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**Review**

# Ghrelin as a Promising Therapeutic Option for Cancer Cachexia

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**Key Words**
Cachexia • Ghrelin • Orexigenic • Ghrelin mimetic • Weight loss • Gut hormone

**Abstract**
Cachexia is a devastating complication of cancer and an important cause of morbidity and mortality and can have a great effect on quality of life, and sense of self-esteem. Unfortunately; there is no standard cure available for cancer cachexia. Ghrelin; a 28 amino acid orexigenic gut hormone and its mimetics have shown potential benefits in reversing the breakdown of protein and weight loss in catabolic states like cancer cachexia. Ghrelin has effects on several vital pathways in the regulation of appetite, and composition of the body. It increases the secretion of growth hormone and reduces energy expenditure. It plays an important role in regulation of processes associated with cancer and antagonizing protein breakdown in catabolic conditions such as cancer cachexia. Additionally, ghrelin has anti-inflammatory, anti-apoptotic and anxiolytic effects. Administration of ghrelin for short-term has been found to be well-tolerated and safe. These versatile actions of ghrelin and its safety can render it as a potentially useful novel therapy for patients with cancer cachexia. However; there is a need to generate more evidence to support the use of ghrelin in the management of cancer cachexia.



## Introduction

Cachexia is a devastating complication of cancer and an important cause of disability and mortality for which there is no approved treatment [1]. This complex clinical condition strikes more than 50% of patients with different cancers, affects 60%–80% of all cancer patients in advanced stages and is responsible for death of as a minimum as 20% of all cancer patients [2]. Cancer cachexia has been classified into stages of pre-cachexia, cachexia and refractory cachexia [3]. Hallmarks of cachexia include reduced muscle mass, reduced total lean body mass, and reduced strength in limbs. It has been showed that in progressive cancer cachexia; body fat is lost more speedily than lean mass [4]. Pathophysiology of cachexia is multifactorial and is still not well-understood. It is advocated to be the result of tumor-host

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interactions [5]. Systemic and chronic inflammation also contributes to symptoms of cancer cachexia. Inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-γ (IFN-γ) have been reported to be involved in anorexia, skeletal muscle loss, hyper-metabolism, metabolic abnormalities, and hormonal changes observed in cancer cachexia. Drugs for cancer therapy are also involved in catabolic losses of muscle. Cachexia can have an impact on survival, quality of life, and sense of self-esteem. It lowers the tolerance of chemotherapy and its response [3, 6].

Despite high prevalence of cancer cachexia, efficient treatments are yet inadequate and no complete pharmacological cure is available to tackle the pertinent constituents of this syndrome [7–12]. There is a convincing necessity for further efficient appetite-stimulatory cures for patients with this condition.

Treatment for cancer cachexia must comprise of treatments that targets inflammatory status, oxidative stress, catabolic drive, reverse the reduced body weight and should improve skeletal muscle mass, skeletal muscle strength, exercise capacity, anemia, immunosuppression, fatigue and survival [13–15]. The ultimate management target for cachexia must be turn-around of lost body weight and lost muscle mass [6]. Unfortunately; there is no standard treatment available for patients of cancer cachexia [3]. Supplementation of nutrition cannot singly reverse cancer cachexia [15]. Appetite stimulants like megestrol acetate, l-carnitine, and serotonin receptor antagonists do not provide clinically meaningful benefits [16]. Progestational agents have possible clinical side-effects and increase only fat mass [6, 13]. The efficacy of short-term corticosteroids on appetite is modest [17]. Evidence of long-term benefits of corticosteroids are lacking and they are not safe due to the risk of its incapacitating adverse effects [17]. A number of promising new drugs like selective COX-2 inhibitors, ghrelin mimetics, olanzapine, selective androgen receptor modulators, oxandrolone are being established. However, these drugs are not as yet considered as standard of care [18]. Drugs like bortezomib, antiserotoninergic drugs, and anti-tumor necrosis factor (TNF)-alpha monoclonal antibody have not revealed univocal effects in clinical trials [6, 18, 19]. Other drugs like gastroprokinetic agents, eicosapentanoic acid, thalidomide, pentoxyphylline, as well as ghrelin and ghrelin agonists (like anamorelin) are being investigated for treating cancer cachexia [14].

Experts under the umbrella of the European School of Oncology have advised that emphasis of treatment of cancer cachexia should shift from treating end-stage wasting to promoting patients' nutritional and functional state during the protracted course of anti-cancer treatment [20]. It has been held that; oncologists should consider three issues of palliative care for all cancer patients: ensure adequate energy and protein consumption, ensure physical activity to conserve muscle mass and reduce systemic inflammation; if any [20]. Thus; a combination of approaches is required in cancer cachexia [21].

A novel gut hormone; ghrelin has shown promising positive results and is being established as a promising treatment option for cancer cachexia [22, 23]. However; its mechanisms of action are yet partly elucidated [8, 24]. Owing to its orexigenic nature as well as other effects on metabolism; ghrelin has a potential advantage in reversing catabolism of protein as well as reversing weight loss in catabolic conditions like cancer cachexia, end stage renal and cardiac diseases, and age-related fragility [22, 25]. Ghrelin is an orexigenic mediator and acts in a pleotropic fashion on appetite, lean and fat mass, energy storage, and gastrointestinal system [22]. In this review; we try to explore the possibility to identify ghrelin as an effective and well-tolerated treatment option to reduce cachexia in cancer patients.

## Ghrelin

Ghrelin; a 28 amino acid gut hormone; was first reported as a vital stimulator of hunger and an inhibitor of energy expenditure. Principally secreted by the stomach; it plays a vital role in a metabolic, endocrine, immunological, cardiovascular, reproductive and other physiological processes [23]. Ghrelin is produced mainly by A-like cells enteroendocrine cells of the oxyntic mucosa of stomach and, to a lesser extent, by colon, pituitary, hypothalamus, endocrine pancreas, lung, cardiomyocytes, placenta, ovaries, and testes. Ghrelin has an n-octanoyl ester at its third Serine residue [26]. It was first identified in 1999 by Kojima from stomach as an endogenous ligand for growth hormone secretagogue receptor (GHS-R) that later came to be known as ghrelin receptor [26].

*Forms of ghrelin*

Ghrelin is primarily acylated by octanoic or decanoic acid on the N-terminus of serine-3 amino acid [27, 28]. Acylation of ghrelin is carried mainly in stomach by an enzyme ghrelin-O-acyltransferase (GOAT) [29]. However; several other forms of ghrelin: octanoyl ghrelin, n-decanoyl ghrelin (C10:0, no double bonds), decanoyl (C10:0, with double bonds), des-acyl ghrelin, obestatin, In1-ghrelin (which retains intron 1) have been found in circulation [30, 31].

Increased ghrelin formation and secretion has been found in variety of tumours like bronchial carcinoid tumors [32], gastrointestinal neuroendocrine tumors [33–35], and pancreatic tumors [34]. Ghrelin is secreted from variety of different cell lines of colorectal cancer [36], stomach cancer cell line [37], thyroid cancer [38], leukemia [39], and prostate cancer [40]. Studies have tried to figure out if cancer cells yield octanoylated ghrelin, des-acyl ghrelin, or both. Human Erythroleukemic Cell Line (HEL), Human promyelocytic Leukemia Cell Line (HL-60), monocytic THP-1 and lymphoblastic SupT1 cell lines secrete acylated as well as unacylated ghrelin, but comparably higher acylated ghrelin [39, 41]. Acyl ghrelin and des-acyl ghrelin bind to a mutual receptor in breast cancer cells where they inhibit cell proliferation [42]. A number of ghrelin transcript isoforms and ghrelin natural antisense transcripts are expressed in cancer. A proghrelin isoform lacking exon 3 has been noted in prostate cancer tissue and cell lines [43] and overexpressed In1-ghrelin has been found in breast cancinoma [44]. There is no clear evidence regarding specific effects of these different forms of ghrelin in patients of cancer cachexia.

*Ghrelin gene*

Ghrelin gene (GHRL) spans 5 kb on chromosome 3 [45]. Compared to other pre-prohormones, the genomic structure of ghrelin is relatively simple, consisting of four coding exons and a short, 20 bp first exon [45–48]. Ghrelin gene is transcribed as a preproghrelin mRNA isoform, that leads to translation of preproghrelin; a 117 amino acid peptide [26]. Exon 1 encodes the preproghrelin signal peptide while exon 1 and part of exon 2 encodes ghrelin.

*Ghrelin receptors*

Ghrelin is a natural ligand for growth hormone secretagogue receptor (GHSR) in the pituitary gland, and therefore fulfills the principle of a gut-brain peptide [49]. The brain-gut axis affects anabolism by regulating growth, food intake, and metabolism via vagal afferents [49]. GHSR1a is extensively expressed in metabolically active tissues, like liver, pancreas, adipose tissue, pituitary glands, thyroid, kidneys, heart and gonads [50, 51]. In the central nervous system, GHSR1a is expressed in cortex, ventral tegmental area, dorsal raphe nuclei, hypothalamus, substantia nigra and hippocampus [52–55]. This widespread expression of GHSR1a is accountable for the wide range of biological functions of ghrelin in glucose metabolism [56–58], lipid metabolism [59, 60], in promoting appetite [61–64], gastric

acid secretion [65], gut motility [65], regulation of growth hormone secretion [26, 66, 67], fertility [68–70], memory [57], learning and reward related pathways [62, 71, 72]. Ghrelin receptors are additionally expressed in cancers throughout gastrointestinal tract [73]. Its level of expression probably correlates with the type of organ, histological grade of cancer, and nutrition status of the patient [73].

*Functions of ghrelin*

Lots of efforts are being made to understand the possible cellular and molecular mechanisms modulating the effects of ghrelin. Though ghrelin was initially labeled as a potent growth hormone (GH) secretagogue [26]; unearthing of its role in promoting hunger [64] and adiposity [74] have made this hormone interesting.

Many disorders; related to infection, inflammation, and malignancy of gastrointestinal tract are associated with altered ghrelin levels [75]. Studies on ghrelin and ghrelin receptor agonists have shown their efficacy in management of gastrointestinal disorders including anorexia nervosa and cancer cachexia [76–81], gastroparesis [82–84], chronic constipation [84–90], postoperative ileus and inflammatory bowel disease [91]. Ghrelin has also been shown to be effective in chronic heart failure [92–95] and chronic respiratory conditions [96–98].

*Ghrelin expression & Plasma ghrelin in fasting and fed states*

Circulating ghrelin comprises of acyl (acylated) ghrelin and des-acyl (unacylated) ghrelin, which fluctuate in their quantities with time, because of quick alteration of acylated to unacylated ghrelin that seems to happen through circulating esterases [29, 99]. Though the precise ratio of circulating acyl (AG) to des-acyl (DAG) ghrelin fluctuates according to the metabolic status, ghrelin mostly circulates in the des-acyl ghrelin form [100]. Binding of AG to the ghrelin receptor is 1000 times more effective than DAG. Hence, AG is believed to be the only form adept of activation of ghrelin-receptor. The term 'ghrelin' therefore usually denotes to acyl or 'active' form of ghrelin [101]. Nevertheless, DAG seems to have numerous biologic functions, comprising alteration (agonism or antagonism) of a number of actions of ghrelin [102–104].

Ghrelin secretion and mRNA expression is augmented by weight loss, control of caloric consumption [54, 74], and hypoglycemia [105]. Concentration of ghrelin in blood depends on diet, hyperglucemia, adiposity and blood leptin levels [65]. It is secreted 1-2 hours before a meal and its concentration decreases drastically after meals [65]. This pre-prandial rise suggests the role of ghrelin in appetite and initiation of meal [106]. It is still unclear whether higher glucose levels and insulin directly impede ghrelin secretion. The influence of ghrelin on appetite, utilization of fuel, body weight, and body composition enhances the complexity in regulation of energy balance.

*Plasma ghrelin levels in cachectic cancer*

Plasma ghrelin levels and body mass index (BMI) are generally inversely related. Although plasma ghrelin levels are not likely to be used as a biomarker for cancer; they may be valuable as a marker for cancer cachexia [23]. Total plasma ghrelin levels are raised in most patients of cancer cachexia compared with patients without cancer or cancer patients without cachexia [107–111]. Plasma ghrelin concentrations in tumor-bearing rats were found be greater than free-fed normal rats, but lesser than pair-fed normal rats [112]. Ghrelin peptide and mRNA levels in stomach were upregulated in tumor-inoculated mice [113]. Immunoreactivity for ghrelin was demonstrated in seven of 22 tumors while Immunoreactivity for the ghrelin receptor was shown in five out of ten tumors [114].

Interestingly, cancer cachectic patients did not show increased appetite, despite their increased ghrelin levels. Although mechanisms causing increased ghrelin levels in cachexia remain unclear; elevated ghrelin may signify a compensatory mechanism in energy imbalances observed in cachectic patients. Ghrelin may be secreted as a compensatory mechanism in response to weight loss, negative energy balance, reduced appetite, and

inflammation associated with cachexia [23, 108, 115, 116]. The rise in ghrelin levels may be due to higher secretion as well as reduced inactivation of ghrelin [109].

Ghrelin serum levels were significantly elevated in Non-small cell lung cancer (NSCLC) patients, mainly in patients diagnosed with cachexia [117]. Cachexia associated with gastrointestinal cancers is accompanied with changes in ghrelin concentrations as altered ghrelin levels were found in patients with esophageal, gastric, pancreatic, colonic, and rectal cancers as compared to normal subjects [118, 119]. Serum active ghrelin levels were significantly greater in patients with uterine leiomyoma compared to women without uterine leiomyoma thereby suggesting a role of active ghrelin in the development of a myoma [120]. Mean active ghrelin were low at the diagnosis of acute lymphoblastic leukemia (ALL) as compared to control subjects [121]. Later; ghrelin levels wavered and steadied at considerably greater levels after chemotherapy thereby suggesting that ghrelin may have a role in the pathogenesis of anorexia-cachexia syndrome in children with ALL [121]. Plasma ghrelin levels were significantly elevated in cancer patients that could have lead to release of growth hormone and thereby neoplasia [122].

## Mechanism of action of ghrelin in cancer cachexia

Ghrelin mRNA and protein are expressed in many cancer and tumor tissues [23]. Ghrelin has effects on several key pathways in the regulation of appetite, body weight and body composition. It increases secretion of growth hormone and reduces energy expenditure and inflammation. Ghrelin also regulates cancer-associated processes including cell proliferation, cell invasion, cell migration, apoptosis, inflammation, and angiogenesis [23]. Nevertheless; additional studies are required to establish the role of ghrelin in progression of cancer [23].

While endogenous ghrelin levels are elevated in animal models of cancer cachexia and in humans with cancer cachexia; administration of ghrelin and other GHSR-1a agonists have demonstrated consistent results in improving appetite and weight gain [123]. Increase of ghrelin is regarded favorable in numerous pathologic states manifested by malnutrition, wasting and cachexia, seen in cancer, chronic heart failure, chronic infections or chronic pulmonary disease [124]. Ghrelin disturbs vicious cycle of cachectic pattern via its orexigenic, anabolic, and anti-inflammatory effects [125].

*Anti-inflammatory action*

In response to cancer; cancer cells or host immune system releases cytokines that causes anorexia–cachexia; neurochemical mechanisms for which are yet unclear. In mouse models of lung adenocarcinoma; administration of ghrelin inhibited inductions of tumor necrosis factor-α, C-reactive protein, interleukin-1β, and interleukin-6 (Fig. 1) [126]. Ghrelin has been found to inhibit production of these anorectic pro-inflammatory cytokines and thereby regulate systemic inflammation in cancer patients [127]. Evidences for efficacy of ghrelin in prevention of inflammation associated in murine intestinal carcinogenesis models suggests its safety in subjects of colitis-associated cancer [80].

*Promotion of appetite/ stimulating hunger*

Ghrelin plays a vital role in stimulating appetite and preserving energy homeostasis by acting on central nervous system as well as peripheral tissues [128]. It improves appetite by enhancing number of meals; without changing the quantity, and by eliciting several appetitive feeding behaviors [129].

Ghrelin exerts its central orexigenic effect via stimulation of numerous hypothalamic and brain stem neurons (Fig. 1) [130]. Ghrelin has been found to increase the expression of orexigenic cannabinoid-1 and MCH-1 receptors on vagal afferents (Fig. 1) [131]. Peripheral administration of ghrelin stimulates food intake in animal models of cancers and cancer patients [74, 112, 113, 132]. Decreases in food intake in tumor-bearing rats improved after administration of ghrelin [112]. Long-term administration of ghrelin to cachectic

cancer patients with solid tumors increases food intake, and decreases catabolism [133]. Ghrelin administration increased food intake and body weight [134]. However; weight loss in turn increased ghrelin levels [134].

Ghrelin stimulates growth hormone (GH) secretion [66]. As GH is an anabolic hormone; during conditions of caloric restriction; protein stores are spared at the cost of fats. Thus, ghrelin demonstrates anti-cachectic effects through both GH-dependent as well as GH-independent mechanisms [127]. Ghrelin plays a role in promoting a more effective storage of food components as well as stimulating food intake. It acts as a counterpart of leptin in regulating appetite and utilization of fats [135].

Ghrelin is primarily a component of gut-brain axis [66]. Most vital function of ghrelin seems to regulate satiety signal from stomach to the hypothalamus. Other gastrointestinal functions like gastric acid secretion and gastro-intestinal (GI) motility also appears to be influenced by ghrelin (Fig. 1) [136]. Ghrelin regulates GI motility by stimulating central as well as enteric neurons, including neurons of the Paraventricular nucleus. It does this by stimulating GHSR and NPY pathways, and peripheral muscarinic acetylcholine receptors [136].

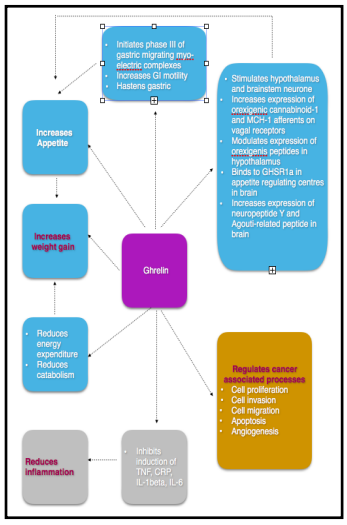


**Fig. 1.** Mechanisms of action of ghrelin in promoting appetite and weight gain.

Ghrelin principally regulates feeding behavior via alteration of expression of orexigenic peptides in hypothalamus [129, 137]. It binds to the GHSR1a in appetite-regulating centers in brain and increases the expression of neuropeptide Y and agouti-related peptide in the hypothalamus. With receptors on melanocortinergic neurons; ghrelin improves appetite via melanocortin modulation and thereby improve symptoms of cachexia [138].

Ghrelin stimulates AMP-activated protein kinase in hypothalamus, whereas inhibits it in liver and adipose tissues [139]. Numerous intracellular targets or mediators of the appetite-inducing effect of ghrelin like AMP-activated protein kinase and its upstream kinase calmodulin kinase 2 have been recognized in the hypothalamus [130].

*Muscle catabolism*

Ghrelin and its mimetics have a probable role in alienating protein breakdown and weight loss in catabolic states like cancer cachexia [140]. Newer understanding has shown that ghrelin has muscle-specific action via activation of anti-atrophic molecular cascade [24].

*Action on gastrointestinal tract*

Administration of ghrelin in tumor-bearing rats recuperated decrease in GI motor activities [112]. Human ghrelin and human motilin, belong to ghrelin/motilin-related peptide family and have 36% amino acid sequence similarity. Also human ghrelin receptor displays 50% similarity with human motilin receptor. Ghrelin and motilin contribute in initiating phase III of gastric migrating myoelectric complexes (motilin) in the stomach [84]. It also accelerates gastrointestinal motility, hasten gastric emptying, and stimulate "gastric hunger"[84].

A study demonstrated that peripheral administration of Acyl ghrelin exerted strong prokinetic effect [141]. Ghrelin particularly speeded gastric emptying and transit of the small intestine, but did not accelerate emptying of the colon [141]. Another study demonstrated the prokinetic function of acyl ghrelin to colon [142]. Injection of acyl ghrelin in rats and mice have shown to trigger migrating motor complexes under fasting states [143–145]. In humans; alteration of circulating ghrelin levels is related with gastric migrating motor complexes [146] thereby signifying a strong physiological role of ghrelin in gastrointestinal motility [145].

*Anxiolytic effect*

Raised ghrelin aids animals tackle anxiety by anxiolytic-like response . Humans and animals models of cancer have higher 5-HT and lower NPY and dopamine in the hypothalamus. Stimulation of 5-HT2cR in tumor-bearing rats reduces ghrelin secretion and thus induces anorexia which improved after administration of ghrelin [147].

*Anti-apoptotic effect*

Cancer cachexia is accompanied with myofiber damage. Tumor-factors harm regeneration of myofiber by stimulating myoblast apoptosis. Ghrelin is a versatile hormone with an anti-apoptotic effect. However; its mechanism of action is not completely known. A study established that co-culture of myoblasts with colon carcinoma cells encouraged myoblast apoptosis and raised tumor necrosis factor (TNF)-α in the culture medium. Furthermore, the co-culture inhibited Akt activity, raised mitochondrial Bax/Bcl-2 ratio, raised cytosolic cytochrome c levels, and stimulated caspase-3/poly (ADP-ribose) polymerase (PARP) cascade in myoblasts. Moreover; this study found that acylated ghrelin or un-acylated ghrelin inhibited these changes thereby advocating a probable usage for acylated ghrelin or un-acylated ghrelin in treating subjects of cancer cachexia [148]. A recent study demonstrated that ghrelin suppresses mitochondrial dysfunction under high glucose/ high lipid conditions, and reduces endothelial apoptosis by inhibiting c-Jun N-terminal kinase (JNK) and p38 signaling [149].

*Effect on tumor growth*

Ghrelin exhibits anabolic properties via transient upsurges in growth hormone. However; elevated growth hormone and insulin-like growth factor-1 (IGF-I) in cancer patients builds apprehensions that ghrelin treatment may possibly encourage tumor growth and cancer progression [150]. So; action of ghrelin and anamorelin on tumor growth in a murine non-small cell lung cancer (NSCLC) xenograft model was explored which revealed that despite elevated levels of growth hormone and elevated levels of IGF-1; neither ghrelin nor anamorelin encouraged tumor growth [150].

Another study explored results of ghrelin on molecular mechanisms related to cancer advancement, comprising cell viability, proliferation, resistance to apoptosis, and mitochondrial activity using human lung adenocarcinoma cell line HLC-1 [151]. The study found that treatment with ghrelin had no effect on viability or proliferation capacity of the cell and hence concluded that ghrelin had no effect on cancer progression in lung adenocarcinoma cells [151].

Together with the capacity to improve body weight; these effects back the clinical advancement of ghrelin as a therapeutic option for anorexia/cachexia associated with cancer.

*Reducing adverse effects of chemotherapy*

Cisplatin dispensed to cancer patients may cause gastrointestinal conditions and hinder continuance of chemotherapy [152]. Exogenous administration of ghrelin at the commencement of cisplatin-based chemotherapy stimulates appetite and lessens side effects of cisplatin [152]. Thus; ghrelin can be a potentially therapeutic option for curtailing adverse effects associated with chemotherapy [152].

*Role of ghrelin agonists in cancer cahexia*

Half-life of ghrelin is less than 30 minutes and has to be administered by parenteral route. Studies are therefore exploring the use of ghrelin receptor agonists with longer half-life and good bioavailability.

*Anamorelin*

It is a novel oral ghrelin-receptor agonist which when administered orally; can improve appetite, improve body weight and increase the anabolic activity. Anamorelin has been shown to have significant clinical, and patient-rated effects in cachexia associated with cancer [153].

Treatment with anamorelin for twelve weeks demonstrated a satisfactory clinical response in subjects with cancer anorexia-cachexia syndrome [11, 81, 153]. Also; administration of anamorelin in subjects with non-small cell lung cancer (NSCLC) increased food intake, body weight and lean body mass [11, 81] but not motor function [11]. Anamorelin is a safe, well-tolerated anabolic agent with no dose-limiting toxicities [11, 81] and without virilizing adverse effects of other anabolic drugs [154]. However; long-term safety remains unknown. A Systematic review and meta-analysis on anamorelin for advanced non-small-cell lung cancer with cachexia demonstrated that anamorelin significantly increased lean body mass and improved quality of life and hence can be a promising therapeutic choice for Cancer anorexia-cachexia syndrome in patients with advanced non-small-cell lung cancer [12]. Management of patients of cancer cachexia with anamorelin can offer palliation of cachexia, an unfulfilled requisite in supportive oncology.

*Rikkunshito (RKT)*

It is a Japanese herbal medicine (Kampo) and improves symptoms of cancer cachexia via ghrelin-signaling dependent and independent mechanisms [155]. RKT is advised for management of dyspepsia, gastroesophageal reflux disease, gastrointestinal symptoms in patients after gastrointestinal surgery, and chemotherapy-induced dyspepsia in cancer subjects [77, 155–157]. Rikkunshito raises plasma ghrelin levels in humans, mice [158] and dogs [159] and also restores reduced plasma ghrelin levels [158] brought by serotonin release. RKT improves appetite and gastrointestinal motor activities [112]. It ameliorates anorexia mediated by stimulating ghrelin secretion and/or potentiation of ghrelin signaling [76, 112, 160, 161]. RKT improves anorexia in a gastric cancer cachexia model and in a bleomycin-induced acute lung injury model by regulating lung inflammation independent of the ghrelin signaling systems [160]. RKT has been shown to improve nausea, loss of appetite and cachexia associated with cancer or cancer chemotherapy [6, 162].

*Z-505 hydrochloride (Z-505)*

Z-505 hydrochloride (Z-505) is a novel oral growth hormone secretagogue receptor 1a (GHSR1a) agonist. A study demonstrated that Z-505 notably improved appetite, reduced muscle wasting, prevented weight loss, and augmented anabolic factors like insulin and IGF-1 [163]. However; it did not increase levels of catabolic factors like IL-6 and corticosterone [163]. Another recent study showed that Z-505 improved cisplatin and 5-FU-induced anorexia via stimulation of GHSR1a, signifying its utility in the protective management of loss of appetite during chemotherapy [164]. These results imply that Z-505 may be useful in the management of cachexia through elevated anabolic hormones encouraged by stimulation of GHSR1a.

*Safety of ghrelin in cancer cachexia*

Existing evidences suggests that short-term administration of synthetic ghrelin appears to be safe and well tolerated [22, 150, 165] with some concern for rises in blood glucose because of reduced insulin sensitivity [166]. However; safety with long-term use, including evaluation of mortality, is needed [166]. Adverse effects related to anamorelin were hyperglycemia, nausea, and dizziness. However adverse effects were mild and no patients withdrew due to adverse effects [167].

## Conclusion

Ghrelin is an orexigenic mediator and acts in a pleotropic fashion in improving appetite, lean and fat mass, energy storage, growth hormone secretion, regulation of processes associated with cancer and antagonizing protein breakdown in catabolic conditions such as cancer cachexia. These versatile actions of ghrelin and its safety can render it as a potentially useful novel therapy for patients with cancer cachexia. However; there is a need to generate more evidence to support the use of ghrelin in the management of cancer cachexia.

## Disclosure Statement

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