Advances in Immunonutrient Application to Treat Cancer Cachexia Syndrome

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Abstract: Cachexia is a multifactorial syndrome characterized by the loss of body weight, and has been observed in more than 50% of cancer patients. It arises as a result of anorexia and increased energy expenditure, leads to a reduced tolerance of cancer therapy and a reduced quality of life, resulting in a poorer prognosis and decreased survival. In the past few years, tremendous achievements have been made in cancer cachexia research. Systemic inflammation has been proven to play important roles in the etiology of cancer cachexia, leading to functional impairment and rapid deterioration, which suggests that anti-inflammatory agents may represent a promising strategy for cancer cachexia treatment. Thus, a variety of agents have been postulated to treat cachexia, with modulation of inflammation, the immune response, and reactive oxygen species being the most promising. Some immune-enhancing nutrients, ‘immunonutrients’, such as ω-3 fatty acids, arginine, nucleotides, L-carnitine, probiotics, phytochemicals, and specific minerals have been tested for their anti-inflammatory and anti-oxidative properties. They have also been used to treat, prevent or attenuate cancer cachexia in both experimental models and clinical trials. A number of studies on the use of immunonutrients for the treatment of cancer cachexia have been published over the past decade, with some promising results supporting the routine use of immune-enhancing formulas in patients with cachexia. However, the effects and efficacy of these substances have not been conclusively proven. In this review, we discuss recent studies on the molecular mechanisms underlying cancer cachexia and the application of several immunonutrients.

Key words: Immunonutrients; Cancer; Cachexia; Treatment; Inflammation

Introduction

Cancer cachexia is a severe syndrome characterized by anorexia, excess catabolism, elevated energy expenditure, a negative protein balance, progressive loss of body mass (especially skeletal muscle and adipose tissue), and systemic inflammation, which frequently occurs in patients with advanced cancers. Cachexia is associated with a deterioration in the quality of life, resistance to chemotherapy, multiple organ dysfunction, and shortened survival [1]. Cachexia is regarded as one of the greatest refractory complications during treatment, because it not only causes functional impairment and psychological distress, but also impacts the tolerance of and response to treatment. It has been observed that about 50%–80% of all cancer patients experience rapid weight loss. More importantly, it was estimated that cachexia accounts for 20% of cancer-related deaths [2].

Despite the above reports, cachexia is still under-diagnosed and often untreated. Traditionally, clinical strategies have focused on increasing nutritional intake, in the hopes of ameliorating the energy supply and reversing cancer cachexia. However, because the deficiencies in the nutritional supply are only part of the problem, increased food intake is usually insufficient in patients with advanced cancers, and does not yield the desired results [3].

In recent decades, there has been immense interest in researching the mediators of cancer cachexia. Studies indicate that cachexia involves diverse mediators derived from both cancer cells and immune cells. Other mediators originating from the endocrine, metabolic and central nervous systems also participate in this process. Importantly, tumor cells produce a variety of pro-inflammatory factors, which play important roles in the occurrence and development of cachexia. For instance, tumor necrosis factor alpha (TNF)-α, interleukin (IL)-1, IL-6, and other pro-inflammatory cytokines, as drivers of systemic inflammation, are involved in the activation of transcription factors that might underlie the pathology of cachexia [4]. In short, cachexia is a pathological phenomenon associated with various morbidities such as functional, metabolic and immune disorders, which contributes to the onset of a persistent catabolic state. In an international consensus statement issued in 2011, cancer cachexia was defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support, resulting in progressive functional impairment [5].

In recent years, as the mechanisms underlying cachexia have started to be uncovered, multimodality therapy has
gradually been applied for the management of cancer cachexia. Some therapeutic methods, when provided as palliative treatment, could not only postpone cancer progression, but also improved the quality of life of patients. The popular perception is that a multidisciplinary approach comprising nutritional support, pharmacological intervention, and appropriate exercise will be necessary to alleviate cachexia. To date, adequate nutritional support remains a mainstay of cachexia therapy, while other medical interventions with the ability to mediate catabolic processes and inflammation are currently under investigation.

It is well known that nutrients play an important role in the development and functions of the immune system. The use of immune-enhancing nutrients, such as ω-3 fatty acids, arginine, nucleotides, L-carnitine, probiotics, phytochemicals, and some specific minerals with antioxidative and anti-inflammatory effects, has been proposed to modulate the metabolism and immune responses in patients with cancer cachexia. Some studies have demonstrated positive effects of these therapies, such as weight maintenance and prolonged survival, indicating that such treatment may have clinical benefits (Figure 1).

In this review, we discuss the roles of various immunonutrients, as components with the potential ability to alleviate muscle weakness and muscle mass loss, in patients with cancer cachexia. We also describe the postulated mechanisms of action, and reported effects such as inflammation reduction, immune regulation, improvements in the quality of life and survival.

**Omega-3 fatty acids**

Omega-3 (ω-3) polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid, have been suggested to promote health and prevent disease [6] (Figure 2). Since inflammation is a key factor in cachexia, EPA may exert anti-cachectic effects in patients by modulating proinflammatory cytokines. It has been reported that PUFAs down-regulate the activity of proinflammatory cytokines, including prostaglandin E2 (PGE2), and cyclooxygenase-2 (COX-2). Along with decreasing the production of proinflammatory cytokines, mainly IL-1, TNF-α, and IL-6, exposure to PUFAs inhibited muscle protein degradation pathways [7,8]. For instance, the COX-2 enzyme was upregulated by proinflammatory signals and inhibited by EPA, and has been shown to play an important function in tumor progression. One study suggested that the ability of EPA to generate PGE3 through the COX-2 enzyme might be critical for EPA-mediated tumor growth inhibition, which is at least partly due to down-regulation of Akt phosphorylation by PGE3 [9].

On the other hand, ω-3 PUFAs play important roles as signaling molecules that exert potent anti-inflammatory and antiproliferative effects [10]. For example, the transcription of NF-κB is inhibited by EPA, leading to the down-regulation of multiple proinflammatory cytokines [11]. EPA can inhibit both NF-κB activation and IL-6 production in esophageal cancer cells, and can also induce apoptosis. These effects of EPA may be of benefit in improving the outcome of patients with esophageal cancer [12]. EPA also inhibits the ubiquitin proteasome pathway by reducing the nuclear migration of NF-κB. ω-3 PUFAs inhibit MAP kinase signaling, particularly Ras/ERK1/2, and suppress AP-1 transcription factor expression, resulting in

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**Figure 1** Characteristic of cancer cachexia.
antiproliferative effects on tumor cells. EPA also attenuates cigarette smoke-induced lung inflammation by inhibiting ROS-sensitive inflammatory signaling [13], and suppresses the inflammatory responses of lipopolysaccharide-stimulated mouse microglia by activating SIRT1 pathways [14]. Moreover, fish oil may suppress muscle proinflammatory cytokine production via regulation of TLR and NOD signaling pathways, thereby attenuating lipopolysaccharide (LPS)-induced muscle atrophy, possibly through a mechanism involving Akt/FOXO signaling [15]. Furthermore, oro Inca oil, rich in alpha linoleic acid, was also reported to improve cachexia parameters in rats, such as glycemia and triacylglycerolemia, and suppressed the plasma expression of IL-6 and TNF-β [16]. Additionally, a 2013 study showed that shark liver oil (SLOil) was able to restore cachexia parameters to control levels, similar to the anti-cachectic capacity of fish oil [17].

Other mechanisms have also been implicated in the anti-cachexia effects of ω-3 PUFAs. EPA attenuates protein degradation by activating the ATP-ubiquitin-dependent proteolytic pathway that is considered to play a major role in muscle catabolism in cachexia by down-regulating the expression of proteasomal proteins, and up-regulating the expression of myosin, thus inhibiting tumor growth and suppressing skeletal muscle atrophy [18]. Furthermore, EPA inhibits necrosis and apoptosis of differentiating murine skeletal muscle cells by reducing the levels of TNF-α, thereby contributing to reduced muscle loss [19]. In addition, via a G-protein-coupled signaling pathway that decreases intracellular cyclic AMP, EPA inhibits ω-6 PUFA uptake by the tumor and inguinal fat tissue in vivo, resulting in both antitumor and anticachectic effects [20]. EPA also attenuates lipolysis mediated by tumor-derived lipolytic factor, which is known to preserve adipose tissue and lipid stores [21]. Conversely, a double-blind, randomized trial published in 2000 indicated that short-term oral EPA ethyl ester (EE) supplementation did not significantly inhibit lipolysis or lipid oxidation in weight-losing cancer patients or in healthy subjects [22]. As for the anti-tumor effects, evidence suggested that EPA slowed the growth of cancer cells via inhibition of oncogenic transcription factors such as Ras, AP-1 and MAPK [23]. In support of this evidence, ω-3 fatty acids were reported to inhibit xenograft tumor growth in mice treated with doxorubicin, with noted suppression of glutathione peroxidase (GPX) activity [24]. Moreover, lifelong consumption of ω-3 PUFAs improved the survival and decreased cachexia parameters in Walker-256 tumor-bearing rats [16]. Evidence also showed that ω-3 PUFAs, particularly EPA and DHA, have potent anti-angiogenic effects through inhibition of angiogenic mediators such as VEGF, PDGF, PGE2, NFK-B, and beta-catenin [25]. EPA supplementation inhibits tumor growth, potentially through alterations in the expression of the pro-angiogenic VEGF-alpha [26]. In the offspring of Walker-256 tumor-bearing rats, maternal nutritional supplementation with fish oil and/or leucine improved the liver antioxidant responses and ameliorated the cachexic state [27].

Due to these potential benefits, especially their anti-inflammatory properties, ω-3 PUFAs, have been explored for the treatment of cachexia for many years. However, the clinical efficacy of PUFAs for cancer cachexia treatment remains controversial. Pancreatic cancer is the most widely studied cancer where ω-3 PUFAs were used as immunonutrients. In patients with pancreatic cancer-related cachexia, an early study showed that EPA down-regulates the acute-phase response, which is likely to involve suppression of C-reactive protein (CRP) and interleukin-6 production by mononuclear cells [28]. Another study revealed that EPA supplementation stabilized the weight in cachectic pancreatic cancer patients [29]. In 2003, a randomized double-blind trial proved that an EPA-enriched

![Figure 2 Sources and effects of omega-3 fatty acids on cachexia.](image-url)
oral supplement resulted in a net gain of weight, lean tissue, and improved quality of life in cachectic patients with advanced pancreatic cancer [30]. The differences in the results observed in different studies may be because the source of ω-3 PUFAs may influence their effects on cancer cachexia. For example, Werner K et al. [31] found that low-dose omega-3 fatty acid, either as fish oil or via marine phospholipid supplementation, had the capacity to maintain weight and appetite in pancreatic cancer patients with cachexia. Nevertheless, compared with fish oil supplementation, the marine phospholipids were better tolerated and caused fewer side effects.

A recent review indicated that dietary ω-3 fatty acid supplementation, in association with an anabolic stimulus, could potentially promote anabolic stimuli and counteract sarcopenia, contributing to the prevention of cachexia [32]. Furthermore, a systematic evaluation suggested that the consumption of ω-3 polyunsaturated fatty acids improves the clinical outcomes and prognosis in pancreatic cancer patients [33]. In 2017, a double-blind, randomized, controlled trial found that intervention with low-dose ω-3 fatty acid supplementation, either as fish oil or marine phospholipids, resulted in similar and promising weight and appetite stabilization in pancreatic cancer patients [31]. In addition, a study suggested that enteral ω-3 fatty acid supplementation could significantly increase the skeletal muscle mass in patients with bile duct or pancreatic cancer undergoing chemotherapy, which may improve cancer cachexia [34]. It was also reported that ω-3 PUFA supplementation could enhance the tumor response to antineoplastic treatments and attenuate the side effects of chemotherapy in patients with advanced colorectal cancer [35]. In cancer patients receiving radiotherapy, nutritional intervention with fish oil, specific oligosaccharides, protein, and leucine, could increase the percentage of EPA and DHA in white blood cell phospholipids and reduce the serum levels of the inflammatory mediator PGE2 [36].

In recent years, ω-3 PUFAs have also been used as immunonutrients in patients with other cancers, especially gastrointestinal cancer. In 2017, a retrospective chart-review study reported that both a higher CRP level and elevated serum AA/EPA ratio were associated with a decrease in the psoas muscle area, suggesting that these markers might serve as a predictor of skeletal muscle depletion in cachexic patients with advanced gastrointestinal cancers [37]. A systematic review indicated that ω-3 PUFAs significantly increased the weight of patients with gastrointestinal cancer, providing clinical benefits in the pre-cachectic population [8]. It was also reported that 4-hydroxyhexenal and 4-hydroxynonenal are mediators of the anti-cachectic effects of ω-3 and ω-6 polyunsaturated fatty acids on human lung cancer cells [38].

On the contrary, a study in 2014 showed that while food supplements containing ω-3 PUFAs are usually healthful, but they may potentiate some of the side effects of glucocorticoids [39]. In a clinical trial, immunonutritional therapy using a nutritional supplement with a high blend ratio of ω-3 fatty acids from 2 weeks before surgery until 2 weeks after surgery was not effective for maintaining the nutritional status of head and neck carcinoma patients [40]. In 2012, as part of an EPCRC cachexia guidelines project, a systematic review of 38 publications showed that there is not enough evidence to support a net benefit for ω-3 FA against cachexia in patients with advanced cancer. On the other hand, adverse effects were infrequent, with no severe adverse effects reported. The results from the review led to a weak negative GRADE recommendation [41].

Amino acids

As a complex wasting syndrome, cancer cachexia involves muscle wasting, protein degradation and the release of amino acids (AAs) in skeletal muscle, which might be driven by the secretion of different tumor-derived mediators. Recently, it was suggested that some amino acids, such as arginine and leucine, might act as intracellular signals to promote protein synthesis in addition to being substrates. Amino acids have already been used in cachexia treatment as immunonutrients based on their positive effects against skeletal muscle atrophy. Evidence from one study demonstrated that amino acid supplementation is a promising coadjuvant treatment for cancer cachexia [42]. A recent retrospective chart review showed that a high serum essential amino acid level acts as a predictor of skeletal muscle depletion in patients with cachexia and advanced gastrointestinal cancers [43]. Low serum glutamine and histidine levels and high phenylalanine levels were also associated with systemic inflammation, advanced cancer stages and poorer cancer-specific survival in colorectal cancer patients [44].

On the other hand, with attenuation of muscle loss and even muscle gain, protein anabolism might be achievable before the weight loss evolves into refractory cachexia. A previous phase II trial involving thirty-two patients indicated that a mixture of beta-hydroxy-beta-methylbutyrate, glutamine, and arginine (HMB/Arg/Gln) increased the fat-free mass (FFM) among patients with advanced (stage IV) cancers, with arginine and glutamine specifically found to slow the rates of protein breakdown and improve protein synthesis, although the evidence was relatively weak [45]. Another study demonstrated that supplementation with a combination of HMB, arginine, and glutamine can be safely used to treat muscle wasting associated with AIDS and cancer, with improvements in the hematological parameters [46]. Conversely, a phase III trial (RTOG 0122) that enrolled 472 advanced cancer patients was unable to adequately test the ability of HMB/Arg/Gln to reverse or prevent lean body mass wasting among cancer patients [47]. Another study, which was designed to appraise the relationship between enteric neuropathy and oxidative stress in cancer cachexia under a L-glutamine-supplemented diet, revealed that the
L-glutamine-supplemented diet extenuated NO-mediated damage to the myenteric plexus, although it had only a small benefit on oxidative stress [48].

Arginine, an important player in numerous biological processes, has been investigated due to its importance in cellular growth. Arginine deprivation therapy has been examined as a treatment for advanced malignancies [49], and a series of early studies showed that arginine has a certain degree of anti-tumor activity. It was reported that the plasma arginine concentrations were lower in patients with cancer, irrespective of tumor type, weight loss, tumor stage, or body mass index. These disturbances in arginine metabolism might contribute to the cascade of metabolic events leading to cancer cachexia [50]. Moreover, arginine/NO metabolism is disturbed in patients with cancer. The body will try to correct this perturbation by mobilizing arginine and glutamine from muscles. Thus, the decreased arginine levels and the disturbed NO production activate several cascades, which in turn inhibit protein synthesis and promote proteolysis, leading to or worsening cachexia [51]. Furthermore, one study suggested that plasma levels of amino acids, especially arginine, tryptophan, indolelactic acid, and threonine, were decreased in cachexia patients compared with non-cachectic patients, which might be related to the pathophysiology of the condition [52].

Experiment evidence further supported that arginine has the potential to treat cachexia. In 1998, Millis RM et al. found that dietary replacement of L-methionine with NALM and supplementation with L-arginine suppressed the growth of a subcutaneously transplanted Morris hepatoma [53]. Immunosuppression is a feature of cancer cachexia. In 2016, it was reported that elevating the L-arginine levels induced global metabolic changes in activated T cells, such as a shift from glycolysis to oxidative phosphorylation, which enhanced their survival capacity and anti-tumor activity in a mouse model [54]. In the gastrocnemius muscle of mice bearing cachexia-inducing MAC16 tumors, daily treatment with EPA reduced protein degradation by 88%, although it had no effect on protein synthesis. Combining EPA with amino acids leucine, arginine and methionine led to a doubling of protein synthesis, which suggests that combination therapy for cancer cachexia involving both the inhibition of the enhanced protein degradation and stimulation of the reduced protein synthesis may be more effective than either treatment alone [55]. In addition, a report revealed that supplementation with glutamine appears to improve the efficacy of chemoradiotherapy while reducing the toxicity to non-tumor tissues, thus improving the outcomes of treatment. Perioperative supplementation with arginine was also shown to reduce the incidence of complications and significantly increased the long-term survival [56].

Glutamine, the most abundant amino acid, is considered to be a nonessential amino acid that has a variety of biological functions. However, in the critically-ill patient, glutamine becomes an essential amino acid for recovery, restoration, and repair at the cellular level. A previous article reported that the glutamine levels in both plasma and skeletal muscle were decreased in tumor-bearing rats [57]. Cancer cachexia severely affects the intrinsic innervation of the jejunum and ileum to various degrees, and this injury seems to be associated with adaptive neural plasticity. It was shown that L-glutamine supplementation in cachexia subjects led to protective effects on the enteric innervation, possibly by attenuating oxidative stress [58]. Additionally, L-glutamine supplementation promoted an improved energetic balance in Walker-256 tumor-bearing rats, which could be attributed, at least partly, to increased intestinal gluconeogenesis and insulinemia, and better glycemic maintenance [59]. Supplementation with L-glutamine also prevented tumor growth and cancer-induced cachexia, and restored the proliferation of intestinal mucosal cells in Walker-256 tumor-bearing rats [60]. As the main substrate for DNA and fatty acid synthesis, glutamine was also found to reduce oxidative stress by stimulating glutathione synthesis, nourish the immune system and reprogram the metabolism, thus inhibiting the process of cancer cachexia [61]. Moreover, glutamine supplementation could attenuate protein loss in the muscle in tumor-bearing animals and protected the immune and gut-barrier function during radiochemotherapy in patients with advanced cancer [57]. Another study showed that light aerobic physical exercise in combination with a leucine- and/or glutamine-rich diet can improve the body composition and muscle protein metabolism in young tumor-bearing rats [62]. On the contrary, a phase III study evaluated the effects of oral supplemental glutamine and transforming growth factor-beta 2 on chemotherapy-induced toxicity and showed that this treatment was not effective to reduce the grade 3 or 4 non-hematological toxicities induced by chemotherapy in patients with GI neoplasms [63].

Three common amino acids, leucine, valine, and isoleucine, are called branched-chain amino acids (BCAA), or compound branched-chain amino acids. Similar to glutamine and alanine, the initial site of BCAA catabolism is skeletal muscle [64]. BCAA might promote anabolism (muscle growth) in two distinct ways: promoting insulin release and promoting growth hormone release. A 2016 study suggested that a leucine-rich diet increased the protein synthesis in skeletal muscle in tumor-bearing rats, possibly through the activation of eIF factors and/or the S6 kinase pathway [65]. Another study showed that leucine and valine caused a significant reduction in the loss of body weight in mice bearing a cachexia-inducing tumor (MAC16), resulting in a significant increase in skeletal muscle wet weight, through an increase in protein synthesis and a decrease in degradation [66]. Treatment with leucine was also shown to increase the phosphorylation of mTOR and p70(S6k), induce the hyperphosphorylation of 4E-BP1, reduce the amount of 4E-BP1 associated with eIF4E, and...
caused an increase in the eIF4G-eIF4E complex, together with a reduction in the phosphorylation of eEF2. These changes would be expected to increase protein synthesis.

In 2009, a report suggested that dietary supplementation with a specific combination of high protein, leucine, and fish oil improved muscle function, reduced cachectic symptoms and improved the functional performance in cancer cachectic mice [67]. Tumor growth induced a decrease in muscle protein synthesis and increased the catabolic process, which was associated with an increase in the expression of ubiquitin-proteasome subunits (20S, 19S, and 11S) [68]. However, the implementation of an exercise program minimized the muscle degradation process and increased the muscle myosin content. Leucine supplementation also modulated the expression of proteasome subunits, especially 19S and 11S, leading to an improvement in protein turnover [68]. Leucine supplementation attenuated the increase in total plasma amino-acid concentrations, and irrespective of changes in muscle protein breakdown markers, reduced muscle wasting in tumor-bearing cachectic mice [69]. Light aerobic exercise in combination with a leucine and/ or glutamine-rich diet improved the body composition and muscle protein metabolism in young tumor-bearing rats [70]. Leucine was shown to modulate the effects of Walker factor, a proteolysis-inducing factor-like protein from Walker tumors, on gene expression and cellular activity in C2C12 myotubes [70]. Supplementation with a leucine-rich diet also modulated fetal muscle protein metabolism impaired by Walker-256 tumor, thus protecting the fetal muscle [71]. In a comparison of the antitabotic effects of leucine and Ca-β-hydroxy-β-methylbutyrate (Ca-HMB) on cancer cachexia, both leucine and Ca-HMB were found to attenuate the increase in protein degradation and the decrease in protein synthesis in murine myotubes induced by proteolysis-inducing factors, lipopolysaccharide, and angiotensin II [72]. However, Ca-HMB was more potent than leucine [72]. Data previously published by our group suggest that a leucine-rich diet can reduce the heart damage, cardiomyocyte proteolysis, and apoptosis driven by cancer cachexia in tumor-bearing Wistar rats [73]. Dietary supplementation of L-leucine modulated muscle protein degradation and increased pro-inflammatory cytokines in tumor-bearing rats [74]. In a 2017 study, oral administration of functional dietary supplement (FDS) containing coenzyme Q10, branched-chain amino acids, and L-carnitine enhanced the maintenance of suprahypoid muscles, resulting in an extended feeding period and suppression of tumor growth and metastasis in tumor-bearing mice [75].

In contrast, in 2016, a trial that examined the effects of supplementation with branched-chain amino acids, particularly leucine, on the metabolism of the tumor-bearing host found that the leucine rich-diet did not affect Walker 256 tumor growth and led to metabolomic alterations. In addition, leucine supplementation differentially enhanced pancreatic cancer growth in lean and overweight mice.

These findings show that leucine supplementation enhances tumor growth in both lean and overweight mice through diet-dependent effects in a murine model of pancreatic cancer, suggesting that leucine supplementation should be used with caution for the purposes of skeletal muscle enhancement in cachectic patients because it may increase tumor growth [76]. However, it was recently reported that oral supplementation with branched amino acid appears to reduce the length of hospital stay, decrease morbidity and improve the quality of life for patients, without any changes in mortality [56]. Therefore, more research is needed on the effects of leucine supplementation (timing, dosage, etc.) to determine whether it has net beneficial or detrimental effects in patients with different types of cancer.

L-carnitine

L-carnitine supplementation leads to beneficial effects on several critical mechanisms involved in pathological skeletal muscle loss, which appear to be mediated through improvements in the nitrogen balance, an increase in protein synthesis, a reduction in proteolysis, inhibition of apoptosis and/or a reversal of inflammatory processes [77]. Studies indicated that L-carnitine supplementation may represent a multi-targeted therapy for cancer-related cachexia, with effects such as inhibition of proteasome activity, modulation of apoptosis, and a decrease in the proteolytic rate [78]. It was also recently reported that oral administration of L-carnitine improved cachexia parameters, ameliorated liver inflammation and decreased serum pro-inflammatory markers in cancer cachectic mice partly via the PPAR-γ signaling pathway [79, 80].

As early as 2006, a phase I/II study demonstrated that the administration of exogenous L-carnitine was safe at doses up to 3,000 mg/day in patients with advanced cancer [81]. Since then, a series of studies about L-carnitine supplementation for cachexia amelioration has been carried out. In 2009, a double-blind, placebo-controlled study confirmed that L-carnitine supplementation increased the L-carnitine serum levels in patients with advanced cancer and carnitine deficiency [82]. Then, a randomized phase III clinical trial showed that L-carnitine supplementation at 4 g/d decreased the Glasgow Prognostic Score (GPS) and significantly decreased the levels of proinflammatory cytokines in patients with cancer cachexia [83]. In 2012, a trial in patients with invasive cancer showed that a 4-week oral administration of 2 g of L-carnitine resulted in a significant carnitine plasma level increase, but did not improve fatigue in patients with invasive malignancies and a good performance status [84]. In patients with pancreatic cancer, a randomized multicentre trial showed that oral supplementation of L-Carnitine improved the nutritional status (body cell mass and body fat) and quality-of-life parameters, and led to a trend towards an increased overall survival and a reduced hospital stay [85].

L-carnitine is often used in combination with other
nutritional components in the treatment of cachexia. A study in tumor-bearing mice showed that oral administration of a functional dietary supplement (FDS), containing coenzyme Q10, branched-chain amino acids, and L-carnitine, enhanced the maintenance of supraphyoid muscles and suppressed tumor growth and metastasis [75]. Then, a phase III randomized study in 2008 reported the efficacy and safety of polyphenols plus antioxidant agents, which showed an improvement of cancer cachexia in subjects treated with L-carnitine, thalidomide or medroxyprogesterone acetate/megestrol acetate plus pharmacologic nutritional support. This included an increase of the lean body mass and total daily physical activity, a decrease in the resting energy expenditure (REE), interleukin-6 and tumor necrosis factor-alpha levels, and an improvement of fatigue [86]. In 2012, a multi-institutional, randomized, exploratory trial (JORTC-CAM01) performed in Japan indicated that an amino acid jelly, Inner Power® (IP), a semi-solid, orally administrable dietary supplement containing coenzyme Q10 and L-carnitine, was safe and effective in controlling moderate-to-severe cancer-related fatigue (CRF) in breast cancer patients [87]. Moreover, a randomized phase III clinical trial published in 2012 showed that combined treatment with carnitine, celecoxib, and megestrol acetate increased the lean body mass in patients with cancer cachexia [88]. In addition, another phase III clinical trial indicated that combined treatment with megestrol acetate (MA) plus L-carnitine improved the lean body mass, resting energy expenditure, fatigue, appetite, and global QoL, while it decreased some markers of inflammation and oxidative stress such as IL-6, TNF-α, CRP, and ROS in patients with advanced gynecological cancers [89].

Phytochemicals

Phytochemicals play important roles in cancer cachexia treatment by suppressing oxidative stress-induced DNA damage and modulating several oxidative stress-mediated signaling pathways. For instance, Withania somnifera, an herb commonly used in Ayurvedic medicine, was reported to modulate cancer cachexia-associated inflammatory cytokines and cell death in leukemic THP-1 cells and peripheral blood mononuclear cells (PBMC’s) [90]. Silibinin, the most active component of a natural polytherapy formulation, was found to diminish cell growth and the cachectic properties of pancreatic cancer cells both in culture and in animal models, by diminishing c-MYC expression and reducing STAT3 signaling [91]. Sosihotang ameliorated cachexia-related symptoms in mice bearing colon adenocarcinomas by reducing systemic inflammation and muscle loss [92]. Morin, a polyphenol isolated from Maclura pomifera, indirectly prevents the muscle wasting induced by cancer cachexia by suppressing cancer growth via binding to RPS10 [93]. Conversely, acai seed extract, which has documented antioxidant effects, showed no beneficial effects against anorexia-cachexia syndrome induced by Walker-256 tumors [94]. Quercetin is a natural phytochemical compound with anti-inflammatory, antioxidant, and anticarcinogenic properties. A study showed the quercetin supplementation positively affected several aspects of cachexia progression in a mouse model of colorectal cancer, although it did not improve the treadmill run-time-to-fatigue, hyperglycemia, or hyperlipidemia [95]. A randomized, double-blinded and placebo-controlled trial examining the feasibility of used Sipjeondaebotang for the treatment of cancer-related anorexia is currently underway [96]. A randomized-controlled trial showed that Echium oil effectively increased erythrocyte ω-3 eicosapentanoic acid (EPA) and n-6 GLA, however, it failed to protect against weight loss, or improve nutritional parameters including the body composition, nutritional status or quality of life in head and neck cancer patients [97].

Probiotics

Recent studies have reported that gut permeability and the translocation of components of the intestinal microbiota are closely associated with chronic inflammatory, autoimmune, and neoplastic diseases by eliciting immune-mediated mechanisms. Improvements in intestinal microbiota and the gut barrier function might therefore be beneficial for cachexia treatment [98]. Evidence showed that probiotics could favorably influence the development and stability of the microbiota, strengthen the mucosal barrier, and stimulate both specific and nonspecific components of the immune system [99]. For instance, Lactobacillus rhamnosus GG (LGG) was reported to be effective and safe for maintaining remission in patients with ulcerative colitis [100]. Probiotics composed of Lactobacillus spp. and Bifidobacterium spp. have been regarded as safe even in patients with neutropenia, and were proven to decrease gastrointestinal symptoms [101]. In 2016, a study showed that feeding a human commensal microbe, Lactobacillus reuteri, to mice reduced systemic indices of inflammation and inhibited cachexia by stimulating FoxN1 and the thymic functions that regulate inflammation [102]. Taken together, these findings suggest that probiotics may offer a novel strategy to treat cancer cachexia, but further studies are warranted. Several published studies have been conducted to explore other diverse antioxidant agents in the prevention and/or treatment of cachexia. A recent study demonstrated that pyrroloquinoline quinone attenuates cachexia-induced muscle atrophy via suppression of reactive oxygen species, which depends on inhibiting the atrophy of C2C12 myotubes induced by TNF-α, together with increasing the MHC levels and decreasing the ROS, MAFbx and MuRF-1 levels [103].

Vitamins

Fresh fruits and vegetables provide rich fiber and vitamins. Some vitamins are essential micronutrients for immune function and both cellular and overall metabolism.
In recent years, studies with vitamin supplements have shown some positive effects against cancer cachexia. First, due to its effects on myogenic precursor proliferation and differentiation, vitamin D supplementation has been reported to improve muscle weakness in prostate cancer patients [104]. Low circulating levels of vitamin D were associated with decreased muscle strength and physical performance [105]. Vitamin D treated myoblasts did not differentiate properly, fusing only partially and forming multinucleated structures with aberrant shapes and a low myosin heavy chain content [105]. In contrast, another study showed that the combination of catechins, quercetin, and vitamin C reduced survival and enhanced cachexia in C26 tumor-bearing mice [106]. Furthermore, as an important antioxidant, vitamin E also has the potential to be used in the treatment of cancer cachexia. A phase II study with an integrated treatment consisting of diet with a high polyphenol content, antioxidant treatment (alpha-lipoic acid + carboxysteine lysine salt + vitamin E + vitamin A + vitamin C), ω-3-PUFA, medroxyprogesterone acetate, and celecoxib, showed efficacy and safety in patients with cancer cachexia [107].

Minerals

Cancer cachexia may be partly explained by the deleterious and pro-inflammatory actions of reactive oxygen species (ROS). Oxidative stress results in increased ROS levels, increased oxidation-dependent protein modification, and decreased antioxidant system functions [108]. A series of nutrients with antioxidant activity could theoretically reduce oxidative stress, therefore playing a role in treating cachexia. In recent years, an increasing number of studies have explored the use of mineral substances and other supplements for the treatment of cancer cachexia.

Magnesium and selenium have been the main two mineral elements used for the treatment of cachexia. However, there is not yet strong enough evidence to recommend the use of these minerals. So far, only one study on mineral supplementation has explored the application of magnesium in a randomized controlled trial, which investigated the effects of magnesium supplementation on the response to and toxicity of chemotherapy. The results showed that oral magnesium supplements were of considerable benefit and had no harmful effects on patients receiving cisplatin treatment [109]. Selenium is an essential micronutrient that plays a crucial role in the development of a wide variety of physiological processes. Reportedly, a combination of aerobic interval training and selenium nanoparticles decreased the expression of IL-15 and the IL-10/TNF-α ratio in the skeletal muscle of mice bearing 4T1 breast cancer with cachexia [110]. In addition, in tumor-bearing mice receiving chemotherapy, supplementation with fish oil and selenium prevented increases in the levels of IL-6, TNF-α and myostatin, thereby inhibiting muscle atrophy [111].

Conclusions

Cancer cachexia is a multifactorial metabolic syndrome experienced by more than 50% of terminal cancer patients, which is characterized by anorexia, dysregulated metabolic homeostasis, increased basal energy expenditure, skeletal muscle depletion, and adipose tissue loss. Cancer cachexia may be associated with a poorer quality of life, poorer performance status and higher mortality rate in cancer patients. However, no effective therapy or standard treatment has been recommended for the management of cachexia.

Progressive weight loss is an important feature of cachexia. Unfortunately, simple nutritional supplementation does not correct the malnutrition in patients with cachexia, which has been postulated to be because of the complex mechanisms underlying the condition. Besides nutritional deficiency, immune dysfunction, systemic inflammation, and oxidative stress are important features of cancer cachexia. Some specific nutrients with immunological and pharmacological effects, such as glutamine, arginine, nucleotides, L-carnitine, probiotics, phytochemicals, vitamins, and minerals might be used as immunonutrients, with the potential to alleviate inflammation, enhance immunity and reduce oxidation, in addition to providing nutrients or regulating the energy supply. Although there have been many recent advances in understanding the molecular mechanisms underlying their effects, the roles of immunonutrients in cachexia still need further investigation and discussion.

The roles of ω-3 PUFAs in cancer cachexia treatment have been extensively studied, but the exact mechanisms are still not fully understood. It has been speculated that ω-3 PUFAs are involved in several pathways such as the NF-kB, Ras/ERK1/2, SIRT1, Akt/FOXO, and ROS-sensitive signaling pathways. A series of studies showed that oral supplementation with enriched ω-3 PUFAs had the ability to ameliorate the energy balance, delay weight loss, inhibit tumor growth, and improve the quality of life, and this was accompanied by the suppression of various pro-inflammatory factors. In addition to being substrates, various amino acids, including arginine, leucine, glutamine, and some branched-chain amino acids (BCAA), might participate in the intracellular signaling that promotes protein synthesis in skeletal muscle. Dietary supplementation with BCAA, such as leucine, valine, and isoleucine, could increase the protein synthesis in skeletal muscle and reduce cachectic symptoms in patients with cancer cachexia. L-carnitine supplementation represents a multi-targeted treatment for cancer-related cachexia, leading to improvements in protein synthesis, the nitrogen balance and skeletal muscle loss [77, 78]. In addition, some probiotics, phytochemicals, minerals, and vitamins D, C, and E, were proven to have anticachexia potential through a variety of mechanisms, especially due to their antioxidant capacity. Conversely,
some clinical trials were unable to identify any positive effects, or actually showed adverse effects, for the use of immunonutrients in patients with cancer cachexia. Taken together, although the mechanisms underlying cachexia are complex and still being elucidated, the use of immunonutrients has shown promising preliminary results, and should be examined in further research for the prevention or treatment of cancer cachexia.

Conflict of interests
The authors declare no conflicts of interest.

References


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