

Plant Extracts for Cachexia

Subjects: Plant Sciences | Oncology

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A **natural product** is a chemical compound or substance produced by a living organism—that is, found in **nature**.

Sequela is a result or condition that follows from a disease or illness

Cachexia is a condition that causes extreme weight loss and muscle wasting. It is a symptom of many chronic conditions, such as cancer, chronic renal failure, HIV, and multiple sclerosis.

Keywords: cancer sequela ; cachexia ; plant extracts ; antioxidants ; reactive oxygen species ; oxidative stress ; inflammation

1. Cancer Therapies and Cachexia

Cancer is a major public health problem worldwide and causes a high mortality rate of 53% ^[1]. Excluding non-melanoma skin cancer, 18.1 million cases of new cancer diagnosis and 9.6 million deaths were reported and the leading causes of cancer-related deaths in both sexes were lung cancer (18.4%), colorectal cancer (9.2%), stomach cancer (8.2%) and liver cancer (8.2%) ^[1]. To reduce the cancer morbidity, there have been various approaches to treat cancer. It includes surgery ^{[2][3]}, chemotherapy ^[4], radiotherapy ^{[5][6]}, immunotherapy ^[7], hormone therapy ^[8] and so forth.

1.1. Limitation of the Current Cancer Therapies

Some sequela can limit the benefits of these treatments. Surgery is followed by the risk of pain, infection and micro metastasis. Some surgeries also induce deterioration of the function of the organ under surgery. For example, about 75% of sixty-nine patients were reported that usual interstitial pneumonias were diagnosed after 60 lobectomies and 9 segmentectomies compared to the results of preoperative high-resolution computed tomography ^[9]. Chemotherapy and radiotherapy can damage normal cells and cause secondary cancer. They can also cause fatigue, anorexia, edema, fever for general disorders. There are gastrointestinal, blood, cardiac, nervous system, skin and respiratory disorders, too. These are treatment-related side effects that cannot be avoided in cancer treatment. For example, Cisplatin is known to indicate an anticancer action that suppresses the division of cancer cells by causing DNA damage of cancer cells. However, the patients who were treated with cisplatin suffer from experienced nausea ^{[10][11]} or side effects of various neurological symptoms ^[12] and kidney failure ^{[12][13]}. Likewise, there are also the adverse effects of radiotherapy. It is used with anticancer drugs or to reduce the size of preoperative cancer and the possibility of postoperative recurrence but there is also a high risk of side effects that cause brain metastasis ^[14], as in the case of brain radiation therapy.

Beyond each symptomatic side effect of those treatments, those antineoplastic drugs have been shown to induce oxidative stress which can interfere with cell cycle progression and apoptotic pathways ^[15]. This can lower the effect of antineoplastic activity from chemotherapy and affect normal cells. Also, radiation therapy produces oxidative stress related to reactive oxygen species (ROS) signaling, deoxyribonucleic acid (DNA) damage response, membrane lipid peroxidation, mitochondrial damage, endoplasmic reticulum stress (ER stress) and autophagy ^[16]. During this cellular stress, p53 may play a pivotal role and it is supposed to ameliorate radiation-induced oxidative stress ^[17]. As a result, certain antioxidants appear to prevent some chemotherapy-induced side effects and there are also some plants that can get involved in some mechanisms from radiation-induced oxidative stress.

1.2. Plants-Derived Drugs for Side-Effects of Cancer Therapies and Cachexia

Until now, research has been conducted on how to suppress the cancer therapeutics. However, including sequela of anti-cancer treatments, pharmacological clinical studies of cachexia have not been fully conducted. Considering patients' treatment rates and quality of life, we should develop a way to handle them with minimal risks in the future. In spite of the complex mechanisms and symptoms related to oxidative stress, the efficacy of suppressing the side effects and cachexia

is being studied with natural products including plant extracts. Therefore, those studies regarding antioxidant and anti-inflammation mechanisms of plant-derived drugs were reviewed in this study for the first time which manage side effects of cancer treatments and cachexia.

2. Cachexia and Plant Extracts

2.1. Cachexia

Patients commonly undergo not only treatment-related symptoms but also cancer-induced symptoms which can be categorized as cancer cachexia. In cancer patients, cachexia is characterized by systemic inflammation associating with decreased caloric intake, anorexia, decreased muscle strength and fatigue [18][19]. Cancer cachexia has been regarded as non-curable symptom and has devastating impact on patient's quality of life and survival. Nevertheless, the severity tends to be underestimated [20][24]. The energy wasting has been attributed to inefficient adenosine triphosphate (ATP) production due to mitochondrial dysfunction. Dysfunctional mitochondria produce high levels of ROS causing oxidative damage to lipids and proteins with enhanced inflammation [22]. It is related to ER stress induced unfolded protein response (UPR) pathways and it causes catabolic conditions [23]. This may lead to myofibrillar protein breakdown, increased lipolysis, insulin resistance, elevated energy expenditure, reduced food intake and psychological factors related to quality of life [24]. These also do not act as a single variable but are related to the whole. This is why clinical research on cachexia treatment has been insufficient.

2.2. Clinical Difficulties in Treatment of Cachexia

Current therapies focus on palliation of symptoms rather than cure. However, therapies such as simple improvement of nutritional intake are not enough considering that mechanisms of cancer cachexia are complex and multifactorial [25]. Numerous cytokines, hormones, metabolism and neurologic factors involve in the etiology of cancer cachexia. TNF- α , IL-6 and IL-1 mimic leptin signaling and suppress orexigenic ghrelin and neuropeptide (NPY) signaling, which result in weight loss and anorexia [26]. Upregulation of myostatin, an extracellular cytokine regulating hypertrophy, was observed in the pathogenesis of muscle wasting during cachexia [27]. Fatigue is induced by serotonin dysregulation, hypothalamic-pituitary-adrenal (HPA) axis disturbance, alteration in circadian rhythms, ATP dysregulation, vagal afferent nerve activation and cytokine dysregulation [28]. Treatment should be developed based on understanding of molecular mechanisms that induce cachectic symptoms. Absence of established guideline and insufficient clinical evidence for cancer cachexia treatment are another difficulty. Appetite stimulants, currently used to supplement calories and improve anorexia, do not always lead to weight gain. Agents affecting cachectic mediators or signaling pathways such as EPA, β -Hydroxy- β -methylbutyrate (HMB), Thalidomide, NSAIDs are also being used but further studies are required to confirm their efficacies [29]. Thus, the further research and clinical practice of cancer cachexia are needed to promote antioxidant and therapeutic effect.

2.3. Plant-Derived Drugs and Cachexia

There have been significant advances in cancer therapies. In spite of these progress, half of all patients with cancer commonly undergo cachexia which is associated with quality of life, poor response to cancer therapy and finally survival [20]. The symptoms include weight loss, anorexia, muscle atrophy, fatigue, anemia and so forth. Some compounds and extracts of plants were observed to decrease these symptoms (Table 1) and their mechanisms were organized in Figure 1. Li, B et al. elucidated that Bicalin, which is isolated from *Scutellaria baicalensis*, ameliorated the anorexia, weight loss and muscle atrophy [30]. CT26 adenocarcinoma inoculated male BALB/c mice was administered 50, 150 mg/kg of Bicalin by intraperitoneal injection for 15 days. These observing groups were demonstrated that p-p65/GAPDH band intensity was decreased and inhibitor of nuclear factor kappa B (I κ B α)/GAPDH expression was elevated. This result suggests that Bicalin inhibits NF- κ B activation which leads muscle wasting. Kim et al. observed that water extract of *Citrus unshiu* Markovich ameliorated weight loss, muscle wasting and Hb loss when its dosage was 150 and 500 mg/kg for 17 days [31]. The treatment not only decreased the levels of p-p38, extracellular signal-regulated kinase (ERK), JNK, I κ B α and STAT3 but also mitigated lipopolysaccharide (LPS)-induced NO, iNOS expression and pro-inflammatory cytokine production. Also, it alleviated the CT-26-mediated C2C12 myotube wasting and changed myosin heavy chain (MyH), Akt phosphorylation and p65 phosphorylation. Curcumin and green tea extract, extracted from *Curcuma longa* and *Camellia sinensis* respectively, ameliorated weight loss and muscle wasting [32]. This treatment was implemented on C2C12 myotubes for 24 h as its dosage of 10 μ g/mL. Such results were shown when TNF- α and proteolysis-inducing factor (PIF) was combined with not only curcumin and green tea extract but eicosapentaenoic acid (EPA). Rikkunshito was demonstrated to ameliorate anorexia and weight loss by upregulating hypothalamic orexigenic neuropeptide Y (NPY) and decreasing thyrotropin-releasing hormone (TRH) in paraventricular nucleus (PVN) [33]. However, Rikkunshito treatment did not affect the elevated plasma ghrelin levels and growth hormone secretagogue receptor (GHS-R) gene expression. Such

results showed when 1 g/kg/day of Rikkunshito was orally administered twice daily for 7 days to 85As2 cells inoculated six-week-old male F344/NJcl-rnu/rnu rats. Shen et al. also reported that the oral administration of SiBaoChongCao (1, 2 g/kg for 20 days) which is isolated from *Cordyceps sinensis* ameliorated weight loss and muscle atrophy with shrinking adipocyte cell [34]. The muscle atrophy was alleviated by decreasing myosin heavy chain (MHC), myogenic differentiation antigen (MyoD), myogenic regulatory factors (MyoG), target of rapamycin kinase complex 1 (TORC1) and peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC- α) and upregulating AKT and mammalian target of rapamycin (mTOR) pathway. This result suggests that it could facilitate myoblast protein synthesis in muscle tissue not regardless of blocking protein degradation. Choi et al. observed that Sipjeondaebo-tang ameliorated cancer-induced anemia and anorexia including weight loss and muscle wasting in CT-26 tumor-bearing mice [35]. In this process, Sipjeongdaebo-tang suppressed IL-6 and monocyte chemoattractant protein-1 (MCP-1) but not TNF- α . It also affected anorexia by regulating glucagon like peptide-1 (GLP-1) and peptide YY (PYY) but not ghrelin and leptin. Finally, it increased the levels of RBC, Hb and hematocrits (HCT), which means treating anemia. Such results were shown when its dosage was 6.784, 67.84 and 678.4 mg/kg for 21 days. Kim et al. reported that oral administration of Soshio-tang (50, 100 mg/kg for 18 days) was identified to alleviate weight loss, muscle wasting and improve appetite [36]. As a part of the result, Soshio-tang strongly prevented LPS-induced p38, I κ B α , IKK α β and STAT3. However, the levels of ERK and JNK were not because this treatment inhibited p65 nuclear translocation, which can block NF- κ B activation and attenuated muscle atrophy. Zhuang et al. demonstrated that Zhimu and Huangbai herb pair which was isolated from *Anemarrhena asphodeloides* and *Phellodendron amurense* ameliorated body weight loss and muscle protein catabolism [37]. This effect was carried out by activating insulin-like growth factor 1 (IGF-1)/Akt signal and increasing the expression of microtubule-associated protein 1A/1B-light chain 3 (LC3B) and sirtuin1 (SIRT1). Such results were shown when 104 mg/kg of Zhimu and Huangbai herb pair was administered to colon-26 adenocarcinoma inoculated Male C57BL/6 mice for 18 days.

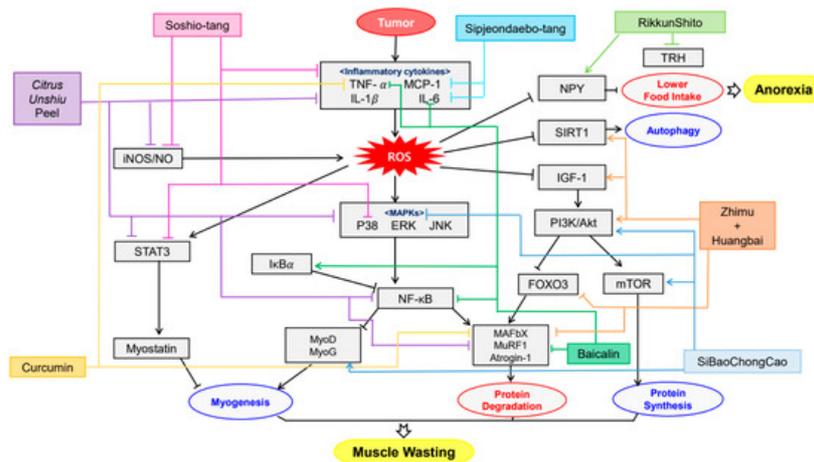


Figure 1. Schematic diagram of anti-inflammatory & antioxidant mechanisms of plant-derived drugs in cachexia.

Table 1. Plant-derived drugs and cachexia.

Compound/Extract	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Baicalin	<i>Scutellaria baicalensis</i>	CT26 adenocarcinoma inoculated BALB/c mice	50, 150 mg/kg; 15 days	Amelioration of anorexia, weight loss and muscle atrophy	↓ I κ B α ↓ NF- κ B, TNF- α , IL-6, MURF1, Atrogin-1, p65	[30]
Citrus unshiu peel water extract	<i>Citrus unshiu</i> Markovich	CT26 adenocarcinoma-induced cancer cachexia BALB/c mice	250, 500 mg/kg; 17 days	Amelioration of weight loss, muscle wasting and Hb loss	↑ MyH, p-Akt ↓ MAFbx, MuRF-1, IL-6, NO, iNOS, IL-1 β , TNF- α , p-p38, ERK, JNK, I κ B α , STAT3, p-p65,	[31]
Curcumin green tea extract	<i>Curcuma longa</i> , <i>Camellia sinensis</i>	C2C12 myotubes	10 μ g/mL; 24 h	Amelioration of weight loss and muscle wasting	↓ 20S proteasome subunits, p42, MuRF1, MAFbx, PIF, TNF- α	[32]

Compound/Extract	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Rikkunshito	<i>Atractylodes lancea</i> , <i>Panax ginseng</i> , <i>Pinellia ternate</i> , <i>Poria cocos</i> , <i>Zizyphus jujuba</i> , <i>Citrus unshiu</i> , <i>Glycyrrhiza uralensis</i> , <i>Zingiber officinale</i>	85As2 cells inoculated F344/NJcl-rnu/rnu rats	1 g/kg/day; 7 days	Amelioration of anorexia and weight loss	↑NPY ↓TRH	[33]
SiBaoChongCao	<i>Cordyceps sinensis</i>	C26 tumor-bearing BALB/c mice	1, 2 g/kg; 20 days	Amelioration of weight loss, muscle wasting and adipocyte cell reduction	↑MHC, MyoD, MyoG, p-AKT, p-mTOR, AMPK α , ERK, TORC1, PGC-1 α ↓IL-6, TG, AMPK, p38 MAPK, p-HSL, UCP1	[34]
Sipjeondaebotang	<i>Angelica gigas</i> , <i>Astragalus membranaceus</i> , <i>Atractylodes japonica</i> , <i>Cinnamomum cassia</i> , <i>Cnidium officinale</i> , <i>Glycyrrhiza uralensis</i> , <i>Paeonia lactiflora</i> , <i>Panax ginseng</i> , <i>Poria cocos</i> , <i>Rehmannia glutinosa</i>	CT-26 inoculated-BALB/c mice	6.784, 67.84, 678.4 mg/kg; 21 days	Amelioration of anorexia, weight loss, muscle wasting and anemia	↓IL-6, MCP-1, PYY, GLP-1	[35]
Soshio-tang	<i>Bupleurum falcatum</i> , <i>Glycyrrhiza uralensis</i> , <i>Panax ginseng</i> , <i>Pinellia ternata</i> , <i>Scutellaria baicalensis</i> , <i>Zingiber officinale</i> , <i>Zizyphus jujuba</i>	J774A.1 macrophage cell line inoculated CT-26-bearing mice	50, 100 mg/kg; 18 days	Alleviation of weight loss, muscle wasting and appetite loss	↓NO, iNOS, IL-6, IL-1 α , IL-1 β , TNF- α , p38, NF- κ B, I κ B α , IKK α β , STAT3	[36]
Zhimu and Huangbai herb pair	<i>Anemarrhena asphodeloides</i> , <i>Phellodendron amurense</i>	colon-26 adenocarcinoma inoculated C57BL/6 mice	104 mg/kg; 18 days	Amelioration of weight loss and muscle wasting	↑IGF-1, Akt, LC3B, SIRT1 ↓TNF- α , IL-6, atrogen-1, MuRF1, FOXO3	[37]

Common symptoms of cancer cachexia, including anorexia, weight loss and muscle atrophy, were ameliorated by plant-derived drugs through various mechanisms. Bicalin inhibited NF- κ B activation [30], *Citrus unshiu* extract suppressed the production of pro-cachectic cytokines [31] and curcumin and green tea enhanced protein degradation through TNF- α and PIF [32]. Effectiveness of plant-derived drugs was prominent in herbal formulas or herbal pairs. It can be assumed that such tendency is due to complex and multifactorial characteristic of cachexia. Rikkunshito attenuated anorexia and weight loss by upregulating hypothalamic orexigenic NPY and decreasing TRH [33]. SiBaoChongCao facilitated myoblast protein synthesis in muscle tissue, preventing weight loss and muscle atrophy with shrinking adipocyte cells [34]. Sipjeondaebotang ameliorated cancer-induced anemia and anorexia [35]. Soshio-tang inhibited p65 nuclear translocation, which can block NF- κ B activation [36]. Zhimu and Huangbai herb pair activated IGF-1/Akt signal, therefore preventing body weight loss and muscle protein catabolism [37].

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