fujitsuka et al. (2011)	Wistar rats, AH-130 hepatoma cell	Rikkunshito* (powdered extract, 125, 250, 500, and 1000 mg/kg)	Untreated or cisplatin	Hypothalamic CRF (↓), Ca^{2+} in NPY neurons (↑) Food intake (↑) Median survival (↑)
		Atractylodin		Median survival (↑)
Terawaki et al. (2014)	F344/NJcl-rnu/rnu rats, 85As2 cells (human stomach cancer cell)	Rikkunshito* (powdered extract, 1000 mg/kg)	Untreated	Weight loss (↓), loss of total muscle weight (↓), loss of fat free mass (↓), loss of total fat (↓), food and water intake (↑)

To be continued

Table 1

Author (year)	Animal model, implanted cancer cell	Interventions (dose)	Control	Outcome measurements and results
Ohbuchi et al. (2015)	Wistar rats, AH-130 hepatoma cell	Rikkunshito* (powdered extract, 1000 mg/kg)	Untreated	Glucarate (↑) in serum
		Glucarate (metabolite) (2, 6, and 18 mmol/kg)	Untreated	IFN-γ (↓), TNF-α (n.s.), and IL-10 (n.s.) in plasma Weight loss (↓), loss of gastrocnemius muscle weight (↓)
Choi et al. (2014)	Wistar rats, AH-130 hepatoma cell	Sipjeondaebo-tang* (water extraction, 6.784, 67.84, and 678.4 mg/kg in water)	Untreated	TNF-α (n.s.), IL-6 (↓), MCP-1 (↓), PYY (↓), GLP-1 (↓), active ghrelin (n.s.), and leptin (n.s.) in serum Weight loss (↓), loss of muscle weight (↓), food intake (↑)
Kim et al. (2016)	BALB/c mice, CT-26 cell	Sosiho-tang* (50 and 100 mg/kg)	Untreated	IL-6 (↓), TNF-α (n.s.), and IL-1β (n.s.) in serum Weight loss (↓), loss of gastrocnemius muscle weight (↓), loss of epididymal fat (↓) Tumor size (↓)
Zhuang et al. (2016)	C57BL/6 mice, C26 colon adenocarcinoma cell	Anemarrhena Rhizoma and Phellodendri Cortex (50% ethanol extraction, 104 mg/kg)	Untreated	IL-6 (↓), TNF-α (↓), and IGF-1 (↑) in serum and gastrocnemius muscle, atrogin-1 mRNA (↓) and MuRF-1 mRNA (↓), p-AKT (↑), LC3B (↑), Sirt1 (↑), and FOXO3 (↓) in gastrocnemius muscle Weight loss (↓), loss of gastrocnemius muscle weight (↓) Tumor size (n.s.), survival rate (↑)

↓: significantly decrease as the compared with the control group; ↑: significantly increase as compared with the control group; n.s.: no significant difference; IL: interleukin; 5-FU: 5-fluorouracil; QSYQT: Qing-Shu-Yi-Qi-Tang; TNF-α: tumor necrosis factor-α; NF-κB: nuclear factor-κB; MCP-1: monocyte chemoattractant protein-1; MuRF-1: muscle RING finger protein-1; CRF: corticotropin-releasing factor; NPY: neuropeptide Y; IFN-γ: interferon-γ; PYY: peptide YY; GLP: glucagon-like peptide; IGF-1: insulin-like growth factor-1; p-AKT: phosphorylated Akt; LC3B: light chain 3B; FOXO3: forkhead box O3. * No detailed information for herbal formulas

Wistar rats with AH-130 hepatoma cells and C57BL/6 mice with Lewis lung carcinoma were used the most frequently and were each used in three studies. A total of fourteen herbal medicines or their compounds were explored. Of them, Rikkunshito (RKT) was investigated the most and was used in three trials, and Qing-Shu-Yi-Qi-Tang (QSYQT) was studied the second most frequently, in two studies.

As shown in Table 2, only two studies reported that they were randomized. None of the studies reported allocation concealment, blinded assessment of the outcome, sample size calculations, or the number of excluded animals. Nine studies mentioned compliance with regulatory requirements. Additionally, eight studies reported possible conflicts of interests. Regarding an overall score for each item, one study was scored "yes" in three of seven items, eight studies were scored "yes" for one of the seven items, and four studies scored "yes" for two of the seven items.

3.2 Herbal medicines for the treatment of cancer cachexia

3.2.1 Coptidis Rhizoma and berberine

Coptidis Rhizoma, the root of *Coptis chinensis* Franchet, is a popular herbal medicine and is commonly used for diverse diseases, especially inflammation-related diseases and digestive tract ulcers (Feng et al., 2008; Choi et al., 2013; Jang et al., 2013). Berberine, a major compound of Coptidis Rhizoma, has been shown to have positive effects on metabolic syndrome, diabetes, congestive heart failure, diarrhea, and cancer in preclinical and clinical studies (Kumar et al., 2015; Wang et al., 2015).

Iizuka et al. (2000) demonstrated that the oral administration of Coptidis Rhizoma to nude mice implanted with YES-2 cells significantly attenuated weight loss without a change in food intake or tumor growth and lowered the tumor interleukin-6 (IL-6) levels. Additionally, the authors reported that the

Table 2 Quality assessment of the included studies

Author (year)	Randomized allocation	Allocation concealment	Blinded assessment of outcome	Sample size calculation	Number of excluded animal and its reason	Compliance with regulatory requirements	Possible conflicts of interest
Iizuka et al. (2000)	N	N	N	N	N	Y	N
Iizuka et al. (2002)	N	N	N	N	N	Y	N
Xu et al. (2005)	N	N	N	N	N	Y	N
Beckett et al. (2008)	N	N	N	N	N	Y	N
Chou et al. (2012)	N	N	N	N	N	N	Y
Wang et al. (2012)	N	N	N	N	N	N	Y
Yae et al. (2012)	Y	N	N	N	N	N	Y
Fujitsuka et al. (2011)	N	N	N	N	N	N	Y
Terawaki et al. (2014)	N	N	N	N	N	Y	Y
Ohbuchi et al. (2015)	N	N	N	N	N	Y	Y
Choi et al. (2014)	Y	N	N	N	N	Y	Y
Kim et al. (2016)	N	N	N	N	N	Y	N
Zhuang et al. (2016)	N	N	N	N	N	Y	Y

Y: yes; N: no

treatment of YES-2 cells with berberine reduced the IL-6 mRNA expression of YES-2 cells in vitro. These observations demonstrate that Coptidis Rhizoma might have an anticachectic effect on esophageal cancer, and an effect was associated with berberine via the downregulation of tumor IL-6 production. This phenomenon was reconfirmed in mice bearing colon 26/clone 20 carcinoma cells (Iizuka et al., 2002).

3.2.2 Bing De Ling

Bing De Ling, a mixture of seven herbs, *Astragalus membranaceus*, *Rheum palmatum*, *Atractylodes macrocephala*, *Isatis tinctoria*, *Scutellaria baicalensis*, *Cornus officinalis*, and *Dryopteris crassirhizoma*, has been prescribed for common colds, influenza, chronic fatigue syndrome, herpes simplex, and chemotherapy-induced toxicities (Xu et al., 2005). Bing De Ling was reported to respond to increased immunologic activity and anti-tumor activity because of the activation of p53 (Niu et al., 2000; Zhang et al., 2010).

Xu et al. (2005) demonstrated that the oral administration of Bing De Ling to CT26 mouse colon cancer cell-bearing mice via 5-fluorouracil (5-FU) chemotherapy significantly enhanced 5-FU-induced tumor growth inhibition. The oral administration of Bing De Ling also enhanced the survival rates and reduced weight loss in tumor-free mice receiving 5-FU compared to tumor-free mice that received 5-FU alone. This study showed that Bing De Ling enhances the antitumor responses of 5-FU and ameliorates its side effects.

3.2.3 Curcumin

Curcumin is the active ingredient isolated from the rhizome of *Curcuma longa* Linné, with usage as a treatment for inflammatory conditions in East and Southeast Asia. Curcumin is shown to be a highly pleiotropic molecule that interacts with numerous inflammatory molecular targets. Thousands of in vitro and in vivo studies have explored the molecular basis of curcumin's attributed antioxidant, anti-inflammatory, antibacterial, antiapoptosis, and anti-cancer activity. In addition, hundreds of clinical trials have investigated the effects of curcumin in various chronic diseases, including diabetes, cancers, cardiovascular, neurological and psychological diseases (Naksuriya et al., 2014; Devassy et al., 2015; Ghosh et al., 2015; He et al., 2015; Shanmugam et al., 2015).

Beckett et al. (2008) demonstrated that curcumin for Lewis lung carcinoma- or B16 melanoma-bearing mice reduced the tumor mass in mice with B16 melanoma without reducing splenomegaly or preserving

body weight or muscle mass in either model. This study showed that curcumin may not be beneficial for treating cancer cachexia. However, the evidence of its antitumor effects in animal models suggested that clinical trials of curcumin for cancer patients would be warranted.

3.2.4 Qing-Shu-Yi-Qi-Tang and *S. baicalensis*

QSYQT, composed of *Astragalus membranaceus* Bunge, *Panax ginseng* C. A. Meyer, *Atractylodes chinensis* Koidzumi, *Cimicifuga foetida* Linné, *Atractylodes macrocephala* Koidzumi, *Alisma orientale* Juzepzuk, *Citrus reticulata* Blanco, and Massa Medicata Fermentata, has been used for treating fever and pulmonary disorders in East Asia (Chou et al., 2012). *A. membranaceus*, *A. chinensis*, and *P. ginseng*, the major ingredients of QSYQT, have been investigated for their immunomodulatory and anti-inflammatory activity (Cho and Leung, 2007a, 2007b; Li et al., 2007; Dong et al., 2008; Agyemang et al., 2013; Fu et al., 2014; Li et al., 2014; Ru et al., 2015). Scutellariae Radix, the root of the medicinal plant *S. baicalensis*, has been widely used for various diseases. *S. baicalensis* shows many therapeutic effects, including tumor growth inhibition, apoptosis induction, and anti-angiogenesis (Li et al., 2011; Muluye et al., 2014; Wu et al., 2016).

Chou et al. (2012) reported that the oral administration of QSYQT water extract to Lewis lung cancer cell-bearing mice significantly prevented weight loss without affecting food intake or tumor growth. Additionally, the authors reported that the levels of IL-1, IL-6, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) in the serum and nuclear factor-κB (NF-κB) expression in the spleen were significantly reduced in tumor-bearing mice treated with QSYQT.

Wang et al. (2012) demonstrated that the oral administration of QSYQT with *S. baicalensis* to Lewis lung cancer cell-bearing mice via 5-FU chemotherapy significantly regained body and muscle weights in addition to improving immune status. The authors also reported that the serum levels of monocyte chemoattractant protein-1 (MCP-1) and the expression levels of NF-κB and muscle RING finger protein-1 (MuRF-1) decreased when the herbal combination was administered. Based on these observations, it was concluded that QSYQT exerted an anti-cachectic effect on Lewis lung carcinoma-induced cachectic mice, and this effect was associated with the modulation of IL-6 production through NF-κB. Furthermore, with the combination of *S. baicalensis*, QSYQT ameliorated cachectic symptoms and positively stimulated anti-tumor immunity through an increased number of T lymphocytes and enhanced cytotoxicity of natural killer (NK) cells in the spleen.

3.2.5 Hochuekkito

Hochuekkito, Bojungikki-tang in Korean and Bu-Zhong-Yi-Qi-Tang in Chinese, is composed of ten medicinal herbs, Astragali Radix, Atractylodis Rhizoma, Ginseng Radix, Angelicae Gigantis Radix, Bupleuri Radix, Zizyphi Fructus, Citri Unshius Pericarpium, Glycyrrhizae Radix et Rhizoma, Cimicifugae Rhizoma, and Zingiberis Rhizoma Crudus. Hochuekkito has been widely used for the treatment of general fatigue, poor appetite, spontaneous sweating, and intermittent fever in East Asia. It has a variety of biological activity including immunomodulation, anti-inflammation, and anti-cancer effects (Jeong et al., 2010; Yao et al., 2012; Yanagihara et al., 2013; Lee et al., 2014; Yang et al., 2015).

Yae et al. (2012) examined the therapeutic effect of Hochuekkito in the colons of 26 adenocarcinoma cell-bearing mice. Hochuekkito significantly decreased carcass weight reduction, food and water intake, weight of the gastrocnemius muscle and fat tissue around the testes, and serum triglyceride levels. In addition, Hochuekkito treatment significantly reduced serum IL-6 expression levels in macrophages in tissues surrounding the tumor. This study showed that Hochuekkito inhibits the production of pro-inflammatory cytokines, particularly IL-6, by macrophages.

3.2.6 Rikkunshito, hesperidin, and atractylodin

RKT, the traditional herbal formula of East Asia, is composed of Atractylodis Rhizoma, Ginseng Radix, Pinelliae Tuber, Poria Sclerotium, Zizyphi Fructus, Citri Unshius Pericarpium, Glycyrrhizae Radix et Rhizoma, and Zingiberis Rhizoma Crudus (Fujitsuka and Uezono, 2014). RKT is widely used for the treatment of functional dyspepsia, gastritis, and chemotherapy-induced dyspepsia in cancer patients (Tatsuta and Iishi, 1993; Mogami and Hattori, 2014; Saegusa et al., 2015). RKT enhances appetite and gastric motility by increasing endogenous ghrelin or ghrelin signal levels (Takeda et al., 2008, 2010; Fujitsuka et al., 2009,

2011; Saegusa et al., 2011; Yamada et al., 2013; Nahata et al., 2014). Additionally, several clinical trials showed that RKT was effective in ameliorating dyspepsia, epigastric pain, and postprandial fullness. Hesperidin and atractylodin, the active compounds of RKT, are known to have antioxidant, anti-inflammatory, or antibacterial activity (Chen et al., 2012; Iranshahi et al., 2015; Parhiz et al., 2015).

Fujitsuka et al. (2011) demonstrated that the oral administration of RKT to AH-130 hepatoma cell bearing-rats showed improved food intake and median survival. Furthermore, the oral administration of hesperidin and atractylodin also improved the median survival. In addition to these results, the authors reported that RKT suppressed the serotonin (5-HT)-corticotropin-releasing factor (CRF) neuronal pathway and sensitized the ghrelin receptor in NPY neurons in the arcuate nucleus of the hypothalamus.

Terawaki et al. (2014) reported that the oral administration of RKT to rats implanted with 85As2 human stomach cancer showed improved food and water intake and ameliorated the loss of body weight, fat-free mass, total body water, and muscular weight.

Ohbuchi et al. (2015) studied the oral administration of RKT to AH-130 hepatoma cell bearing-rats. The authors reported significant elevations of glucarate in the metabolome analysis of plasma in these animal models, and the administration of glucarate delayed weight loss, improved muscle atrophy, and reduced plasma IFN-γ level.

Based on these observations, RKT ameliorates cancer cachectic symptoms via a physiologic pathway, including the 5-HT-CRF neuronal pathway, sensitized by the ghrelin receptor in NPY neurons in the arcuate nucleus of the hypothalamus, and anti-inflammatory activity is achieved by attenuating glucarate in the plasma.

3.2.7 Sipjeondaebo-tang

Sipjeondaebo-tang (SJDBT), Shiquandabu-tang in Chinese and Juzentaihoto in Japanese, is composed of ten species of herbs, which are *Angelica gigas* Nakai, *Astragalus membranaceus* Bunge, *Atractylodes japonica* Koidzumi, *Cinnamomum cassia* Presl, *Cnidium officinale* Makino, *Glycyrrhiza uralensis* Fischer, *Paeonia lactiflora* Pallas, *Panax ginseng* C. A. Meyer, *Poria cocos* Wolf, and *Rehmannia glutinosa* Liboschitz ex Steudel. SJDBT is prescribed for patients suffering from anemia, fatigue, anorexia, scaly skin, and dryness of the mouth (Matsumoto et al., 2000; Saiki, 2000).

Choi et al. (2014) examined the oral administration of SJDBT in CT-26 tumor-bearing mice. The authors reported that SJDBT was more significantly effective in a treatment model where it was administered after anorexia and cachexia than in a prevention model on the basis of parameters such as muscle and whole-body weight and food intake. Moreover, SJDBT inhibited the productions of IL-6, MCP-1, peptide YY (PYY), glucagon-like peptide-1 (GLP-1) and ameliorated cancer-induced anemia. Based on these observations, the authors concluded that SJDBT might be useful for treating cancer-associated anorexia and cachexia.

3.2.8 Sosiho-tang

Sosiho-tang, Xiaochaihu-tang in Chinese and Shosaikoto in Japanese, is composed of *Bupleurum falcatum* Linne, *Pinellia ternata* Breitenbach, *Scutellaria baicalensis* Georgi, *Zizyphus jujuba* Miller var. inermis Rehder, *Panax ginseng* C. A. Meyer, *Glycyrrhiza uralensis* Fischer, and *Zingiber officinale* Roscoe. Sosiho-tang is clinically used for the treatment of various fever diseases including the common cold and chronic hepatic diseases (Ikegami et al., 2006; Takahashi et al., 2014).

Kim et al. (2016) demonstrated that the administration of Sosiho-tang for cancer-induced cachexia in CT-26-bearing mice significantly retarded tumor growth and prevented the loss of final body weight, carcass weight, heart weight, gastrocnemius muscle, and epididymal fat compared with saline-treated control mice. Furthermore, serum IL-6 levels elevated by cancer were decreased by the administration of Sosiho-tang. The author concluded that Sosiho-tang is a safe and useful anti-cachectic therapy for cancer patients with severe weight loss.

3.2.9 Anemarrhena Rhizoma and Phellodendri Cortex

Zhimu and Huangbai (ZBHP, Anemarrhena Rhizoma and Phellodendri Cortex) has been used in East Asia to treat various diseases (Ma et al., 2008). ZBHP was previously phytochemically investigated for constituents with anti-cancer or diabetes properties among others (Tang et al., 2012). Rrecent research has demonstrated that ZBHP could reverse muscle

atrophy in streptozotocin-induced diabetic mice (Zhang et al., 2014).

Zhuang et al. (2016) investigated oral administration of ZBHP to mice implanted with colon-26 adenocarcinoma. ZBHP showed significant alleviation of the tumor-free body weight reduction and cachexia-induced changes in cytokines and prolonged survival. ZBHP inhibited muscle atrophy-related genes as well as activated the insulin-like growth factor-1 (IGF-1)/Akt and autophagy signal pathways to facilitate protein synthesis.

4 Discussion

Recent studies have provided a greater understanding of the molecular mechanisms and new therapeutic approaches for cancer cachexia, but cancer cachexia still requires an efficacious remedy. Herbal medicines and their compounds have been extensively reported to have anti-cachectic effects, and this has become an active research area in the treatment of cancer cachexia. In this study, we summarized the herbal medicines and their active compounds that showed anti-cachectic effects in animal studies. We identified thirteen in vivo studies through four electronic databases. As described in Table 1, the majority of herbal medicines and their active compounds, except curcumin, have been shown to ameliorate symptoms of cancer cachexia, which include weight loss, poor intake, and muscle atrophy. Ten of the thirteen studies explained the anti-cachectic effects of herbal medicines through anti-inflammation. As described in the results, many studies suggested that the included herbal medicines had anti-inflammatory effects for various diseases, and it was no surprise that the majority of the studies focused on anti-inflammatory mechanisms. Coptidis Rhizoma, berberine, Bing De Ling, QSYQT, Hochuekkito, SJDBT, Sosiho-tang, and ZBHP were shown to inhibit the production of pro-inflammatory cytokines, mainly IL-6. In addition, QSYQT with *S. baicalensis* and SJDBT were reported to inhibit MCP-1, which is an important mediator activating transcription factors in the early inflammatory response. RKT was shown to ameliorate inflammation partly by the elevation of glucarate in the plasma. Two studies explored how herbal medicines affected the regulation of the ubiquitin proteasome system and inhibited protein synthesis. ZBHP was reported to alleviate muscle atrophy through the inhibition of atrogin-1 and MuRF-1, and the activation of the IGF-1/Akt pathway. In addition, QSYQT with *S. baicalensis* was shown to downregulate NF-κB and MuRF-1. These effects might be related to the herbal medicine's anti-inflammation mechanisms, as ZBHP and *S. baicalensis* are known to have anti-inflammatory effects. RKT was shown to ameliorate anorexia via regulation of the neuroendocrine pathway, including the 5-HT-CRF neuronal pathway and the ghrelin receptor in NPY neurons in the ARC of the hypothalamus. Additionally, SJDBT was reported to improve anorexia via the down-modulation of gut hormones PYY and GLP-1.

Based on these results, herbal medicines might represent a potential therapeutic approach for cancer cachexia as well as adjuvant therapy. However, several issues need to be addressed. First, the methodological quality of the included studies is weak. Only two of the thirteen studies reported randomization, and none of the included studies reported allocation concealment, a blinded assessment of the outcome, a sample size calculation or the number of excluded animals. Because the risk of bias could affect the observed outcome, a well-designed study is needed. Second, the molecular mechanisms of the anti-cachectic effects of some herbal medicines were studied, but the majority of herbal medicines have not been fully studied at the level of underlying mechanisms. More detailed studies about the molecular mechanisms of herbal medicines and their active compounds are necessary. Furthermore, these studies should include clinical control trials. We believe that herbal medicines are sufficiently worthy as potential therapy agents for cancer cachexia if more profound studies about the underlying mechanisms of herbal medicines with improved methodological quality are undertaken.

Contributors

Bongki PARK, Sooseong YOU, and Myeong Soo LEE designed the research and wrote the first draft. Bongki PARK, Sooseong YOU, and Jun-Yong CHOI searched the databases and performed the data extraction. William C. S. CHO and Jun-Yong CHOI provided expertise advice and revised the draft. All authors read the final draft and agreed to publish in the journal.

Compliance with ethics guidelines

Bongki PARK, Sooseong YOU, William C. S. CHO, Jun-Yong CHOI, and Myeong Soo LEE declare that they have no conflict of interests.

This article does not contain any studies with human or animal subjects performed by any of the authors, and does not need to obtain the Institutional Review Board of human or animals.

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中文概要

题　目：中草药对治疗癌症恶病质动物模型有效性的系统性回顾

概　要：本综述总结利用中草药治疗癌症恶病质的临床前研究及其潜在的机制，是首个针对中草药治疗癌症恶病质动物模型成效进行系统性回顾评价的研究。本文通过检索 PubMed、EMBASE、Allied and Complementary Medicine Database 以及 Web of Science 四大代表性的资料库（检索时间至 2016 年 12 月），就中草药治疗癌症恶病质的随机对照动物试验进行系统性回顾分析，并采用 CAMARADE 评分清单进行质量评价。分析结果显示：在十四项中草药及其化合物中，除了姜黄素外其他如黄连、黄连素、病得灵、清暑益气汤、黄芩、补中益气汤、六君子汤、橙皮苷、苍术呋喃烃、十全大补汤、小柴胡汤、知母及黄柏等都已被证实可以通过抗炎、调节神经内分泌途径、调节泛素蛋白酶体系统或蛋白质合成来改善癌症恶病质的症状。因此，利用中草药治疗癌症恶病质是一种有效的方法。然而该结论尚需要有更详细的分子机制和活性化合物的实验研究验证。

关键词：癌症；恶病质；中草药；传统东亚医学系统性回顾

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