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Addressing cancer anorexia-cachexia in older patients: potential therapeutic strategies and molecular pathways

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Abstract

Cancer cachexia (CC) syndrome, a feature of cancer-associated muscle wasting, is particularly pronounced in older patients, and is characterised by decreased energy intake and upregulated skeletal muscle catabolic pathways. To address CC, appetite stimulants, anabolic drugs, cytokine mediators, essential amino acid supplementation, nutritional counselling, cognitive behavioural therapy, and enteral nutrition have been utilised. However, pharmacological treatments that have also shown promising results, such as megestrol acetate, anamorelin, thalidomide, and delta-9-tetrahydrocannabinol, have been associated with gastrointestinal and cardiovascular complications. Emerging evidence on the efficacy of probiotics in modulating gut microbiota also presents a promising adjunct to traditional therapies, potentially enhancing nutritional absorption and systemic inflammation control. Additionally, low-dose olanzapine has demonstrated improved appetite and weight management in older patients undergoing chemotherapy, offering a potential refinement to current therapeutic approaches. This review aims to elucidate the molecular mechanisms underpinning CC, with a particular focus on the role of anorexia in exacerbating muscle wasting, and to propose pharmacological and non-pharmacological strategies to mitigate this syndrome, particularly emphasising the needs of an older demographic. Future research targeting CC should focus on refining appetite-stimulating drugs with fewer side-effects, specifically catering to the needs of older patients, and investigating nutritional factors that can either enhance appetite or minimise suppression of appetite in individuals with CC, especially within this vulnerable group.

Keywords: cancer cachexia; anorexia; muscle wasting; sarcopenia; nutrition; drugs

1. Introduction

An urgent necessity to identify effective treatments for cancer cachexia (CC), a fat and muscle wasting condition, is highlighted by its high prevalence (up to 80%) in advanced malignant cancers [1]. In this review, we explore CC with a specific focus on the anorexia aspect, which is a key component of the syndrome, characterised by weight loss, muscle mass reduction, and a diminished desire to eat [2, 3]. This condition contributes significantly to the lower quality of life (QoL) [4], morbidity, and mortality rates, with approximately 20-30% of cancer patient deaths attributed to this condition [5]. The impact can be more pronounced in older cancer patients due to the combined effects of ageing and cancer-related muscle wasting. Its increasing global prevalence is particularly alarming in light of the escalating cancer rates, especially in developed countries such as the USA, where approximately 70% of cancer cases occur in older adults over the age of 65 [6]. The combination of ageing, sarcopenia, cancer, and cachexia presents unique challenges in this population [7, 8]. While direct comparisons of cancer cachexia prevalence in younger versus older patients are limited, evidence suggests a higher susceptibility in older adults. Older patients with cancer cachexia tend to display lower Geriatric Nutritional Risk Index scores than younger patients, which may be linked to greater risk of weight loss, muscle wasting, and elevated inflammatory markers [9, 10]. These findings align with the observations that older patients often have lower baseline levels of skeletal muscle mass, increased muscle attenuation, and a lower body mass index (BMI), all of which are indicative of sarcopenia and have been associated with an increased risk of mortality [11-14]. Addressing sarcopenia in older adults with cancer is therefore crucial to preserving their independence, improving their quality of life, optimising their ability to tolerate and respond to cancer treatments, with implications for healthcare resource optimisation [14]. All these concerns come in the context of the overall growing burden of non-communicable diseases, including cancer, cardiovascular disease, and diabetes [15]. In 2020, cancer alone led to 10

74 million deaths and 19.3 million new diagnoses [15], a trend projected to worsen, which could
75 further stress health systems and financial stability [16]. Moreover, the prevalence of CC in
76 older cancer patients often coincides with sarcopenia, further complicating their clinical
77 management and exacerbating the challenges in treating this demographic.

78

79 Sarcopenia, a disease characterised by the loss of muscle mass, strength, and function, is a
80 major health concern due to its high prevalence in older adults and its negative impact on QoL,
81 survival rates, surgical complications, and length of hospital stay in cancer patients [17-22].
82 This condition, also prevalent in cancer patients [23], shares pathophysiological mechanisms
83 with CC [24], and its key feature, pronounced muscle mass loss with or without accompanying
84 losses in adipose tissue, contributes to reduced QoL [5]. While aging is the primary cause of
85 sarcopenia, other factors such as disease and physical inactivity may also contribute to its
86 development (i.e., secondary sarcopenia) [21]. Addressing protein and energy deficiencies is
87 crucial for combating sarcopenia in older adults, whether they are healthy or recovering from
88 disease [25, 26]. However, this is complicated by age-related anorexia as older adults typically
89 have a reduced appetite compared to younger adults [27]. Challenges in increasing energy and
90 protein intake in hospitalised older patients with advanced cancer further contribute to
91 malnutrition [28]. Given these difficulties, alongside the heightened risk and prevalence of
92 dysphagia [29], anabolic resistance [30], and a higher incidence of oral health diseases in older
93 adults [31], focused attention on this demographic is crucial.

94

95 Cancer cachexia (CC), a condition marked by a diminished desire to eat, independently predicts
96 of mortality in cancer patients and significantly exacerbates sarcopenia by impairing appetite
97 and nutrient intake [32-34]. This condition contributes to the decline in health of older adults
98 affected by diseases such as cancer, highlighting the need of diagnosing CC [35, 36].

Chemotherapy side effects, such as appetite suppression, fitness loss, and susceptibility to infections, can exacerbate CC [34], a key component of cachexia [37, 38]. Additionally, nutrition impact symptoms, such as mucositis and other treatment-related or tumour-related abnormalities in gastrointestinal function, may reduce food intake [39]. However, early satiety is a primary cause of decreased consumption in cancer patients [40]. Therefore, addressing these symptoms may assist patients at various treatment stages in improving clinical outcomes, managing their disease more effectively, and enhancing their quality of life. When tackling CC through pharmacological or non-pharmacological interventions, it is essential to consider factors such as the appetite-suppressing properties of protein-rich foods [41, 42] and the phenomenon of exercise-induced anorexia [43] to ensure a more effective approach.

In the context of cancer patients, particularly older adults, the interrelated issues of anorexia, cachexia, and sarcopenia represent significant challenges due to age-related factors that contribute to decreased appetite and accelerated muscle wasting [44, 45]. Addressing these intricately linked conditions is critical to improving clinical outcomes and managing the health of these patients. Therefore, this narrative review aims to elucidate the molecular mechanisms underpinning CC and propose pharmacological and non-pharmacological strategies to mitigate this syndrome. By doing so, it aspires to inform future research and interventions that can enhance patient care and outcomes in this critical area of medical research.

2. Cancer Cachexia: a multifaceted challenge in diagnosis, progression, and impact on skeletal muscle health

Building on our focus on anorexia within the CC syndrome, as outlined in the introduction, this section expands on the complex interplay between muscle mass breakdown and anorexia in

CC. Diagnosing CC involves a blend of clinical examination, nutritional assessments, and evaluation of biochemical parameters. However, within the UK's National Health Service, full CC assessment often gets sidetracked due to time and resource constraints [46]. The progression of the CC syndrome is multifaceted, involving not only elevated inflammation, proteolysis, and metabolic shifts in multiple tissues, such as muscle and adipose tissue, but also significant changes in appetite and nutritional intake. These factors collectively contribute to the characteristic weight loss seen in cancer patients, with anorexia playing an important role [34, 35, 47], and ageing having an additional impact partly due to age-related suppression of appetite and other physiological changes [22, 27, 48-50]. In this review, we explore the specific molecular pathways contributing to anorexia within CC, examining the interplay between cytokines, hormonal changes, and treatment-related side effects, and how they collectively exacerbate this condition, with a particular focus on how these factors affect older cancer patients.

Specifically, weight loss, a significant marker in cancer patients, can result from both the disease's initiation and the side effects of its treatment [51]. This weight loss has been linked to reduced food intake, as shown by a recent multicentre study [52]; the findings that daily energy intake for patients with severely reduced intake only met about 50% of the measured resting energy expenditure are also consistent with a very low-calorie diet, typically reserved for intentional weight loss in obese patients and used in limited circumstances. Reduced food intake and C-reactive protein (an inflammatory marker) were significant predictors of severe weight loss and overall survival in the same study. Furthermore, the study found that reduced food intake was independently associated with severe weight loss, as was C-reactive protein [52].

Head and neck cancer (HNC) patients, for example, often face challenges in eating due to large tumours or aggressive treatment, which can cause dysphagia, leading predominantly to malnutrition rather than molecularly-driven cachexia [53]. On the other hand, pancreatic ductal adenocarcinoma (PDAC) presents a distinct metabolic pattern. The growth of tumours specifically within the pancreas has been identified as a potential cause of tissue wasting, likely due to diminished exocrine pancreatic function [40]. This distinct phenomenon in PDAC, is indicative of cancer cachexia attributed to compromised exocrine pancreatic function, and therefore pancreatic enzyme replacements can help counteract this tissue loss [54].

Given the prolonged effects of treatment, regular and consistent patient assessments during the cancer survivorship phase are essential. While the UK offers guidelines for nutritional management [55], achieving the recommended nutritional intakes, such as high protein, remains a challenge. With cachexia present in many cancer patients at diagnosis, its link with survival is concerning [56] . The consequences of post-surgical interventions for cachexia are yet to be fully understood. For HNC cases, where CC can result in severe consequences [57], interventions involving the use of feeding tubes have been considered. However, more research is required, especially concerning the prevalence of refeeding syndrome in HNC [58].

The widespread prevalence of CC, especially when food intake is compromised, has a profound impact on life expectancy and QoL, primarily due to muscle loss [1]. To combat this, understanding the intricacies of CC becomes crucial. Central to this fight is the preservation and promotion of muscle mass. An increase in muscle mass is closely linked to appetite and energy intake enhancements, pivotal factors in effectively handling CC [49].

Skeletal muscle size and quality are primarily determined by the balance of muscle protein synthesis (MPS) and muscle protein breakdown (MPB), which are influenced by anabolic signals and proteolytic systems [59]. Disruptions, such as in cancer, tilt this balance towards MPB, causing muscle atrophy [60, 61]. The ubiquitin-proteasome system (UPS) is a major driver of skeletal muscle proteolysis, although, the Ca^{2+}- dependent calpains and lysosomal-autophagy system also play a role [62, 63]. In the UPS, proteins are tagged with ubiquitin molecules (polyubiquitination) through ligases (E1, E2, & E3), signalling their degradation by the 26S proteasome [64]. Large cytoskeletal proteins are first broken down by Ca^{2+} dependent calpains, then further degraded by the UPS [65]. In addition, autophagy is a self-destructive process with deprivation of nutrient and low energy availability as key steps activating autophagy (i.e., AMPK), with autophagy being also a key component of adaptive cell responses during nutrient deprivation [66, 67]. The lysosomal-autophagy system involves the formation of an autophagosome, which selectively engulfs damaged organelles and proteins before fusing with the lysosome to begin enzymatic degradation [68]. Within the acidic lysosomal lumen, the engulfed organelles are degraded by cathepsin proteases [68]. Growth factors such as insulin also play a role in modulating protein balance, as activation of the PI3K/Akt signalling cascade stimulates the mechanistic target of rapamycin complex 1 (mTORc1)-dependent MPS while also inhibiting proteolysis via inhibition of Forkhead Box O (FOXO)-dependent signalling of muscle RING-finger protein-1 (MuRF-1) and atrogin-1 [69]. In cancer, elevated pro-inflammatory cytokines disrupt these pathways [60, 61].

In response to cancer, immune cells secrete interleukins (IL-1, IL-6, and IL-8), tumour necrosis factor-α (TNF-α) and transforming growth factor family members (TGF-β), growth differentiation factors, and Activin A, promoting muscle tissue proteolysis [61]. Interleukin expression, through transducer and activator of transcription-3 (STAT3) signalling, triggers

atrophic genes in muscle [70]. TNF-α interacts with nuclear factor-kappa-B, elevating atrogin-1 and inhibiting skeletal muscle regeneration [71]. TGF family members, likely mediated by glucocorticoids (i.e., cortisol) and chemotherapy, upregulate in CC [61]. Elevated TGFs (myostatin and Activin A) induce Small Mothers Against Decapentaplegic 2/3 (SMAD 2/3) signalling, leading to Akt/mTOR inhibition and nuclear translocation of FOXO [72, 73]. This results in inhibited MPS, impaired satellite cell activation, myoblast proliferation and differentiation, and upregulation of atrophic genes and the UPS via activation of atrogin-1 [74] (Figure 1). Cytoskeletal protein degradation rises in CC, perhaps due to poor Ca^{2+} homeostasis and calcium/calmodulin-dependent protein kinase II activation leading to enhanced calpain activity, as observed in patients with gastric cancer for example [75, 76]. While autophagy's role in CC is unclear, it seems more prominent in cardiac than skeletal muscle atrophy due to the heart's faster protein turnover [77]. Inflammation's role in upregulating the UPS and atrophy has largely been explored in cellular and animal models of CC which help demonstrate the causative effects of inflammation on atrophy [78]. Despite human data associating inflammatory cytokines with CC [79-81], anti-inflammatory drug trials show inconsistent results. Some suggest benefits such as reduced TNF-α expression and increased lean body mass and grip strength in cancer patients [82, 83], however challenges persist due to varied study designs and patient conditions.

Ultimately, CC increases atrophic signalling molecules while concurrently impairing anabolic signalling, leading to a significant imbalance in protein turnover in favour of muscle degradation. The combination of this pro-inflammatory state, undergoing chemotherapy, and decreased muscle mass will only serve to exacerbate the CC conditions due to increased fatigue leading to prolonged bed rest and physical inactivity [84]. This muscle wasting syndrome is indeed difficult to combat, particularly due to the supressed appetite that is synonymous with

CC and ageing populations. Understanding how appetite is regulated in populations with CC who are more likely to be of older age may give insight on how to increase energy and protein intake to alleviate increased muscle protein turnover.

3. Interplay of Age-related Anorexia and Cancer Cachexia: mechanisms and implications

Considering that around 70% of cancer patients are aged 65 or over [6], addressing age-related anorexia is essential when dealing with CC, as this demographic may encounter distinct challenges in sustaining adequate nutrition and appetite control. Age-related anorexia [85] involves multiple mechanisms, including changes in energy balance regulation [86], and disruptions to reward-based hunger drives [87]. Investigating the psycho-biological control mechanisms of satiation and satiety [88] is vital for understanding the interplay between ageing and CC in relation to appetite and dietary intakes. Appetite hormone dysregulation is common in ageing animals and humans [89, 90], with changes in satiety hormone release such as increased cholecystokinin, PYY, insulin, and leptin levels [27], and reduced hunger drive due to lower acetylated ghrelin levels and potential sensitivity to total ghrelin [91]. The combined effects of both age-related and cancer-induced appetite changes add further complexity to this interplay when dealing with older cancer patients. The CC process involves multiple endocrine signals as well as psycho-biological control mechanisms (Figure 2). Furthermore, resting basal metabolic rate (BMR), another major hunger driver, declines with age, largely attributed to the loss of fat-free mass during sarcopenia development [92]. Interestingly, increased fat-free mass in healthy older adults is associated with higher appetite and energy intake [49]. Older individuals also experience reduced taste sensitivity and higher thresholds for the five main

modalities-sweet, salt, bitter, sour, and umami-to varying degrees [93], which is attributed to a decrease in taste bud number and structure. Altered signalling in taste perception and reward centres of the brain has been observed in older adults through functional magnetic resonance imaging (fMRI) studies [86, 94]. These changes may contribute to a reduced hedonic or reward-based hunger drive during ageing, which can also affect CC.

Anorexia of ageing and CC affect appetite, with hypothalamic inflammation (locally activated pro-inflammatory pathways) and ghrelin contributing to observed alternations. The anorexia of ageing is present to a lesser extent in healthy older adults, who also experience reduced hunger and increased satiety [86], while CC remains prevalent across all ages of affected populations (Figure 2). Hypothalamic inflammation may cause neurochemical disturbances that interfere with monoaminergic neurotransmission and serotonergic activity, which are likely influencing hormone levels such as ghrelin, explaining food intake changes in patients with CC [95, 96]. Notably, active ghrelin levels and the active to total ghrelin ratio are significantly higher in patients with cancer-induced cachexia compared to noncancer controls [97], suggesting ghrelin's key role in CC [98].

Neuropeptides and hormones in CC can also influence the regulation of appetite. For example, patients undergoing esophagectomy have shown elevated postprandial levels of glucagon peptide-1 (GLP-1) compared to healthy controls [99]. A recent *in vivo* study demonstrated that cancer-induced dysregulation of neuropeptides promotes CC by tumour cell-secretion of Dilp8 binding to the Lgr3 receptor in the brain, which in turn upregulates the anorexigenic gene NUCB1 and downregulates orexigenic peptides short neuropeptide (sNPF) and NPF [100]. These peptides may promote appetitive visual memories [101] and mediate smell [102]. Interestingly, Dilp8 inhibition enabled the recovery from CC, although it was unable to restore

overall organ wasting [100]. *In vitro* treatment with INSL3 in mouse hypothalamic cells was found to activate NUCB2 and suppress NPY in a Lgr8-dependent manner, leading to significantly reduced food intake, potentially via dysregulation of agouti-related peptide (AgRP) [100]. The same authors reported an increased insulin-like3 peptide (INSL3) profile in patients with pancreatic cancer; a peptide that is secreted from tumour tissues and induces anorexia through the Lgr3 receptor in the brain. Moreover, increased levels of the G-protein-coupled receptor, sphingosine 1-phosphate receptor (S1PR1), in hypothalamic pro-opiomelanocortin (POMC) neurons persistently activating STAT3 and the melanocortin system in rat models may further describe dysregulated energy homeostasis during CC [103]. Disturbance of the hypothalamic STAT3 signalling leads to abnormal neurotransmitter stimulation, accompanied by anorectic responses [104]. Leptin injections could enhance STAT3 activation in multiple hypothalamic regions [105], further elucidating its involvement in CC. Stimulation of calcitonin gene-related peptide (CGRP) neurons may also mediate anorexigenic responses during CC, considering that inactivation of CGRP neurons in the parabrachial nucleus promotes hyperphagia in mice implanted with Lewis lung carcinoma cells [106]. CGRP neurons are stimulated in the external lateral parabrachial nucleus (PBel) and suppress food consumption via inhibition of hypothalamic AgRP neurons that induce orexigenic effects [107].

Dysregulation of neuropeptides and hormones can hinder food consumption in CC, partly due to increased secretion of circulating cytokines such as TNF-a, which has been linked to heightened bitterness in animal models [108]. A murine model can be used for laryngeal chemosensory research, as human and mouse larynges contain chemosensory cells and nerve fibres that respond to chemical stimuli similarly [109]. Elevated serum macrophage inhibitory cytokine 1 (MIC-1)/growth differentiation factor-15 (GDF-15) levels have been implicated in

297 decreased energy intake [110], BMI [111, 112], and severe appetite loss [113]. GDNF-family
298 receptor α-like (GFRAL), a high-affinity receptor for GDF-15, binds to GDF-15 *in vitro* and is
299 necessary for its metabolic effects on body mass and calorie intake *in vivo* in mice [113].
300 GFRAL is solely expressed in hindbrain neurons, suggesting a central mechanism by which
301 GDF-15 controls food intake [113]. MIC-1 may suppress appetite through interaction with the
302 TGF-B type II receptor in the hypothalamus, where it also increases and decreases
303 neuropeptide Y and POMC expression, respectively, in the arcuate nucleus [114]. TNF
304 secretion in sweet and umami taste bud cells expressing the taste receptor T1R3 [115], and
305 interleukin-10 (IL-10) in type II bitter cells [116], suggest that dysregulated inflammatory
306 signalling may alter taste perception, although their peripheral appetite responses in humans
307 remain largely unknown. A recent study found that emergency bowel surgery patients,
308 including cancer patients, experienced worse palatability symptoms than elective cancer
309 surgery patients [117], possibly due to increased inflammatory markers such as TNF-a.
310 However, these markers were not measured in the feasibility study, which focused on
311 postoperative nutritional supplement acceptability. In the context of ageing, individuals with
312 poor physical, mental, or social health may experience exacerbated effects due to factors such
313 as increased inflammation, which has been associated with poor appetite in general hospitalised
314 older populations [118]. Older individuals diagnosed with cancer are likely to exemplify those
315 experiencing worsened anorexia of ageing; however, it is crucial to understand the additional
316 impact specifically of CC on this, considering the high prevalence of cancer in this age group.
317
318
319 ***4. Pharmacological and non-pharmacological means to address and manage CC***
320

Management of CC through pharmacological methods has been a subject of debate due to varying levels of evidence in clinical practice, leading to consensus-based guidelines rather than ones based on large scale clinical trials [119]. In this context, special attention is needed for older cancer patients. Considering the age-related physiological impairments in organ function that affect drug metabolism and pharmacokinetics [120], these patients require pharmacological approaches that are specifically tailored to their altered metabolism and drug sensitivity. Diverse pharmacological options have been proposed to treat CC's complications and symptoms, given its unidentified single aetiology. The options fall into four categories: drugs to alleviate symptoms of nausea, reduce gastric acid secretion, manage diarrhoea and constipation, stimulate mood to aid appetite, and a combination of drugs to potentially enhance the anabolic aspects of metabolism.

In a holistic approach to cancer management, non-pharmacological strategies play a key role in managing CC. These rapidly evolving strategies, including exercise regimes, the use of complementary medicine, psychosocial, and nutritional interventions, complement formal treatment modalities are an integral part of the treatment plan, with special considerations for the unique needs and limitations of older cancer patients, ensuring personalised and effective treatment plans [121].

5. *Pharmacological means to address CC*

5.1. Antidepressants and appetite stimulants

Mirtazapine, a noradrenergic and serotonergic antidepressants that promotes sleep, offers a multifocal approach to addressing CC by promoting sleep, increasing appetite, and regulating mood [122, 123]. Its use in older patients with CC requires careful monitoring due to the increased risk of adverse drug events, medication non-adherence, and potential interactions with other medications commonly prescribed in this age group [124]. It can also improve gastric motility as a 5HT1A receptor agonist, potentially leading to weight gain [125]. While small studies have found that up to 24% of patients gained at least 1 kg after 4 weeks of mirtazapine treatment (15 to 30 mg), larger scale trials are required to confirm these findings [126]. Although weight gain was not reported in terms of muscle mass or body fat, these results are encouraging to avoid negative energy balance states that lead to accelerating muscle catabolism [126]. In contrast, a recent study administering mirtazapine (15 mg/d) for 8 weeks in a younger patient cohort (~50 year average age) with CC did not display greater appetite scores compared to placebo [127], while in an open-label study, 7 weeks with mirtazapine treatment led to small increases in appetite in older cancer patients (average age over 60 years) [128]. Hence, the available evidence for mirtazapine does not currently advocate for its efficacy in promoting appetite, especially in younger cancer patients, but it may be more beneficial in older patients. Other psychotropic medications being explored include olanzapine, which has shown promise in a recent trial [129]. Administered at a low dose (2.5 mg daily) alongside chemotherapy, olanzapine significantly enhanced appetite and weight gain in patients with advanced malignancies, with 60% of patients in the olanzapine group gaining more than 5% body weight. This intervention also led to improved quality of life with minimal side effects, highlighting its potential utility in CC management [129].

Appetite stimulants that have been studied in the context of cancer include ghrelin-receptor agonists and cannabinoids [119]. These agents could be particularly beneficial for older patients with CC, considering their potential to stimulate appetite and address age-related anorexia, a significant contribution to undernutrition and adverse health outcomes in older adults [130]. Ghrelin, while showing promising appetite-stimulating effects in patients with gastrointestinal [131] and oesophageal cancer [132], has limited use due to its short half-life, parenteral mode of delivery, and restricted availability. Anamorelin, a ghrelin-receptor agonist, holds promise for improving appetite scores, meal enjoyment, and physical condition in patients (average age over 60 years) with non-small cell lung cancer over 12 weeks following a 100 mg dose [133, 134], alongside increases in lean mass [135]. Likewise, even lower doses (50 mg/d) for a short duration (3 days) can promote greater appetite and increase body weight compared to placebo [136]. Ongoing 24-week trials (NCT03743064, NCT03743051) are investigating the efficacy of anamorelin in counteracting CC in patients with non-small cell lung cancer. Preliminary findings from one of those studies showed that anamorelin improved body weight and anorexia-related symptoms in patients with CC and a low BMI, demonstrating durable efficacy and favourable safety and tolerability [137]. However, other agents such as melatonin, despite their potential appetite-stimulating properties, by reversing hypophagia in male Wistar rats through suppression of the serotonin type 2A (5-HT(2A)) receptor [138], no benefits have been observed in advanced cancer patients following 4 weeks of 20 mg daily oral administration [139].

Cannabinoids, acting as neurotransmitters through G-protein coupled receptors, have the potential to improve appetite and regulate weight [140]. Their use in older cancer patients necessitates caution due to impaired metabolism, potential for drug interactions, and increased

sensitivity to drug-induced side effects [141]. Strict prescription policies and side effects such as hallucinations, vertigo, and cardiovascular risks limit their use [119]. Delta-9-tetrahydrocannabinol (THC) initially showed promise in stimulating appetite in patients with advanced cancer, however, in a placebo-controlled RCT, subjective appetite scores between groups, which also included a placebo, did not differ following a 2.5 mg dose twice daily for 6 weeks [142]. Interestingly, in a double-blind pilot RCT, THC enhanced chemosensory perception and food taste and led to greater caloric intake in the short-term (18 days). This study adopted an incremental dosage protocol, with the majority of patients receiving 5 mg/d [143]. The discrepancies between these studies [142, 143] studies could be due to various methodological reasons, such as dose protocol, population, and choice of tests to measure appetite. For instance, the study by Brisbois et al. [143] initiated patients at a low dosage during the first three days to build tolerance and minimise adverse effects. They also used tools that were more sensitive than those employed by Strasser et al. [142] to assess appetite. In the latter multicentre instigation [142], which was conducted across different countries and thus implies potential population disparities, there was also a high incidence of adverse events, participant withdrawals, and deviations from the stipulated protocol. Moreover, another cannabinoid, nabilone, has failed to enhance appetite in lung [144] and neck cancer patients [145], concluding that evidence for medicinal cannabis use in enhancing appetite to counteract CC is limited [146]. An ongoing clinical trial utilising an anti-GDF-15 agent is investigating its impact on CC patients with advanced cancer (NCT04803305).

5.2. Anabolic drugs

Anabolic drugs have been suggested for their properties of alleviating anabolic resistance during ageing, but also for their appetite-stimulatory effects, however, they also require careful

consideration in older cancer patients due to the potential adverse effects and medication interactions. In patients following surgery for esophageal cancer, 5 injections (50 mg each) of nandrolone decanoate over 3 months did not display significant changes compared to placebo [147]. No major side effects were observed in the latter study, however, use of anabolic steroids such as nandrolone decanoate can have serious adverse effects, mainly of an endocrine nature [148], which can potentially influence adaptive responses. For example, progesterone analogues such as progestins, a class of anabolic steroids, have been shown to improve the appetite, weight, and quality of life of patients with cancer, although side effects include thromboembolic events, oedema, and are associated with high rates of death [119, 149, 150]. Studies utilizing medroxyprogesterone acetate, a steroid and derivative of progesterone, for 6-12 weeks in advanced cancer stimulated appetite and increased food intake, although these outcomes were insufficient to benefit lean body mass and functional performance [151, 152]. Interestingly, non-steroidal selective androgen receptor modulatory drugs such as enobosarm, have shown increased appetite scores in obese cancer patients following oral administration of 1 mg, however, this effect was alleviated in the groups receiving 3 mg/d [153]. Moreover, administration of the steroid megestrol acetate has been considered the most tested product concerning CC. For over 3 decades, multiple trials have consistently displayed a positive effect against CC, promoting appetite and food intake [154-180]. Side effects of megesterol administration include central nervous system effects, adrenal insufficiency, and thromboembolism at high doses [181]. Research is needed to identify the most effective megestrol acetate dose, duration, patient age, and cancer stage that can be most beneficial. Notably, the development of anabolic drugs that will accompany the appetite-stimulating effects with lower rates of side effects is warranted. Finally, acceptable and effective treatments may include the use of non-steroidal drugs such as long-acting insulin; Lundholm *et al.* (2007) found that insulin stimulated carbohydrate intake and increased whole body fat without

affecting lean tissue mass in patients with mainly advanced gastrointestinal malignancy [150]. Importantly, survival rates in insulin-treated patients improved.

5.3. Cytokine mediators and corticosteroids

The potential of pro-inflammatory cytokines, such as TNF-a, to reduce appetite and influence mood by acting on brain receptors has brought attention to cytokine mediators to regulate appetite. Cytokines act on hunger centres in the hypothalamus; they can induce anorexia, while they can also interfere with glucose transport into the cells, as demonstrated by decreased concentrations of GLUT-4 transporters in stressed muscles as a result of downregulation of protein synthesis by TNF-α [182]. The drug thalidomide, despite its toxicity and serious side effects [183], has been shown to suppress and downregulate the stimulation of the inflammatory cytokine TNF-a and inhibit the transcription factor NFκB, promoting anti-inflammatory properties [184-186]. Daily administration (200 mg) of thalidomide in patients with advanced pancreatic cancer has exhibited small increases in weight gain (0.37 kg) and arm muscle mass (1.0 cm^3) after 4 weeks, while it attenuated weight and lean body mass losses compared to placebo at week 8 [187]. The risk of side effects from thalidomide, such as peripheral neuropathy, may be of particular concern in the older patient population [188]. A shorter-term trial (2 weeks) also showed that 100 mg thalidomide led to lower appetite loss compared with placebo, although the cytokine profile was not statistically different between groups [189]. Other drugs purported to have anti-inflammatory properties, such as pentoxifylline and infliximab, revealed no efficacy in preventing appetite losses during CC [190, 191]. In fact, the trial using infliximab was terminated early due to associations with increased fatigue and reduced quality of life in the intervention group of non-small cell lung cancer patients [190]. In individuals with advanced cancer who were receiving opioids, a 7-

day course of methylprednisolone (16 mg/2x/d) resulted in reduced fatigue and appetite loss, leading to greater satisfaction in patients compared with participants in a placebo group [192].

5.4. Drug combinations

Multiple clinical trials have utilised a combination of pharmacological agents aiming to alleviate appetite losses in CC, with polypharmacy and drug interaction risks being particularly prominent in older patients [124]. A regimen of megestrol and thalidomide have been shown to be more effective in promoting appetite and weight gain than megestrol alone [193, 194], although studies replacing thalidomide with celecoxib did not display more beneficial effects compared to controls [195, 196]. Interestingly, a formula containing megestrol acetate, celecoxib, l-carnitine, and antioxidants vs. megestrol acetate alone for 4 months in patients with gynaecological cancers led to increased appetite, lean body mass, fatigue management, and global quality of life [197]. Another trial has shown a promising impact of formoterol (80 μg/d) and megestrol acetate (480 mg/d) for up to 8 weeks in reducing lack of appetite scores in patients with advanced malignancy, although a control group was not involved [198]. Identical findings regarding higher appetite have been observed in trials incorporating megestrol acetate alongside another pharmacological agent compared to megestrol acetate alone, including olanzapine [199], but not combined with prepulsid [200]. An important focus for future research investigating the efficacy and effectiveness of available treatments is to explore the singular and combined effects of both pharmacological and non-pharmacological interventions.

6. Non-pharmacological means to address CC:

6.1. Exercise

Exercise plays a significant role in the treatment of conditions leading to sarcopenia or cachexia, as loss of muscle mass is a key event in these processes [201]. For older cancer patients, preserving muscle mass through muscle-targeted pro-anabolic strategies is crucial for maintaining independence and quality of life, especially following chemotherapy or during cancer treatment [202, 203]. Recent findings in older healthy adults also suggest that an increase in lean mass is associated with a higher appetite, suggesting the maintenance or alleviation of muscle mass losses may be a potential strategy to combat CC [49]. Exercise not only reverses muscle loss and slows down the acceleration of sarcopenia, but it also enhances immune function, improves energy metabolism, and reduces cancer and tumour progression [204]. Older patients may need tailored exercise programmes considering their specific physical limitations and health status; evidence suggests a shift towards decentralised care, emphasising the development of rehabilitation programmes for older cancer patients before or after anti-cancer therapy [205]. Furthermore, and considering that fatigue, anorexia, and cachexia are some of the most prevalent symptom clusters that significantly worsen quality of life in cancer [206], any therapies to alleviate these symptoms can be hugely beneficial to cancer patients. For example, it is known that exercise can help with the restoration of physical functioning, improvement in quality of life, and mitigation of cancer-related fatigue, therefore, any attempts to engage in exercise pre-, peri-, and post-operatively can improve common cancer-related health outcomes such as anxiety, fatigue, physical functioning, and health-related quality of life [207]. More importantly, patients with low physical functioning and high fatigue are more likely to benefit with regards to fatigue and physical function from exercise interventions during and post-cancer treatment, while during treatment patients benefit with regards to muscle strength and quality of life regardless of baseline values [208]. Astonishingly, exercise is also three times more beneficial than pharmacological treatment for combating fatigue [209]. This is particularly relevant for older patients, who may be more prone to fatigue

[210]. Previous systematic reviews have not confirmed the benefits of any type of exercise (i.e., aerobic or resistance exercise) to stimulate appetite in patients with cancer [211, 212]. However, the above findings are not unexpected for two main reasons: a) appetite is more likely to be enhanced when an exercise intervention is likely to result in an increase in lean mass, as it has been shown in healthy older adults [49], while lean mass was not a key outcome measure in the majority of selected studies; and b) either aerobic or resistance exercise can acutely/temporarily suppress appetite [43, 213, 214] -a phenomenon called exercise-induced anorexia- thus to gain a more accurate picture of the impact of exercise on appetite in cancer patients, appetite data should be obtained across different timepoints and not in close proximity following the completion of exercise. More recent studies have shown that resistance exercise for 12 weeks and intensified physiotherapy consisting of endurance and muscle force exercise may attenuate appetite loss in gastrointestinal cancer patients [215] and after pancreatic cancer resection [216], respectively. However, in one trial, patients were quasi-randomised [215], raising questions about participants' allocation of treatment, while similarly to other studies lean mass was not a key outcome measure. Finally, the mechanistic link between intensified physiotherapy and appetite modulation in CC is currently unknown. It is also important to note that exercise is often part of a multimodal intervention approach combined with nutrition, pharmacological, and psychological strategies to improve outcomes in CC. Therefore, a comprehensive, synergistic approach to combining exercise with other treatments is anticipated to have a greater impact on preserving lean mass and improving clinical outcomes than exercise alone.

6.2. Nutrition

Nutritional interventions for cancer-related cachexia are dependent upon the defined stage of cachexia (pre-cachexia, cachexia, or refractory cachexia), and its functional impact [217].

Unlike starvation, which can be addressed by refeeding, cachexia is less responsive to nutritional interventions, and current data suggests that it cannot be reversed by feeding alone. The catabolic state, inflammatory basis, and negative protein–energy balance of cachexia, combine to reduce Activities of Daily Living (ADL) and QoL [217]. Optimal nutritional interventions are therefore multimodal in nature, combined with exercise and pharmacotherapy to address muscle mass loss. The inclusion of dietary supplements, such as probiotics, has been identified as a promising area for further research. Studies have demonstrated that probiotics can reduce serum pro-inflammatory biomarkers, which may in turn alleviate some symptoms of CC and increase the tolerability of chemotherapy by reducing its side effects [218]. This highlights the potential of probiotics to improve treatment outcomes in CC by supporting both nutritional and therapeutic needs without adding side effects. For older patients, achieving the recommended targets for energy and protein intake in particular [219] can be challenging, necessitating more personalised and feasible dietary strategies.

CC is a disease-related sub-type of malnutrition, and decisions on nutritional intervention therefore benefit from utilising defined key criteria; a weight loss greater than 5% in the previous 6 months or corresponding to 2–5% for patients with a BMI $\leq$ 20 kg/m^2 or with sarcopenia [217]. Alternatively, cachexia can also be defined through the Evans' criteria, accompanying weight loss of at least 5% in 12 months or less (or BMI $\leq$ 20 kg/m^2) and three of the following factors: decreased muscle strength; fatigue; anorexia; low fat-free mass index; abnormal biochemistry (increased CRP, IL-6; haemoglobin < 12 g/dL; serum albumin < 3.2 g/dL) [220].The American Society of Clinical Oncology (ASCO) [221], European Society for Oncology (ESMO) Clinical Practice [222], and ESPEN practical guidelines [223] all recommend detailed nutritional assessment and screening as the basis for interventions. While nutritional requirements for CC are evolving, the focus remains on increasing or at least

maintaining energy and protein intake. ESPEN suggests an energy intake of 25 - 30 kcal/kg/d and protein intake between 1g/kg/day to 1.5g/kg/d [223] with some advocating even higher protein intakes of 1.2–2 g/kg/d, especially for patients with high sarcopenia prevalence [222]. The above recommendations (i.e., energy intake ~ 30 kcal/d and protein intake ~1.2 g/d) have been integrated into the official guidance for the nutritional management of HNC, for example [55], but achieving these targets can be a challenging and lengthy process. Recent findings indicate that protein intakes below 1.2 g/kg may lead to muscle wasting in cancer patients, even when within recommended levels; in contrast, a mean intake above 1.4 g/kg has been associated with muscle maintenance during treatment in patients with high sarcopenia prevalence cancers [224], highlighting the need for higher protein intake thresholds and revised dietary guidelines for older cancer patients undergoing treatment. Additionally, the source of protein should be considered, as a combination of both animal- and plant-based proteins is suggested to provide the most beneficial amino acid profile for muscle anabolism in cancer patients [225]. Furthermore, emerging evidence suggests that dietary supplements, especially probiotics, may play a beneficial role in managing CC by modulating systemic inflammation and improving nutrient absorption, thus supporting the nutritional status of GI cancer patients [218]. In the context of CC, bioelectrical impedance analysis emerges as a valuable and practical tool for older adults for non-invasive assessment of body composition, offering insights into the effectiveness of interventions aimed at mitigating muscle wasting and improving nutritional status [226].

Nutritional interventions typically follow a staged nutrition approach, starting with dietary enrichment with energy and protein, then introducing oral nutritional supplements, with the understanding that this should be pre-emptive and initiated early in the cachexia process [223]. However, one of the key recommendations is that dietary provisions that restrict energy intake

589 should be avoided by cancer patients with or at risk of malnutrition should avoid dietary
590 provisions that restrict energy intake. It is worth noting that protein, including both intact food
591 and supplement sources, is the most satiating of all macronutrients [22, 227-229] and may
592 therefore suppress appetite and influence energy intake [22, 228]. A number of mechanisms
593 may be responsible for the satiating effects of protein [88, 230, 231], but it has recently been
594 proposed that non-essential amino acids, which could activate orexin cells and reduce feeding
595 via greater hypothalamic orexin activity [232], are partly responsible for the appetite-
596 suppressing properties of protein. Therefore, dietary provisions, that may include
597 supplementation with all or certain essential amino acids (EAAs), may be a more effective way
598 for optimising daily and "per-meal" protein intake since a) the effective management of
599 sarcopenia depends on the quantity and quality (i.e., EAAs) of protein consumed on a more
600 refined 'per meal' basis [233], with the associated increase in plasma concentration of essential
601 amino acids (EAAs) and L-leucine as key drivers for the increase in protein synthesis rates
602 [234-236]; b) EAAs are not resulting in suppression of appetite to the same extent as protein
603 and ultimately will not exacerbate energy deficiencies.
604
605 Indeed, anorexic patients with cancer following consumption of branched chain amino acids
606 (BCAAs) (4.8 g/3x/d) showed a lower rate of anorexia in 7 days vs. baseline compared to
607 placebo [237]. Furthermore, EAA-based supplementation may promote non-satiating
608 properties and serve as an effective strategy to improve musculoskeletal health in individuals
609 at high risk of anorexia and negative energy balance [25]. This has been confirmed by previous
610 research, in which authors administered older women with an L-leucine-enriched EAA-based
611 gel or bar supplement alongside a breakfast meal, which revealed higher appetite scores
612 compared to the comparator group (received no intervention) [238], while the same group also
613 showed that EAA supplements in gel format are superior to protein supplements since they

resulted in an increase in both energy and protein intakes [228]. In another study, 36 g/d of protein supplementation for 12 weeks also exhibited greater appetite in patients with colorectal cancer compared to controls, however, the amino acid composition of the product was not mentioned [239].

While fish oil supplementation has shown promise in counteracting CC by enhancing appetite and caloric intake in CC [240-243], and when combined with protein supplementation [244, 245], the results are mixed, and further research is needed to determine the minimum effective treatment duration. For instance, one study reported no significant differences in subjective appetite response with 1 g/d of fish oil compared to placebo, possibly due to a relatively short treatment duration (2 weeks) [246]. The aforementioned studies showed a benefit at 8 weeks, therefore, it is critical to consider a minimum effective treatment duration. Supplementary research has indicated significant benefits from baseline after 6 weeks [247], although another trial failed to assist appetite, utilising an identical duration [248]. The proposed mechanism for fish oil's appetite-stimulating effects involves the free fatty acid receptors FFA1 and FFA4, which play an important role in regulating energy metabolism [249]. Similarly, marine phospholipids have also demonstrated a significant benefit in stimulating appetite in patients with CC [250, 251]. In contrast, other nutritional supplements, such as creatine monohydrate, have not shown any benefits in CC [252].

Clear guidance for a more aggressive nutritional approach using enteral nutrition (EN) is predicated on an inability to meet energy requirements, which can be defined as less than 50% of the requirement for more than one week or only 50-75% of the requirement for more than two weeks [223]. With no evidence of proven benefits, ASCO Guidance strongly recommends that neither enteral nor parenteral nutrition be used in advanced cachexia [221]. This

recommendation is consistent with the observation that while EN can improve body weight and energy intake, it does not enhance survival [253, 254]. Nevertheless, a recent meta-analysis showed that EN may be a suitable strategy for CC patients aiming to improve their appetite profile [255].

6.3. Psychosocial interventions

Psychosocial support in the form of nutritional counselling, cognitive behavioural therapy (CBT), and therapeutic counselling are all modes of enhancing the treatment of CC for the patient [256, 257], exerting positive effects on appetite [258]. These interventions may be especially beneficial for older cancer patients, helping them cope with the psychological burden of cancer and cachexia and improve adherence to nutritional and treatment plans [259]. Mindfulness, motivational reframing, and relaxation techniques help achieve the patient's nutritional goal through a multipronged approach of dieticians, family members, and clinicians [121]. These help the patient's self-management goals to continue with plans that have been designed and agreed upon maintaining positive behaviour change to manage symptoms and provide feedback about their adherence. There are robust theories that underpin the processes employed to help a patient with CC cope and adapt to achieving their goals of nutrition and compliance with pharmacological treatments; these empower the individual to navigate their journey of cancer as a whole, but also enable them to take control of the treatment and management required to address CC [260] (Figure 3).

6.4. Strengths and limitations

This article provides a comprehensive overview of the molecular mechanisms underpinning CC, offering detailed insights into several pharmacological and non-pharmacological treatments, with a particular focus on older individuals. The multidisciplinary approach of the

review, involving clinicians, practitioners, and researchers in both cancer and exercise physiology and nutrition disciplines, is a significant strength. The detailed exploration of molecular pathways also offers novel insights, enhancing our understanding of potential therapeutic strategies for CC. Nevertheless, there are several limitations to this review. The increased heterogeneity across studies, especially those relevant to specific types and stages of cancer, hinders the generalisability of our findings, potentially limiting the effectiveness of treatment strategies across the broad spectrum of CC. The rapid evolution of research in this area means that new studies may have emerged during the submission, peer review, and publication process of this article. Consequently, some of our conclusions might not fully reflect the most current developments in research treatments. The quality of the evidence from the included studies may vary since a systematic approach to individually assess and grade each study was not undertaken. This could affect the reliability of our conclusions. Due to the subjective nature of evaluating the impact of each treatment and the increased heterogeneity across studies, quantifying the effectiveness of individual treatments is challenging. Therefore, future meta-analyses may provide more objective measures of effectiveness amongst different options aimed at counteracting CC.

7. Conclusions

Cancer cachexia, a significant factor in cancer-related muscle wasting, requires a comprehensive treatment approach, especially in older patients. This approach should combine pharmacological options such as megestrol acetate, anamorelin, thalidomide, THC, and olanzapine alongside non-pharmacological strategies such as nutritional counselling, cognitive behavioural therapy, enteral nutrition, and essential amino acid supplementation. Emerging evidence on the efficacy of probiotics in enhancing gut microbiota and systemic inflammation control adds a promising dimension to these treatments. Our review highlights the central role

of cytokines in the molecular pathways of cancer cachexia, especially in exacerbating muscle wasting and anorexia in older patients, which can guide the development of targeted therapeutic strategies. A critical focus remains on addressing protein and energy intake, particularly during periods of energy deficit. Future research should strive to refine appetite-stimulating drugs with fewer side effects and understand how nutritional factors can specifically enhance appetite or minimise suppression of appetite in older populations. Effectively managing cancer cachexia in this demographic is key to improving clinical outcomes, patient satisfaction, and the overall success of both pharmacological and nonpharmacological interventions.

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Figures

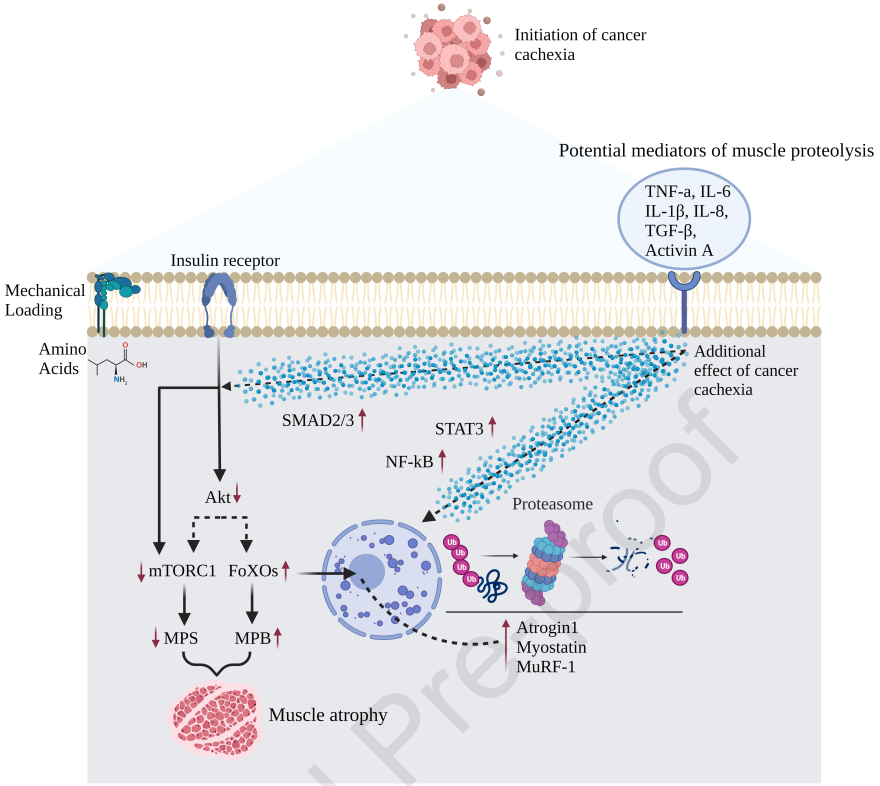
Figure 1. Potential mechanisms related to inflammatory responses describing the extra impact of CC on muscle proteolysis based on animal and human studies. Akt, protein kinase B; FoXOs, forkhead box transcription factors; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; MPB, muscle protein breakdown; MPS, muscle protein synthesis; mTORC1, mammalian target of rapamycin complex 1; MuRF-1, muscle RING-finger protein-1; NF-kB, nuclear factor-kappa beta; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TNF-a, tumour necrosis factor-alpha.

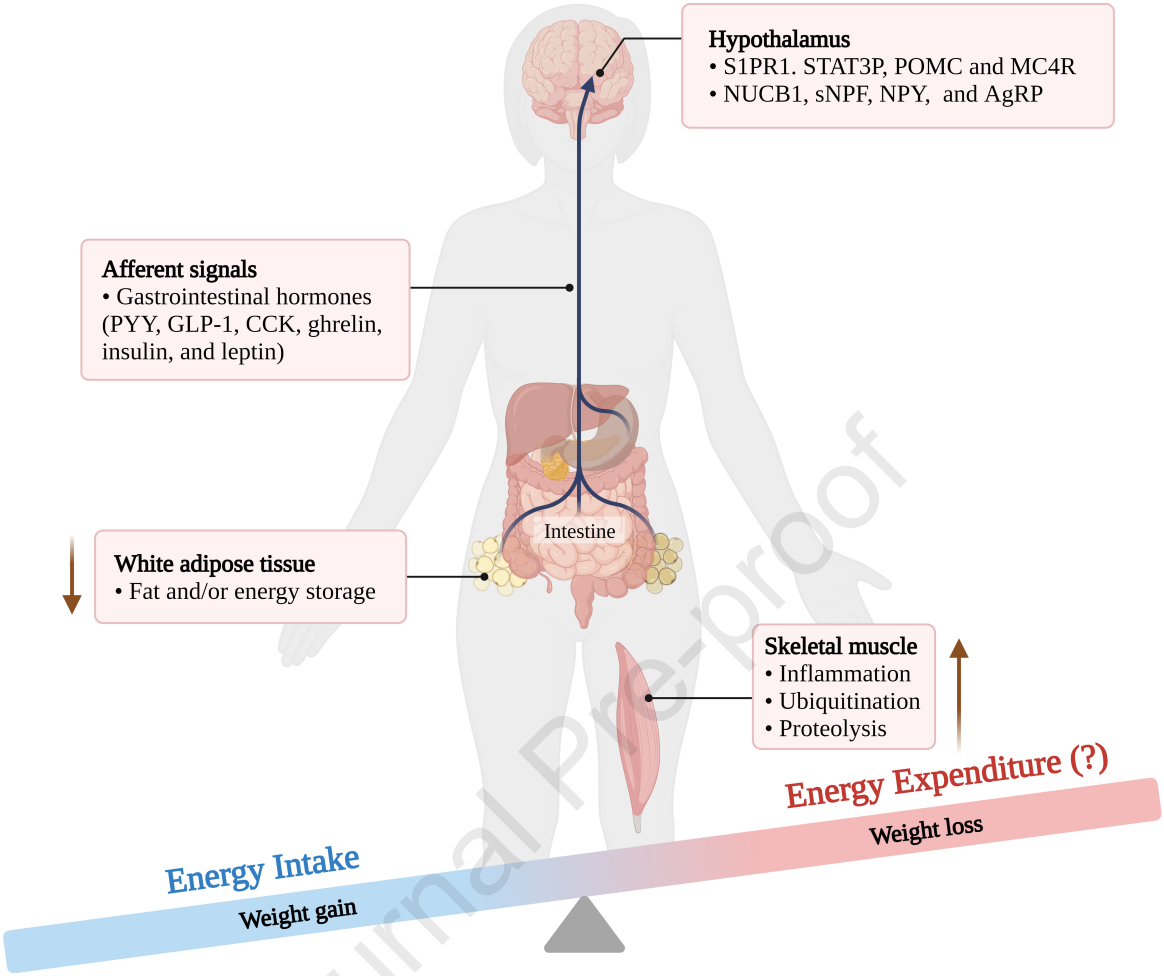
Figure 2. Description of potentially relevant mechanisms involved in appetite dysregulation during CC. AgRP, agouti-related peptide; CCK, cholecystokinin; GLP-1, glucagon peptide-1; MC4R, melanocortin 4 receptor; NUCB1, nucleobindin 1; POMC, proopiomelanocortin; PYY, peptide YY; S1PR1, Sphingosine-1-Phosphate Receptor 1; phospho-signal transducer and activator of transcription; sNPF, short neuropeptide F.

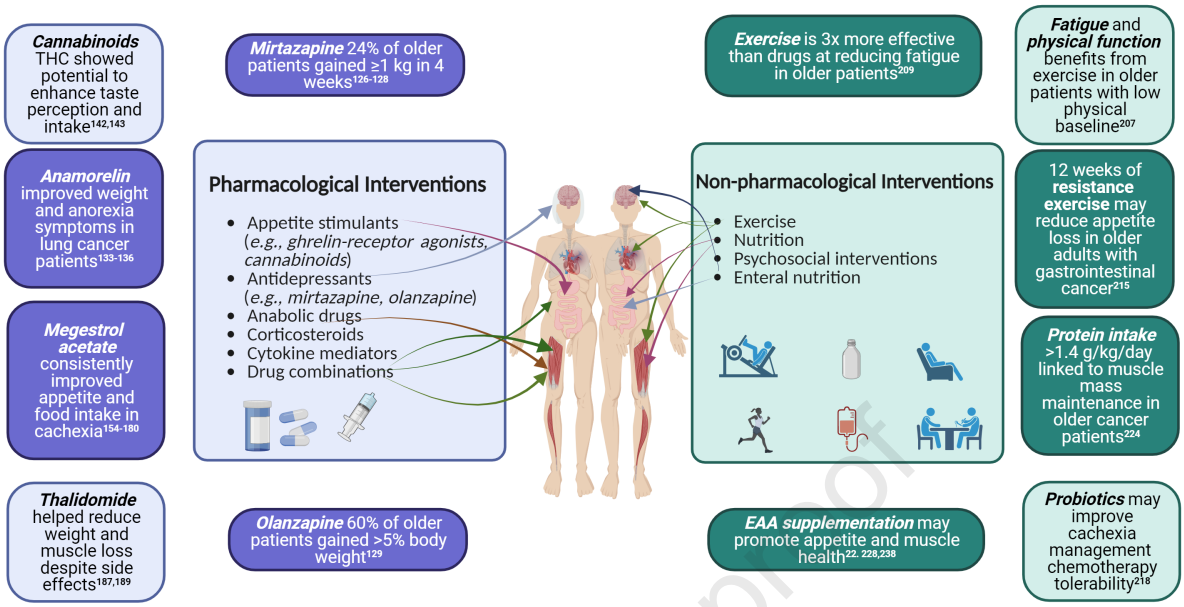
1405

1406 **Figure 3.** Potential investigational, pharmacological, and non-pharmacological strategies for

1407 the treatment of CC.







Practical Considerations

1. Regularly check glucose levels for hyperglycaemia in older patients prescribed corticosteroids.
2. ***Closely monitor for drowsiness and potential polypharmacy interactions with mirtazapine.***
3. Tailor exercise programmes to individual capabilities and limitations of older CC patients.
4. ***Adjust nutritional plans to older cancer cachexia patients' altered taste and digestive function, ensuring high protein and caloric needs are met.***
5. Monitor for gastrointestinal side effects in older patients using anamorelin and other appetite stimulants.
6. ***Consider individual patient tolerance and potential interactions when using nutritional supplements, such as probiotics with other treatments.***

References cited in this figure are listed after those that have been cited in the text.