Review Article

Role of Complementary and Alternative Medicine in the Management of Cancer Cachexia

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ABSTRACT

Cancer cachexia is an important concern in cancer patients in view of advanced stage at presentation. The treatment goal for cachexia is the reversal of the loss of body weight and muscle mass with a variety of pharmacological agents. Various treatment guidelines focus on patients with advanced cancer who are likely to suffer from refractory cachexia. There is a paucity of data on research directed to cancer cachexia on cancer patients. Complementary and alternative medicines (CAMs) are widely use at some or other point of time by the majority of cancer patients in spite of little or no evidence to support that. There are many CAM which have been tried in different set up for cancer cachexia. These medicines are well accepted in view of lesser side effects and easy to use. There is a need for more randomized controlled trials with larger sample size with longer follow-up to generate more evidence in support to the use of CAM in cancer and cancer cachexia.

Key words: Complementary and alternative medicine, cancer cachexia, cancer, herbal medicine, weight loss

Introduction

Cancer cachexia is a debilitating state of involuntary weight loss characterized by anorexia, tissue wasting, progressive functional impairment, poor performance, and ultimately death.^[1] About half of all cancer patients will experience this cancer cachexia syndrome during the process of cancer care.^[2] The prevalence of cachexia increases from 50% to more than 80% before

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death, and in more than 20% of patients, cachexia is the major cause of death.^[3] The prevalence of cachexia is 87% in patients with pancreatic and gastric cancer, whereas it is reported in 61% of patients with colon, lung, and prostate cancer and non-Hodgkin lymphoma and 40% in breast cancer, sarcoma, leukemia, and

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Hodgkin lymphoma.^[4] Cancer cachexia is developed as a secondary disease in cancer patients. Systemic inflammatory response, negative protein-energy balance, and involuntary loss of lean body mass, with or without a decline in adipose tissue may cause progressive dysfunction in cancer patients.^[5] This can be related to mechanical interference in the gastrointestinal tract, such as obstruction or malabsorption, or to surgical interventions or treatment-related toxicity.

In cancer treatment, herbal medicine has been commonly used to promote physical reconditioning and to reduce the adverse effects from chemotherapy or radiation therapy and thus enhance the quality of life (QOL).^[6] The use of herbal medicines with chemotherapeutic agents is quite reasonable because these medicines help the body to restore homeostasis. This review provides a new perspective on the use of complementary and alternative medicine (CAM) in the management of cancer cachexia from a scientific point of view.

Methods

A search was performed on PubMed using the keywords CAM, Herbal Medicine, Chinese Traditional medicine, and Traditional Medicine with Cancer Cachexia for all kind of scientific articles published in the last 15 years. References of articles of search result were also included if found relevant. There were no language restrictions on publications.

Results

A total of 166 search results were found. We selected only articles related to cancer cachexia or weight loss. Overlapped search results were considered as one. The final search was narrowed to 60 articles.

Discussion

The pathogenesis of anorexia and weight loose is complex but not yet well understood. It may be due to release of substances by the tumor or by normal cells in response to the tumor interfere with the carbohydrate, protein and lipid biochemistry, and metabolism. The most important carbohydrate abnormalities are insulin resistance which can lead to an increase in glucose synthesis, gluconeogenesis along with decreased glucose tolerance, and turnover. This whole process leads to dysregulated metabolism in cachexia, causing significant weight loss. The main pathological changes of protein metabolism include increased protein turnover, muscle catabolism, and liver and tumor protein synthesis, whereas muscle protein synthesis is decreased. The main abnormalities found in lipid metabolism are enhanced lipid mobilization, decreased lipogenesis, decreased lipoprotein lipase activity, elevated triglycerides and decreased high-density lipoproteins, increased venous glycerol, and decreased glycerol clearance from the plasma.^[7-10]

Food intake in cancer patients may be affected with the treatment such as pain medications, radiotherapy, and chemotherapy in view of underlying physical obstruction of the gastrointestinal tract, pain, constipation, malabsorption, or any other side effects. Patients with cancer often experience psychological distress as a result of uncertainties about the disease and its diagnosis, treatment, and anticipated final outcome. Patient's state of mind is an important determinant of food intake and it changes very frequently in the treatment process. Thus, cancer anorexia cachexia syndrome is seen as a multidimensional (mal) adaptation that encompasses a variety of derangements that range from physiological to behavioral and is correlated with poor outcomes and a compromised QOL.^[3] Although the etiology of cachexia is not well defined, the roles of cytokines, circulating hormones, neuropeptides, neurotransmitters, and tumor-derived factors have been explored.[11-13]

Complementary and Alternative Medicine

Nowadays, the use of CAM is very common among cancer patients. A multinational survey found that 35.9% of cancer patients were either past or present users of CAM. Herbal medicines were by far the most commonly used group of CAM treatments, escalating in use from 5.3% before the diagnosis of cancer to 13.9% after the diagnosis of cancer. Herbal medicines are believed by the general public to be safe, to cause fewer side effects, and to be less likely to cause dependency.^[14] In cancer treatment, herbal medicine has been commonly used to promote physical reconditioning and to reduce the adverse effects from chemotherapy or radiation therapy and thus enhance the QOL.^[6] For example, herbal medicines such as rikkunshito improve the nausea, appetite loss, and cachexia associated with cancer or cancer chemotherapy, which all worsen the QOL and life expectancy of patients. Homeostasis is regulated through dynamic control mechanisms that defend the host from perturbations that threaten the internal milieu.[15]

Appetite enhancers to increase oral nutritional uptake have been the most common pharmacological intervention in the treatment and/or prevention of cancer cachexia so far. Herbal remedies are believed by the general public to be safe, cause less side effects and less likely to cause dependency.^[16]

Complementary and Alternative Medicine in Cancer Cachexia

Cancer-related loss of appetite and weight is an important issue for many oncologists and cancer patients in every stage of cancer care, but this is of utmost importance when patients are undergoing cancer treatment. The most common measures are directed toward improving appetite by the addition of appetite stimulants such as megestrol, high quality protein supplements, but there are no interventions proven efficacious in reversing the skeletal muscle wasting in cancer cachexia. CAM is used very extensively by cancer patients and its usage is reported in about 50% of the patients with breast or gynecologic malignancies, whereas as much as 5% of this population takes the herbal supplement and garlic.^[17] In the UK, almost half of women with breast cancer taking herbal remedies, vitamins, or other supplements during treatment.^[18] In Australia, more than half of cancer patients also received herbal medicine.^[19] There is a need for an expanded armamentarium against cancer-related weight loss.

Nutrition Therapy

Eicosapentaenoic acid

There is no evidence to prove that the use of oral eicosapentaenoic acid (EPA) in cancer cachexia has better outcomes than placebo. In a study, EPA combined with a protein energy supplementation was compared with protein energy supplementation (without EPA) in the presence of an appetite stimulant (Megestrol Acetate) reported that EPA did not improve symptoms associated with the cachexia syndrome often seen in patients with advanced cancer.^[20]

Oral nutritional intervention

Oral nutritional intervention (ONI) was associated with statistically significant improvements in weight and energy intake compared with routine care. In addition, ONI improves QOL by improving emotional functioning, dyspnea, and loss of appetite, but had no effect on mortality (relative risk = 1.06, 95% confidence interval [CI] =0.92–1.22).^[21]

Vitamins, minerals, proteins, and other supplements

Vitamin E in combination with omega-3 fatty acids reported a significant prolonged survival in a randomized controlled trial, whereas Vitamin D showed improvement of muscle weakness (37%) in a crossover study, and Vitamin C supplementation helped to improve QOL indicators. One study reported no effect of magnesium on weight loss. Combination therapy of β -hydroxy- β -methylbutyrate, arginine, and glutamine showed an increase in body weight after 24 weeks in a study of patients with advanced cancer, whereas the same combination did not show a benefit on lean body mass (LBM) in a large sample of advanced lung and other cancer patients after 8 weeks. L-carnitine reported an increase of body mass index and an increase in the overall survival in advanced pancreatic cancer patients.^[22]

Echium oil

Randomized controlled trial by Pottel *et al.* suggested that Echium oil is not protective against weight loss in head-and-neck cancer patients undergoing curative radio (chemo) therapy, but it was well-tolerated. Therefore, it should not yet be recommended in daily practice, outside of the context of a clinical trial.^[23]

Herbal Medicines

Over the last 10 years, there has been a dramatic increase in the use of herbal supplements in the world. The use of herbal medicines for cancer is both widespread and diverse worldwide, escalating in the use from 5.3% before the diagnosis of cancer to 13.9% after the diagnosis of cancer.^[24] The highest use of herbal medicine (64%) was noted in Taiwan and Italy.^[25] Worldwide, herbal medicine usage in countries such as Australia, Canada, Denmark, Norway, USA, and United Kingdom ranges considerably between 9% and 69%.^[26]

The central purpose of the pharmacological treatment of cachexia is to antagonize its two main symptoms, anorexia, and chronic nausea. The commonly used herbal medicines include essiac, iscador, pau d'arco tea, and cannabinoids and so on.

Essiac

Essiac is comprised of four herbs: Burdock, Turkey rhubarb, sorrel, and slippery elm. Essiac is believed to increase appetite, alleviates and can eliminate pain, and gives a wonderful feeling of well-being.^[27] It is claimed to be nontoxic and to have no side effects.

Iscador

Iscador, a derivative of mistletoe, is popular in Europe. To date, many clinical studies have investigated mistletoe as a cancer treatment, but nearly all of the studies had major weaknesses that raise doubts about the reliability of the findings.^[28]

Pau d'arco tea

Pau d'arco tea is said to be an old Inca Indian remedy for many illnesses. It has no proven role to play in cancer cachexia rather, it induces nausea and vomiting. Despite the absence of scientific evidence, pau d'arco tea is sold as a cancer remedy in health food stores, by mail, and on the Internet.^[27,29]

Cannabinoids

Cannabinoids are used in cancer patients with an aim to improve appetite, leading to weight gain and relief of chemotherapy-induced nausea and vomiting. In a crossover study, significant weight gain was observed in advanced cancer patients who were put on cannabis in comparison to weight loss in the placebo group.^[30] Several studies on the use of cannabis in advanced cancer-associated anorexia have shown some improvement in mood and appetite with either no or some improvement in body weight.^[31,32] One study^[33] had shown that delta-9-THC not only reversed nausea but also appeared to stimulate appetite and mood at well-tolerated doses (5 mg daily) which has been confirmed by another study.^[32]

Chinese Traditional Medicine

In cancer treatment, CTM has been used to promote physical reconditioning and to reduce adverse effects after chemotherapy or radiation therapy, enhancing the QOL. Therefore, CTM aims to increase tumor specificity while minimizing adverse effects on normal tissues.^[6] Qi-ge-kai-wei decoction plus megestrol acetate versus megestrol acetate alone, showed a higher proportion of reported improvement (93.8% vs. 87.5%) for treating anorexia in advanced lung cancer patients. However, there was no statistical significance. Tong-tai decoction and chemotherapy showed more improvement than chemotherapy alone in advanced colorectal cancer patients (55.0% vs. 45.0%), but again no significance difference was found; CHM could significantly reduced pain (pooled WMD: -0.90, 95% CI: -1.69--0.11), compared with conventional intervention; Adverse events were in-frequent and mild.[34]

Asian Traditional Herbs and Formulations

Ginseng

Ginseng (Panax ginseng) is one of the most widely used herbal medicines and has been used as a restorative tonic in China and Japan.^[35]

Rhizome (Da-Huang)/berberis vulgaris root

Rhizoma is traditionally used in the treatment of stuffiness and fullness of the abdomen, diarrhea, vomiting, high fever, and fidgetiness. It can improve circulation, increase blood supply, and aid recovery from weakness after illness.^[36] In future, evidence from large-scale clinical trials will be necessary to incorporate this herb into mainstream cancer therapies.

Radix astragali (Huang qi)

It is traditionally considered to be a tonic that may improve the functions of lung, adrenal gland, and gastrointestinal tract, increase the metabolism, promote the healing, and reduce the cachexia fatigue, and to increase overall vitality. In Korea, a phase II study of astragali radix decoction had been performed in patients with advanced solid tumors.^[37] The herbal decoction improved appetite scores and body weight. Therefore, this herbal decoction shows some potential for the management of cancer-related anorexia. Clinical trials with a larger population should be planned to confirm the efficacy of this herbal decoction.

TJ-48 (Shi Quan Da Bu Tang in Chinese; Juzentaiho-to in Japanese)

It has been used to treat anemia, anorexia, exhaustion, fatigue, and general weakness, which were consist of cachexia symptoms. It contains 10 herbs including *Angelica* sinensis, *Paeonia lactiflora*, *Atractylodes macrocephala*, *Poria* cocos, Cinnamomum cassia, *Astragalus membranaceus*, *Liqusticum wallichii*, *Glycyrrhiza inflate*, and *Rehmannia* glutinosa.^[38]

TJ-41 (Bu-Zhong-Yi-Qi-Tang in Chinese, Hochu-ekki-to in Japanese)

It contains seven herbs including *Pinellia tuber*, *Scutellaria baicalensis*, *Zingiberis rhizoma*, *Zizyphi fructus*, *Coptidis rhizoma*, *Glycyrrhiza radix*, and Panax ginseng. TJ-41 is recommended to reduce the extent of side effects such as leucopenia and intestinal damage and fatigue occurring as a result of radiation or chemotherapy to treat malignant tumors.^[39,40]

PHY906

PHY906 is a modified preparation from the herbal formulation named Huang-Qin-Tang, which has been used for over 1800 years in China to treat a wide range of gastrointestinal symptoms, including nausea, vomiting, cramping, and diarrhea. PHY906 consists of four commonly used herbs, S. baicalensis Georgi, P. lactiflora Pall, Glycyrrhiza uralensis Fisch, and Ziziphus jujube Mill, at a ratio of 3: 2: 2: 2.^[41] Research studies have shown that PHY906 reduces gastrointestinal toxicity, enhances the antitumor efficacy of some anticancer drugs, and alleviates chemotherapy-induced side effects, such as diarrhea.

Rhyo-Jen-Zhu-Tang in Chinese and Rikkunshito in Japanese

Rhyo-Jen-Zhu-Tang or Rikkunshito, a traditional herbal medicine, is a mixture of dried Atractylodis lanceae

rhizoma, ginseng radix, pinelliae tuber, hoelen, Zizyphi fructus, Aurantii nobilis peri-carpium, Glycyrrhizae radix, Zingiberis rhizome, and spray-dried aqueous extract. This is a fixed-ratio formulation of eight medicinal herbs and roots, and the quality and volume of ingredients are uniform.^[42,43]

Treating rikkunshito to cachexia patients may increase the plasma acylated ghrelin level to improve the food intake. Rikkunshito increased the gastrointestinal motor activity. It is widely prescribed for patients with chronic hypofunction of the gastrointestinal tract, including gastric flatulence, anorexia, nausea, and vomiting.^[42-44] Oral administration of Rikkunshito to patients reduced chronic dyspepsia and produced better gastric emptying than the placebo.^[45]

Centella asiatica

The tropical medicinal plant *Centella asiatica* (Linnaeus) is found in India, China, and South Africa. *C. asiatica* has previously been used in the treatment of inflammation due to its promising anti-inflammatory effects.^[46,47] In addition, *C. asiatica* extracts have demonstrated high antioxidant^[48,49] and anti-proliferative activity in many cancerous cell lines.^[50]

Naidoo *et al.* investigated the potential of a *C. asiatica* ethanolic leaf extract (CLE) to modulate inflammatory cytokines, antioxidants, and cell death in leukemic THP-1 cells and normal peripheral blood mononuclear cells (PBMC's). Researchers found that C_{LE} increased oxidant scavenging activity and GSH levels, modulated pro-inflammatory cytokine levels and regulated apoptosis and caspase activity in normal PBMC's and THP-1 cells. C_{LE} may be an effective option in cancer cachexia.^[51]

Withania somnifera

It is a well-known medicinal plant cultivated in India, parts of East Asia and Africa. It is commonly referred to as Ashwagandha and properties include anti-inflammatory,^[52] antioxidant, and immune-modulatory activities.^[53] In order to establish a mechanism of regulation of the immune system, inflammation and apoptosis to prevent/decelerate the rapid depletion of the skeletal muscle and adipose tissue, Naidoo *et al.* investigated the ability of aqueous extract of the root of *W. somnifera* (W_{RE}) to decrease pro-inflammatory cytokine levels and increase cancerous cell death may decrease the development and progression of cancer and cachexia.^[54]

Anamorelin

Anamorelin reported statistically significant improvement in LBM, body weight, insulin-like growth factor-1 level, IGF-binding protein-3 in comparison to placebo. There were side effects in Anamorelin arm but nonsignificant (relative risk [RR] =0.07, P = 0.35).^[55]

Megestrol acetate

Megestrol acetae (MA) showed a benefit in appetite improvement (RR = 2.57, 95% CI = 1.41–3.40) and weight gain (RR = 1.55, 95% CI = 1.06–2.26) in comparison to placebo for cancer cachexia but had shown benefit over other drugs. It is difficult to define the optimal dose of MA but higher doses were associated with better weight improvement than lower doses. MA also helped to improve QOL when compared with placebo (RR = 1.91, 95% CI = 1.02–3.59). Edema, thromboembolic phenomena, and deaths were reported more in cancer patients treated with MA.^[56,57]

Table 1 summarize the herbal medicines used in cancer cachexia and their active ingredients and biological activity.

Acupuncture Therapy

There are studies on benefits of acupuncture in cancer patients by minimizing nausea and vomiting, increasing gastric emptying, and altering functions of gastrointestinal (GI) hormones.^[58-61] Many studies have employed acupuncture to mitigate the symptoms of cachexia and other cancer-related symptoms.^[62,63] A study by Grundmann *et al.* showed that targeted acupuncture using predetermined, reproducible points may provide benefits to some patients with GI cancer cachexia by normalizing metabolic dysregulation but larger study with longer treatment duration may be required to further refine findings of this pilot study.^[64]

Acupuncture and related therapies improved QOL in patients with gastrointestinal cancer in comparison to conventional intervention. Acupuncture and related therapies also showed improvement in anorexia but not significant. Acupuncture and related therapies significantly reduced pain in patients with liver or gastric cancer and fatigue in lung cancer patients; Adverse events of acupuncture and related therapies were infrequent and mild.^[65]

Role of Nurses in Complementary and Alternative Medicine Therapy

The use of CAM is growing, and many health-care organizations have incorporated CAM into their curriculum. American Association of Colleges of Nursing recommends awareness regarding CAM therapies. Many of the nursing board also incorporated CAM in their practices. Nursing professionals shows interest for integrating CAM into their curriculum.^[66] Nurses are the important link between patients and doctor and friendly behavior with patients may help nurses to know if patient is using any kind of CAM therapy and to evaluate any adverse event following such Shankar, et al.: Complementary and Alternative Medicine in Cancer Cachexia

Table 1: Herbal medicines in cancer cachexia ^[35-45]			
Common name	Major active ingredients	Biological activity	Evidence of anticancer activity
Ginseng	Triterpene glycosides, ginsenosides	Immunemodulation, vasorelaxation, antioxidation, anti-inflammation, and anticancer	Preclinical: Inhibits cancer growth and potentiates The anti-tumor effect of chemotherapeutic agents Clinical: Potentiates the anti-tumor effect of cells and attenuates the adverse toxicity of chemo- or radiotherapy
Rhubarb	DPPH	Hydroxyl radical scavenging İnhibitory lipid peroxidation Antioxidant properties	Preclinical: Extensive cytotoxicity to the cells antioxidant potential exhibited efficiency DNA protection Clinical: Potentiates the anti-tumor effect
Radix Astragali	Polysaccharides, saponins, and lavonoids	Immunomodulatory, anticancer, and antiviral	Preclinical: Stimulates the production of IL-6 and TNF and enhances the activity of LAK cells Clinical: Potentiates the activity of therapy agents, prolongs survival, reduces the adverse toxicity
TJ-48	Includes 10 herbs A. sinensis, P. lactiflora, A. macrocephala, P. cocos, C. cassia, A. membranaceus, L. wallichii, G. inflata, R. glutinosa	Immunomodulatory, anticancer	Preclinical: Inhibits cancer growth by the regulation of estrogen receptors or enhancement of systemic İmmunological function Clinical: Improves QOL and survival
TJ-41	Includes seven herbs P. tuber, S. baicalensis, Zingiberis rhizome, Z. fructus, Coptidis rhizome, Glycyrrhiza radix, P. ginseng	Immunomodulatory, anticancer	Preclinical: Inhibits cancer growth by inducing apoptosis, arresting the cell cycle, and enhancing immunity Clinical: Attenuates the adverse toxicity of anti-tumor therapy and chronic fatigue syndrome
РНҮ906	Includes four herbs S. baicalensis Georgi, P. lactiflora Pall, G. uralensis Fisch, Z. jujube Mill	Immunomodulatory, anticancer	Preclinical: Enhances the antitumor efficacy of some anticancer drugs and alleviates side effects of antitumor therapies, such as diarrhea Clinical: Potentiates the anti-tumor effect of chemotherapeutic agents and attenuates chemotherapy-induced side effects
Rikkunshito	Atractylodis lanceae rhizoma Ginseng radix, <i>Z. fructus</i> <i>P. tuber</i> , Hoelen Aurantii nobilis pericarpium Glycyrrhizae radix Zingiberis rhizome Spray-dried aqueous extract	Though a neural reflex involving presynaptic cholinergic and 5-HT3 receptors Enhance cell regeneration	Preclinical: Enhance cytoprotection increases gastrol motility stimulate ghrelin secretion Clinical: İmprove gastric emptying intestinal mucosa protect

DPPH: 2,2-Diphenyl-1- picrylhydrazyl', IL-6: İnterleukin-6, TNF-α: Tumor necrosis factor-α, LAK: Lymphokine-activated killer, QOL: Quality of life, A. sinensis: Angelica sinensis, P. lactiflora: Paeonia lactiflora, A. macrocephala: Atractylodes macrocephala, P. cocos: Poria cocos, C. cassia: Cinnamonum cassia, A. membranaceus: Astragalus membranaceus, L. wallichii: Ligusticum wallichii, G. inflate: Glycyrrhiza inflate, R. glutinosa: Rehmannia glutinosa, P. tuber: Pinellia tuber, S. baicalensis: Scutellaria baicalensis, Z. fructus: Zizyphi fructus, P. ginseng: Panax ginseng, G. uralensis: Glycyrrhiza uralensis, Z. jujube: Ziziphus jujube

therapy, if any.^[67] Position statement released by New York State Nurses Association mentions the important role of nurses in co-ordination and facilitation of CAM therapies.^[68]

Limitation and Strength of the Study

There is a paucity of randomized controlled trial on the use of CAM in cancer cachexia, although many of the therapies are tried in different parts of the world. CAM has been used widely for the symptomatic management of different symptoms associated with cancer cachexia. Many of the agents have shown effects on QOL of patients with cancer and can be used without much of side effects. We did not include articles from different databases as there were a smaller number of articles and irrelevant to the present context. The use of more keywords must have added many more articles but would not have helped us to get any additional information on role of CAM in cancer cachexia.

Conclusion

Cancer cachexia is a debilitating state, characterized by loss of appetite, body function leads to death. The incidence of cancer cachexia is different for different cancers, and it ranges from 80% in GI and lung cancer to 40% in breast cancer. Many therapies have been studied to make QOL of cancer patients, but none of them have shown great results. CAM has been used widely to manage the side effects in advanced and terminal stage of cancer. There has been strong belief about CAM being less toxic and with no or fewer side effects. Awareness about CAM therapy is recommended to oncology nurses as many of the patients use CAM during the cancer management. Many of the nursing board have also incorporated CAM in their practices. Nurses are the important link between patients and doctor and friendly behavior with patients may help nurses to know if patient is using any kind of CAM therapy and to evaluate any adverse event following such therapy, if any. There is a need for more research on different CAM therapies as none of them has been found to be useful in the treatment of cancer cachexia.

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Conflicts of interest

There are no conflicts of interest.

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