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Review Article

Cancer cachexia: Current strategies and future perspectives

Pranali S Kalambe¹, Shubhada V Mangrulkar^{1,*}, Dhanashri T Jawald¹,
Mayuri K Sonkusared¹, Sudarshan Behered¹, Dinesh R Chaplec¹¹Priyadarshini J. L. College of Pharmacy, Nagpur, Maharashtra, India

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ABSTRACT

Cancer cachexia is complex, and can often occur in the presence of malnutrition, age-related changes in anabolism, physical deconditioning and comorbidity. These factors can also form potentially reversible components of the overall 'cachexia burden'. Separating cancer cachexia from the effects and complications after cancer therapy is often difficult. This review aims to briefly describe cancer cachexia and these novel biological agents currently under investigation for the treatment of cancer –related cachexia. Treatment that can be reduces the muscle wasting which is resulting into cancer cachexia. The main aim of review is to the potential treatment for cancer cachexia, which include Pharmacological, non-pharmacological, neutraceutical and investigational new treatments.

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1. Introduction

Cachexia is a multifactorial infection portrayed by weight reduction through skeletal muscle and fat tissue misfortune, awkwardness in metabolic guideline, and decreased food consumption. It is brought about by components of catabolism delivered by tumours in the fundamental course as well as physiological factors, for example, the imbalanced fiery initiation, proteolysis, autophagy, and lipolysis that may happen with gastric, pancreatic, oesophageal, cellular breakdown in the lungs, liver, and entrails malignant growth. Disease cachexia not just adversely influences the personal satisfaction of patients with malignant growth yet additionally lessens the viability of hostile to disease chemotherapy and builds its poisonousness, prompting expanded malignancy related mortality and consumption of clinical assets. Right now, there are no powerful clinical intercessions to totally turn around cachexia and no endorsed drugs. Sufficient

wholesome help is the principle strategy of cachexia treatment, while drugs that focus on the restraint of catabolism, cell harm, and extreme enactment of irritation are under examination.¹

Cancer cachexia is an insidious syndrome that not only has a dramatic impact on patient quality of life, but is also associated with poor responses to chemotherapy and survival. Indeed, cachexia occurs in the majority of terminal cancer patients and, according to Warren, is responsible for the death of 22% of cancer patients.^{1,2} Current therapies focus on palliation of symptoms and the reduction of distress of patients and families rather than cure.³ In many cases, cachexia remains a largely underestimated and untreated condition. Approximately half of all patients with cancer experience cachexia, with the prevalence rising as high as 86% in the last 1-2 week of life, and with 45% of patients losing more than 10% of their original body weight over the course of their disease progression. Death usually occurs when there is 30% weight loss.⁴ The best management strategy of cancer cachexia is to treat the underlying cancer as this will completely reverse the cachexia syndrome. Unfortunately, this remains an

* Corresponding author.

E-mail address: shubhadamangrulkar@gmail.com (S. V. Mangrulkar).

infrequent achievement with advanced cancers. A second option could be to counteract weight loss by increasing nutritional intake, but since in the majority of cachectic patients anorexia is only a part of the problem, nutrition as a unimodal therapy has not been able to completely reverse the wasting associated with cachexia.⁵

2. Mediators of Cancer Cachexia

2.1. Tumor necrosis factors

Tumor necrosis factor alpha (TNF α , otherwise called cachectin) has since quite a while ago been appeared to assume a part in murine models of Cancer Cachexia. But ordinarily engaged with intense stage response setting off and apoptosis, TNF α can likewise advance tumorigenesis and metastasis, furthermore, has been appeared to go about as an autocrine development factor for different tumor types.⁶ Early investigations demonstrated that TNF α had the capacity to restrain separation of both skeletal myocytes furthermore, adipocytes, while it caused decreased protein content also, higher corruption of myofibrillar proteins in separated skeletal myocytes, in a period and portion subordinate way.

2.2. Interleukins

A portion of the cytokines having a place with the class of interleukins (ILs) have been appeared to essentially add to tumor development also, Cancer Cachexia. Most importantly, coursing interleukin-6 (IL-6) is perceived as one of the primary variables prompting the flare-up of cachexia. For example, huge convergences of IL-6 were distinguished in the serum of cachectic mice relocated with a cachexia-prompting colon-26 adenocarcinoma (C26) subtype, where serum level of IL-6—however not that of TNF α —associated with seriousness of the obsessive status.

2.3. Interferon Type II

INF γ , the lone individual from the sort II class of interferons, has a basic part in inborn and versatile invulnerability against viral diseases, advances enactment of macrophages and applies mellow antiproliferative consequences for certain cell types. In any case, a few investigations have announced a part for this cytokine in upgrade of tumor development, metastasis and improvement of CC. Bare mice infused with hereditarily designed ovary tumor cells (CHO) delivering murine INF γ created serious cachexia, in opposition to those vaccinated with the parental tumor cell line (7). In like manner, when mice infused with CHO/INF γ cells were treated with hostile to INF γ monoclonal antibodies, advancement of cachexia was forestalled.⁷ In line with this, early or late treatment of Lewis lung carcinoma (LLC)-bearing mice with against INF γ monoclonal antibodies was appeared to

balance movement of cachexia.

2.4. MicroRNAs

Throughout the most recent decade, a few evidences were acquired about the inclusion of non-coding RNAs, specifically microRNAs (miRNAs), in loss of lean and fat mass under cachectic conditions. In their development structure, miRNAs are 21–23 nucleotides long and apply a very much perceived part in quality guideline. Specifically, miRNAs have been widely read as biomarkers for histological characterization, sickness visualization, clinical reaction to medicines and analysis of malignant growth. Other than applying their activity inside the cell, miRNAs can be delivered into extracellular liquids and are alluded to as extracellular or circling miRNAs. At the same degree of intracellular miRNAs, circling miRNAs are fit to adjust quality articulation in beneficiary cells, deciding, changing or liberating cells' physiological status.

2.5. Toll like receptors

Toll like receptors (TLRs) are other fundamental segments of the inborn invulnerable reaction. TLRs are available either on the cell surface or in endosomes, and are proficient to collaborate with microbial parts, peril related self particles or non-self nucleic acids introducing all around characterized designs. Once invigorated by such cooperations, TLRs actuate two potential flagging pathway prompting downstream immunogenic quality articulation.⁸ One late investigation has confirmed differential articulation of TLR qualities in cachectic LLC-bearing mice contrasted with non cachectic controls.

2.6. Parathyroid hormone-related peptide

Two ongoing works featured the part of parathyroid hormone related peptide (PTHrP) in WAT sautéing under cachectic conditions. Other than being communicated in kidney and bone, PTHrP can be over expressed by numerous tumor types and goes about as an endocrine effect or skilled to instigate thermogenic quality articulation in adipocytes. In addition, its quality in the course corresponds with a more prominent level of squandering in people with metastatic malignancy.

2.6.1. Adipokines

Zinc- α -glycoprotein (ZAG) is an adipokine working as a Lipid mobilising factor (LMF) Zoom is typically communicated by separated adipocytes, yet it was accounted for that other tissues express it also,⁹ including a few malignant growth cells. Cross articulation has been accounted for to be especially raised in AT of mice relocated with cachexia-inciting tumor,⁹ whereby this marvel has been decidedly related with expanded lipolysis and resulting fat misfortune. As a counter evidence, knockout of ZAG

caused huge increments in bodyweight of mice took care of with standard or lipid-rich eating routine when contrasted and wild-type controls.¹⁰

2.7. Stages of cancer cachexia

Cancer cachexia is divided into three consecutive clinical stages: pre-cachexia, cachexia, and refractory cachexia, though patients may not experience all three stages. The incidence and severity of cachexia are highly heterogeneous and depend on the type, location, and stage of the tumour. At present, there are no specific biomarkers for early stage cachexia identification. Staging is determined according to the clinical manifestations and characteristics of the patient. The refractory cachexia phase is determined by the patient's underlying disease and overall condition; diagnosis of this stage requires a low WHO performance status score and a survival period of less than 3 months. The focus of treatment for refractory cachexia moves from aiming to cure and control to maintaining the patient's quality of life. This type of grading system can provide patients with more suitable treatment options at all stages of disease development, and allows for targeted research and treatment for each stage.¹¹

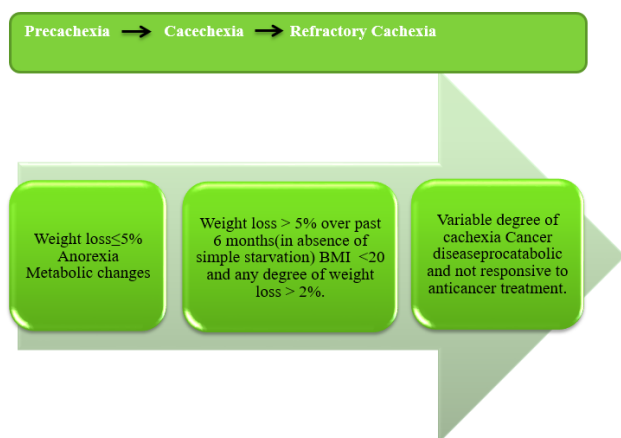


Fig. 1: Three stages of cachectic syndrome and corresponding diagnostic criteria¹²

During tumour development, significant metabolic changes occur in malignancy patients. Along these lines, protein corruption is animated in skeletal muscle, which brings about a huge amino corrosive efflux to the flow. Thus, a progression of nitrogen (for the most part as alanine) from skeletal muscle arrives at the liver, where this amino corrosive is utilized to support gluconeogenesis and furthermore the union of intense stage proteins. Glutamine is moreover traded from the muscle and utilized chiefly in the tumour as a nitrogen contributor for the combination of both protein and DNA. The tumour, contingent upon the accessibility of glucose, can likewise oxidize some glutamine. Fat tissue mass is diminished inferable from the

initiation of lipases, which take an interest in the lipolysis breakdown of triacylglycerol's (TAGs), which produces both unnecessary unsaturated fats (NEFAs) furthermore, glycerol. Glycerol can likewise be utilized to support liver gluconeogenesis while the NEFAs are utilized by the tumour mass, though at extremely low levels. All things being equal, tumour cells utilize colossal measures of glucose and consequently produce lactate, which is then traded to the flow. The liver additionally utilizes lactate as a gluconeogenic substrate, incompletely to make up for the acidosis related with lactate creation. The reusing of lactate comprises a 'Cori cycle' (appeared in purple) between the liver and the tumour, which is connected with high enthusiastic failure, as the transformation of glucose into lactate by the tumour creates considerably less ATP than the sum needed to deliver glucose from lactate. Circumnavigated "+" images demonstrate pathways that are enacted during cachexia.¹³

3. Treatment for Cancer Cachexia

3.1. Pharmacological treatment

There is a wide scope of treatment choices right now accessible for Cancer Cachexia. Healthful help is significant in disease patients, as their food admission is regularly diminished because of manifestations like anorexia brought about by fundamental irritation, sickness, vomiting, and mucositis. Consequently, when patients are diagnosed with malignancy, they ought to be healthfully checked and get both wholesome and metabolic help. Meanwhile, since fundamental irritation is a sign of Cancer Cachexia, the pharmacological focusing of individual proinflammatory cytokines or that of their related receptors has been considered as an expected incredible methodology. Likewise, a few chemicals and chemical inferred exacerbates known to animate hunger and to initiate weight gain have been tried.

3.1.1. $TNF\alpha$, $IL-6$, and $IL-1$ inhibitors

In light of their broadly perceived part in enlistment of cachectogenic impacts, $TNF\alpha$, $IL-6$, and $IL-1\alpha$ had spoken to the ideal objective of a few enemy of cachectic mixes. In any case, in the instance of against $TNF\alpha$ treatment, neither the $TNF\alpha$ receptor-blocker Etanercept nor the illusory IgG1 kappa monoclonal counter acting agent Infliximab had the option to forestall muscle decay or on the other hand improve craving in two randomized controlled preliminaries of terminal cachectic patients. Additionally, Infliximab was found to increment weariness and treatment-related mortality in administrated patients. Similarly, slight recuperation of bulk joined by deteriorating of life or no critical helpful impacts were accounted for by five randomized clinical preliminaries testing two pharmacologists skilled to down regulate articulation of

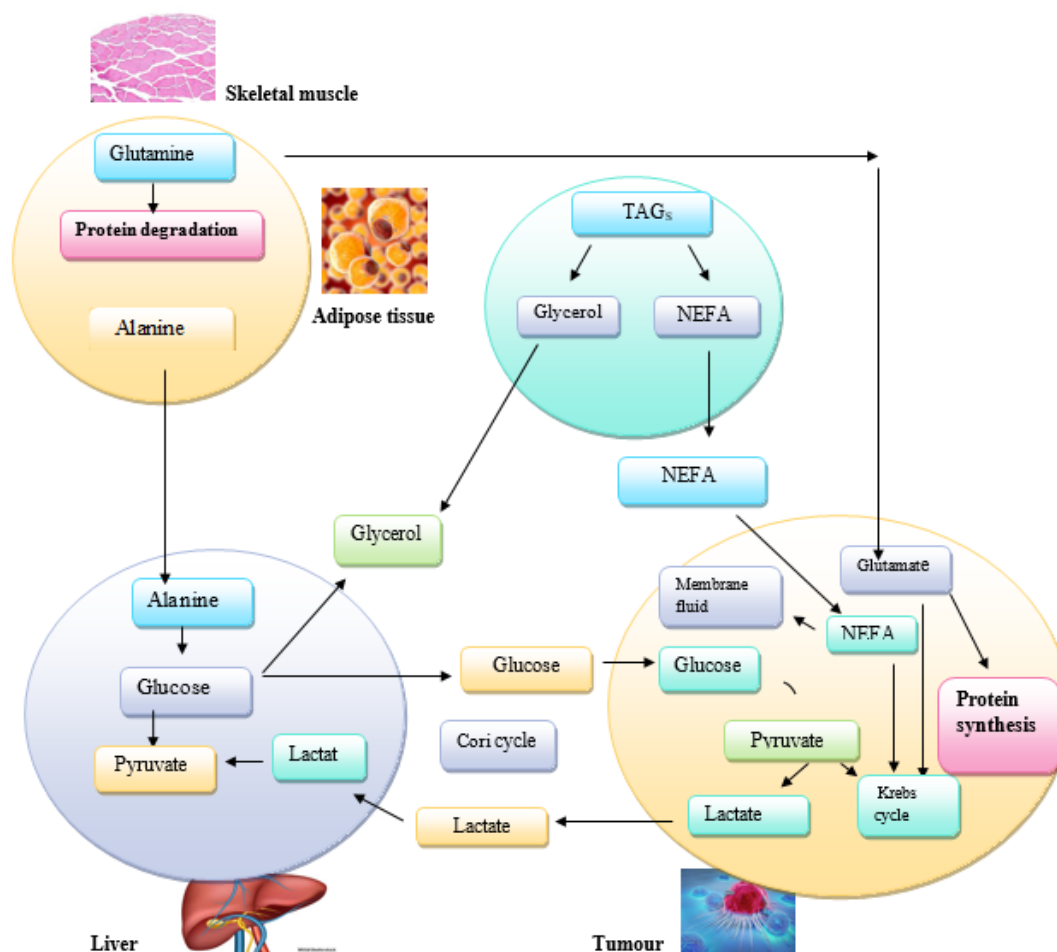


Fig. 2: Molecular mechanism pathophysiology of cancer cachexia

TNF α , to be specific Thalidomide and Pentoxifylline, separately.

Hostile to IL-6 and against IL-1 α pharmacologists appeared promising outcomes throughout clinical preliminaries; regardless, they were uncertain as far as clinical administration of the sickness. In particular, in a Phase I clinical preliminary including patients with cutting edge malignancy, the adapted enemy of IL-6 monoclonal neutralizer Clazakizumab was all around endured, expanded haemoglobin what's more, egg whites levels and turned around weakness in treated patients. During the resulting Phase II randomized controlled preliminary, Administration of Clazakizumab to patients with NSCLC (Non-small cell lung cancer brought about a slight lower level of lean mass exhaustion. Nonetheless, consequences for SM mass were not viewed as acceptable as per the acknowledgment measures and further investigations were required. Essentially, in Phase I and III clinical preliminaries, the IL-1 α -explicit refined monoclonal neutralizer Xilonix was found to forestall modification of body piece and improve

control of thrombocytosis in recalcitrant malignancy patients and progressed CRC (Colorectal cancer) patients with cachexia, individually.

The most regular unfriendly occasions saw toward the finish of these investigations were proteinuria, paleness and expanded focus of both soluble phosphatase and aspartate aminotransferase. A second stage III clinical preliminary endeavouring to further exhibit the adequacy of Xilonix in cutting edge CRC patients (NCT01767857) was halted at its beginning phase as the investigation crossed the forthcoming pointlessness limit of essential endpoint. Aberrant blockage of IL-6 activity by pharmacological restraint of the JAK/STAT3 flagging may speak to another substantial methodology to be perused. In preclinical examinations, the allosteric inhibitor of MAPK/ERK kinase 1 (MEK1) and 2 (MEK2) Selumetinib was demonstrated to apply tumour suppressive movement and forestall cancer-induced IL-6 creation.

However, results from a Phase II preliminary directed in patients with metastatic biliary tumours proposed

that Selumetinib instigated non-liquid weight acquires in administrated patients. Hence, this medication was tried in a Stage II preliminary in patients with cutting edge cholangiocarcinoma, intending to contemplate its potential as modulator of IL-6/JAK/STAT3 flagging and middle person of SM anabolism. In spite of results indicated that Selumetinib adequately advanced SM gain in patients with cholangiocarcinoma, its genuine significance for CC stayed to be illustrated. Also, the particular JAK1/2 inhibitor Ruxolitinib was tested on patients with myeloid fibrosis and was found to diminish splenomegaly and illness related side effects, in the interim instigating a critical expansion in body weight. An open label Stage II preliminary was then begun in 2014 expecting to look at both security and viability of Ruxolitinib just as its impact on generally endurance. Be that as it may, enlistment of members for this study didn't succeed and the preliminary was ineffectively ended toward the start of 2019 because of poor selecting (NCT02072057). Non-steroidal Anti-provocative Drugs Non-steroidal calming drugs (NSAID) have been considered to neutralize persistent aggravation in CC too. Specifically, Celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, fundamentally improved QoL and BMI in cachectic patients versus control. Another examination detailed critical increments of lean mass and upgrades in handgrip strength and QoL in patients with cutting edge malignant growths administrated with Celecoxib.

Moreover, a critical decline in TNF α levels was noticed, and no specific harmful impacts were accounted for. All the more as of late, a few preliminaries have assessed the impacts of a blend of Celecoxib with different medications on cachectic patients, incorporating blend with L-carnitine and mix of these two mixes in addition to Megastore acetic acid derivation. These investigations prompted more viable enhancements in lean mass, complete actual work and diminished feeling of weariness, without poisonous impacts. Myostatin inhibitors As of late, the treatment of cachexia has been centre on myokines, which incorporate cytokines and different proteins delivered furthermore, emitted by SM cells. Among these, Mstn can act as autocrine, paracrine or endocrine effector alongside cytokines like IL-6, IL-8, and IL-15, and is liable for insusceptible and metabolic changes related to exercise or stress. In this manner, Mstn inhibitors have been viewed as promising apparatuses for the treatment of cachexia. In 2012, two Phase I clinical preliminaries under a similar report assessed the wellbeing and decency of the adapted monoclonal immune response to Myostatin LY2495655 in solid subjects and patients with cutting edge malignancy.

As indicated by the outcomes acquired, the adequacy of LY2495655 was very much exhibited on account of sound volunteers, in which it caused an expansion in thigh muscle volume. Expansions in muscle volume were noticed additionally in patients with cutting edge malignancy, in

spite of the fact that solitary when the medication was administrated at generally low portions (21 and 70-mg) without irregular wellbeing concerns. In 2018, a Phase II preliminary was performed on a gathering of inoperable patients or with metastatic pancreatic malignant growth, who experienced cachexia. Here, patients were treated with various portions of LY2495655, and the creators detailed that pre-cachectic patients were more receptive to the treatment than cachectic patients. These outcomes may propose that treatment with LY2495655 ought to be better considered for avoidance muscle misfortune rather than for returning the cycle, albeit more profound examination and extra useful readouts are required.

In 2014, one examination portrayed the properties of the human hostile to Act RII counter acting agent Bimagrumab (BYM338) (196). BYM338 forestalled the official of ligands to the receptors and henceforth the actuation of flagging pathway downstream of Act RII. In vivo, organization of bimagrumab brought about critical SM hypertrophy and expanded muscle fibre distance across. Moreover, it shielded muscles from glucocorticoid-actuated decay and shortcoming through the disability of muscle and tetanic power misfortunes. Finally, Novartis Pharmaceuticals finished a randomized control preliminary of BYM338 for treatment of CC related with pancreatic adenocarcinoma and NSCLC. Patients administrated with Bimagrumab showed huge increments in fit weight and thigh muscle volume, yet additionally had decrement in all out body weight (NCT01433263). Another Myostatin inhibitor is AMG745, a peptibody came about from the combination of a human N-terminal Fc locale of an immunoglobulin and the C-end of a Myostatin-killing peptide. AMG 745 has been effectively tried in different murine models including C26 tumour-bearing mice, where it expanded SM mass, body weight and strength concerning the control gathering. In patients going through androgen hardship as a result of non-metastatic prostate malignant growth, AMG 745 was answered to improve the lower-limit bulk. Digestion and Appetite Modulators One of the primary pharmacological alternatives proposed for the treatment of CC incorporate Megestrol acetic acid derivation, a craving energizer gotten from progesterone fit to improve caloric admission and dietary status. Though its exact system of activity still stays unsure, it has been demonstrated that this hormone derivated drug applies a calming activity, as it has the capacity to down regulate proinflammatory cytokines levels or that of their related receptors. Subsequent to being tried in a few preliminaries, Megestrol acetic acid derivation was answered to improve malignant growth patients' hunger, QoL and weight acquire contrasted with fake treatment gathering, however not when analysed to patients treated with different medications. Consequently, the FDA affirmed it in 1993 for the treatment of anorexia, cachexia and unexplained weight reduction in patients with

AIDS. Nonetheless, Megestrol acetic acid derivation was discovered to be capable of in excess of 40 results, including oedema, thromboembolic scenes and demise. However, a contextual investigation around a 65 year-old man who experienced metastatic renal cell carcinoma uncovered that Megestrol acetic acid derivation can instigate adrenal inadequacy.

Medroxyprogesterone acetic acid derivation is another progesterone subsidiary mulled over for the clinical treatment of malignant growth related anorexia/cachexia condition. At a similar degree of Megestrolacetate, Medroxyprogesterone has been appeared to disable the combination and arrival of a few procachectic cytokines, specifically IL-6, TNF α , and IL-1. In placebo controlled considers, it was accounted for that Medroxyprogesterone by and large improved anorexia, QoL and body weight acquire, despite the fact that the last was brought about by an expansion in AT as opposed to lean mass.

3.2. Erythropoietin

Paleness is an extra component showed by malignancy patients who experience the ill effects of cachexia, and adds to weight reduction and different metabolic modifications. Hence, erythropoietin was tried in unselected malignancy patients on palliative consideration. Patients treated with erythropoietin showed various clinical advantages counting improved exercise capacity and feeling of prosperity. In mouse models of CC, it was demonstrated that treatment with erythropoietin can balance AT squandering and increment the lipogenic rate through the initiation of erythropoietin receptor (EPCOR). In addition, erythropoietin organization improved the endurance of cachectic mice alongside their activity limit, the last being a result of expanded erythrocyte check Megace.¹⁴

Megestrol acetic acid derivation (MEGACE) and Medroxyprogesterone (MPA) are manufactured, orally dynamic subsidiaries of the normally happening chemical, progesterone. MEGACE was first integrated in England in 1963. Created as an oral preventative, the specialist was first tried in the therapy of bosom malignant growth in 1967 and, was subsequently tried for the therapy of endometrial disease. MEGACE is at present used to improve hunger and to expand weight in malignancy related anorexia. From September 1993, MEGACE was affirmed by the Food and Drug Administration in the United States for the treatment of anorexia, cachexia or unexplained weight reduction in patients with AIDS. MEGACE has been found to improve hunger, caloric admission and nourishing status in a few clinical preliminaries.

3.3. Ghrelin

‘Ghrelin-a 28-amino corrosive’-amino acid gastric peptide chemical, was first recognized in the rodent stomach in

1999 as an endogenous ligand for the development chemical secretagogue receptor. The elements of ghrelin incorporate food admission guideline, gastrointestinal (GI) motility, and corrosive discharge in the GI parcel. Many GI problems including disease, irritation, and danger are associated with changed ghrelin creation and emission. Coursing levels of ghrelin are noted to be expanded when human melanoma cells are embedded in bare mice.

3.4. Cannabinoids

Cannabinoids, which are available in pot, are a class of assorted substance aggravates that actuate cannabinoid receptors on cells that stifle synapse discharge in the cerebrum. Cannabinoids definitely affect weight gain and, remembering this, have been utilized to expand food consumption in disease patients. The primary viable constituent of cannabis is delta-9-tetrahydrocannabinol, yet the instrument by which cannabinoids apply their belongings still can't seem to be explained. It has been proposed that they may act by means of endorphin receptors, through restraint of prostaglandin blend, or by repressing IL-1 emission.

3.5. Thalidomide and etanercept

TNF- α , IL-6, and IFN-c have all been involved in the pathogenesis of cachexia, and in cachectic tumour bearing murine models therapy with hostile to TNF- α , against IL-6, and against IFN-c antibodies can weaken the infection cycle, in spite of the fact that it can't stop or oppose disease cachexia. There is additionally some proof that cytokines assume a part in the pathogenesis of cachexia. It has been recommended that by impersonating the hypothalamic impact of extreme contrary criticism motioning from leptin by steady incitement of anorexigenic peptides, or by hindrance of the neuropeptide Y pathway, cytokines could actuate anorexia.⁵

3.6. Preclinical treatment

Investigational cachexia treatments target incendiary pathways as well as the Myostatin/activin type II receptor (Act RII) pathway and incorporate ALD518, MABp1, IP-1510, OHR/AVR118, bimagrumab and REGN1033 (Table 1). For each investigational treatment, the instrument of activity, preclinical information (if accessible), cachexia definition, sign and clinical information (as far as pharmacokinetics, wellbeing/decency and adequacy) are talked about.¹⁵

Table 1:

Drug (Company) and mechanism of action	Definition of cachexia	Phases	Status	Description	Adverse effects profile
ALD518 (Alder Bio pharm, Bothell, WA) Anti-IL-6 antibody	Weight loss > 5% in the prior 3 months; elevated CRP; life expectancy of at least 4 months	I	Complete	Cachexia in patients with advanced cancer MTD: 320 mg iv. once Total enrolment: n = 9	Grade 1 – 3: nausea, vomiting, abdominal pain, diarrhoea Grade 4: none reported 4 SAEs: 3 disease progression, 1 sepsis secondary to obstructed biliary stent DLT: none reported
		II	Complete	Evaluate efficacy of multiple doses of ALD518vs placebo in NSCLC patients with related-fatigue and cachexia Dosing: 80 mg iv. (n = 29); 160 mg iv. (n = 32); 320 mg iv. (n = 32); placebo (n = 31) Total Enrolment: n = 124	Grade 1 – 3: disease progression, dyspnoea, chest pain, fatigue, cough Grade 4: hyperkalaemia, hypokalaemia SAEs: death due to disease progression, rectal bleeding/haemorrhoids DLT: none reported
MABp1 (X biotech, Austin, TX) Anti-IL-1a antibody	Weight loss > 5% in the prior 6 months; Eastern Cooperative Oncology Group £2	I	Complete	Cachexia in solid tumour cancer patients MTD: 3.75 mg/kg iv. once every 3 weeks Total enrolment: n = 36	Grade 1 – 2: proteinuria, nausea, fatigue Grade 3 –4: none reported SAE: none reported DLT: infection
		III	Recruiting: Estimated completion April2014	Evaluate overall survival using MABp1 vs Megestrol acetate in metastatic colorectal cancer patients with cachexia Dosing: MABp1: 3.75 mg/kg iv. once every 2 weeks Megestrol acetate: 800 mg/day (oral)	Grade 1-2: pending Grade 3-4: pending SAE: pending DLT: pending

Continued on next page

Table 1 continued

IP-1510 (Itis Pharm, Melbourne, Australia) IL-1 receptor antagonist peptide	Definition of cachexia not specified	I/II	Complete	Estimated enrolment: n = 656 Evaluate effect on appetite depression, performance status, and quality of life Dosing: 1 mg SC, twice daily injection for 28 days Total enrolment: n = 26	Grade 1 – 2: none reported Grade 3 – 4: none reported SAE: none reported DLT: none reported 6 of 26 patients did not complete the 28-day treatment for reasons not specified
OHR/AVR118 (OHR Pharm, New York, NY) Unknown mechanism of action [40-42]	Definition of cachexia not specified	II	Active, not recruiting	Evaluate the effects of AVR118 on appetite, early satiety and nutritional intake in advanced cancer patients with cachexia Dosing: 4 ml SC per day for 28 days Total enrolment: n = 18	Grade 1 – 2: not reported Grade 3 – 4: not reported SAE: not reported DLT: not reported
Bimagrumab (Novartis, Basel, Switzerland) Anti-Act RII antibody	Unintentional weight loss \pm 5% in the prior 3 – 6 months; BMI \geq 30 kg/m ² ; Life expectancy of at least 4 months	II	Complete	BYM338 vs placebo for the treatment of cachexia in stage IV NSCLC patients or stage III/IV adenocarcinoma of the pancreas	Grade 1 – 2: data not available Grade 3 – 4: data not available SAEs: data not available DLT: data not available
REGN1033 (Rengeron Pharmaceuticals, Tarrytown, NY) Direct Myostatin antagonist antibody	Definition of cachexia not specified	I	Complete	Evaluate treatment emergent adverse events, PK and immunogenicity profiles in healthy adults Dosing: Multiple ascending SC doses, quantity not specified Total enrolment: n = 60	Grade 1 – 2: not reported Grade 3 – 4: not reported SAE: not reported DLT: not reported

3.7. Clinical treatment

Up to this point, malignant growth cachexia has predominantly been concentrated in preclinical models commonly portrayed by transplantation of disease cells or infusion of cancer-causing agents. The most contemplated and best portrayed models are colon-26 adenocarcinoma and Lewis lung adenocarcinoma. In these models, the cross-sectional zone of muscle strands diminishes, and this atrophy is bound to influence type II filaments.

In clinical examinations, little is thought about the potential adjustments in the structure and composing of muscle filaments in patients with disease cachexia have revealed expanded fibrosis and collagen content in skeletal muscle from cachectic pancreatic malignancy patients. Skeletal muscle ultrastructure additionally seems, by all accounts, to be hindered, with an obvious disorder and autophagosome arrangement in gastric malignant growth patients with cachexia. The protein articulation of myosin substantial chains, a significant segment of the strong contractile framework, was expanded (for isoforms 1, 4, and 8), decreased, 4 or unaltered in cachectic patients with gastrointestinal malignancy. Other solid underlying segments have likewise been contemplated. The protein articulation of actin and tropomyosin 1 and 2 was demonstrated to be decreased while that of β -dystroglycan was expanded, and those of β -sarcoglycan and dystrophin stayed unaltered in cachectic patients with gastrointestinal disease. Skorokhod et al. additionally distinguished qualities related (emphatically for a large portion of them) with malignant growth cachexia. These qualities are engaged with muscle withdrawal and advancement (for example actin, titin, tropomyosin, and troponin) and actin cytoskeleton revamp (for example cofilin, dystonin, and vinculin) in pancreatic disease patients. While a critical decrease in the cross-sectional territory of muscle strands was seen in gastrointestinal malignant growth patients with cachexia and muscle misfortune, discovered no such change in cachectic patients with cutting edge non-small-cell cellular breakdown in the lungs contrasted and pre-cachectic patients. At last, no critical modification in fiber composing related with disease cachexia has been accounted for in clinical examinations, both of gastrointestinal or cellular breakdown in the lungs.

The general consequence of clinical investigations proposes the presence of adjustments in skeletal muscle from cachectic malignancy patients. These changes may influence the structure of muscle strands, the various pathways associated with proteolysis and protein combination, lipid digestion (Myosteatosis), and mitochondrial digestion (for example mitochondrial surface and elements and mitochondrial DNA). It is imperative to take note of that for the greater part of the boundaries considered, which could assume a job in muscle squandering, the consequences of clinical investigations

wander.¹⁶

4. Herbal Medicines for the Treatment of Cancer Cachexia

4.1. *Coptidis rhizoma and berberine*

Coptidis Rhizoma, the base of *Coptis chinensis* Franchet, is a mainstream natural medication and is ordinarily utilized for assorted sicknesses, particularly inflammation related illnesses and stomach related ulcers. Berberine, a significant compound of *Coptidis Rhizoma*, has been appeared to affect metabolic condition, diabetes, congestive cardiovascular breakdown, looseness of the bowels, and disease in preclinical and clinical investigations showed that the oral organization of *Coptidis Rhizoma* to naked mice embedded with YES-2 cells fundamentally weakened weight reduction without an adjustment in food admission or tumor development and brought down the tumor interleukin-6 (IL-6) levels. Furthermore, the creators revealed that the treatment of YES-2 cells with berberine diminished the IL-6 mRNA articulation of YES-2 cells in vitro. These perceptions exhibit that *Coptidis Rhizoma* may have an ant cachectic impact on esophageal malignancy, and an impact was related with berberine by means of the down regulation of tumor IL-6 creation. This wonder was reconfirmed in mice bearing colon 26/clone 20 carcinoma cells

4.2. *Curcumin*

Curcumin is the dynamic fixing separated from the rhizome of *Curcuma longa* Linné, with use as a treatment for fiery conditions in East and Southeast Asia. Curcumin is demonstrated to be a profoundly pleiotropic atom that communicates with various provocative sub-atomic targets. A large number of in vitro and in vivo considers have investigated the sub-atomic premise of curcumin's ascribed cell reinforcement, mitigating, antibacterial, anti-apoptosis, and hostile to disease movement. Also, many clinical preliminaries have examined the impacts of curcumin in different ongoing illnesses, including diabetes, malignancies, cardiovascular, neurological and mental sicknesses exhibited that curcumin for Lewis lung carcinoma-or B16 melanoma-bearing mice diminished the tumor mass in mice with B16 melanoma without decreasing splenomegaly or protecting body weight or bulk in one or the other model. This investigation indicated that curcumin may not be valuable for treating malignant growth cachexia. Nonetheless, the proof of its antitumor impacts in creature models proposed that clinical preliminaries of curcumin for disease patients would be justified.

4.3. Soshiho-tang

Soshiho-tang, Xiaochaihu-tang in Chinese and Shosaikoto in Japanese, is made out of *Bupleurumfalcatum* Linne, *Pinelliaternata* Breitenbach, *Scutellariabaicalensis* Georgi, and *Zizyphusjuzuba* Miller var. *inermis* Rehder, *Panax ginseng* C. A. Meyer, *Glycyrrhiza uralensis* Fischer, and *Zingiber officinale* Roscoe. Soshiho-tang is clinically utilized for the therapy of different fever infections including the regular cold and constant hepatic sicknesses showed that the organization of Soshiho-tang for malignancy incited cachexia in CT-26-bearing mice essentially impeded tumor development and forestalled the deficiency of conclusive body weight, remains weight, heart weight, gastrocnemius muscle, and epididymal fat contrasted and saline-treated control mice. Moreover, serum IL-6 levels raised by malignancy were diminished by the administration of Soshiho-tang. The creator reasoned that Soshiho-tang is a protected and valuable enemy of cachectic treatment for malignant growth patients with extreme weight reduction.

4.4. *Anemarrhena rhizoma* and *phellodendri cortex*

Zhimu and Huang bai (ZBHP, *Anemarrhena Rhizoma* and *Phellodendri Cortex*) has been utilized in East Asia to treat different infections ZBHP was beforehand phyto chemically researched for constituents with against disease or diabetes properties among others. Recent research has shown that ZBHP could turn around muscle atrophy in streptozotocin-instigated diabetic mice explored oral organization of ZBHP to mice embedded with colon-26 adenocarcinoma. ZBHP demonstrated critical mitigation of the sans tumor body weight decrease and cachexia induced changes in cytokines and delayed endurance. ZBHP repressed muscle decay related qualities just as initiated the insulin-like development factor-1 (IGF-1)/Akt and autophagy signal pathways to encourage protein union.¹⁷

5. Non-pharmacological Treatment

5.1. Dietary treatment

Since disease cachexia varies from starvation, right now no single methodology treatments utilizing generally applied healthful regimens has prevailing in show any efficacy in improving weight gain, remembering acquire for fit weight, in patients determined to have malignant growth cachexia. The normal calorie deficiency in a weight-losing tolerant is accounted for to be approximately 200 kcal every day in the setting of cutting edge malignant growth and 250-400 kcals/d in those patients with disease cachexia. A normal supplementation of 1 calorie/MI has not been appeared to improve the dietary status of patients getting chemotherapy. The normal protein consumption in patients with malignancy cachexia is about 0.7-1.0 g/kg every day. Food energy consumption needs to increment

by 300-400 kcal every day and protein admission to increment by dependent upon half to affect anabolic opposition (suggested admission 1.0-1.5 g/kg every day). The investigation of a randomized preliminary found that notwithstanding oral nourishing help, the utilization of parenteral sustenance brought about a short (6-8 week) yet critical ($P < 0.001$), prolongation of endurance when wholesome objectives were accomplished. A meta-examination of oral dietary mediations in malnourished patients with disease proposes that oral wholesome intercessions have no impact on endurance and that the impact on body weight and energy admission is conflicting, however genuinely critical upgrades in certain parts of QOL might be accomplished. In this investigation, wholesome intercession was related with a critical expansion in energy consumption (430 kcal every day) and a weight gain of 1.9 kg. There was a valuable impact on hunger and worldwide personal satisfaction.

5.2. Actual exercise

Actual exercise has been proposed as a promising countermeasure for forestalling cachexia. Lamentably, a couple of studies, in both clinical and exploratory settings, have been performed to characterize the viability of activity against cachexia. The reasoning for the utilization of activity depends on the known emotional decrease of muscle strength and perseverance during cachexia. Since it is additionally detailed that activity builds insulin affectability, protein amalgamation rate, and against oxidative chemical action it might prompt a concealment of the provocative reaction and improvement of resistant capacity. There is critical proof that perseverance work out (e.g., a high number of redundancies performed throughout expanded time spans against moderately low opposition) improves malignancy related exhaustion. A randomized preliminary has likewise detailed that, in patients with cutting edge stage malignancy, practice is achievable and that despite the fact that weakness isn't decreased, actual execution is improved fundamentally. Blend of opposition and high-impact muscle preparing has been recommended to be consolidated into cachexia treatment programs. Exercise preparing can increment both strength and perseverance in sound conditions, contingent upon the kind of activity, and in addition, it has been demonstrated to go about as a brilliant anabolic drive for skeletal muscle in blend with anabolic steroids or other muscle anabolic medications.¹⁴

5.3. Nutraceuticals treatment

In tackling the nutrition-related issues in CC, pre-clinical and clinical research is shifting towards promising Nutraceuticals-based schemes. The neologism "nutraceuticals" was coined in 1989 by joining the words "nutrition" and "pharmaceutical" by Dr. Stephen De Felice

to refer to substances that are “a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease”. Nutraceuticals include “functional foods”, which are whole, or “fortified, enriched and enhanced” foods that supply the required amount of essential nutrients (e.g., vitamins, fats, and minerals) to confer health benefits and, most importantly, “dietary supplements”. These latter, as indicated by the Food and Drug Administration (FDA) agency, are “products taken by mouth (as pills, capsules, tablets, or liquid) that contain a dietary ingredient”. Dietary ingredients include vitamins, minerals, herbs, or botanicals, as well as other substances that can be used to supplement the diet. Nutraceuticals, particularly dietary supplements, cannot replace conventional medicine since, accordingly to the FDA agency, they “are not intended to treat, diagnose, cure, or alleviate the effect of diseases”. Nonetheless, some of them provide a promising source of compounds helpful in reducing the risk and/or progression of some widespread diseases, such as atherosclerosis and cancer.

In recent years, several classes of food- and plant-derived nutraceuticals have also shown the potential for limiting CC, and thus for improving patients’ quality of life. Those for which the major experimental evidence is available are discussed below, and their way of action at the molecular level is summarized

5.4. Natural polyphenols

Natural polyphenols comprise a group of heterogeneous organic molecules found in various plants and their derivatives, especially fruit and vegetables, but also herbs, cocoa, and tea. Polyphenols contain multiple phenol units and are classified based on the number and oxidation status of these primary units, as well as the presence of other functional groups. Numerous studies already support their potential health benefits, as modulators of OS, for managing and treating chronic diseases, including cardiovascular diseases and cancers. Supporting evidence also exists for natural polyphenols to limit or restrain Cancer Cachexia.

5.4.1. Other promising nutraceuticals against cancer cachexia alkaloids

Alkaloids are a group of naturally occurring chemical compounds that mostly contain basic nitrogen atoms and are used in clinical practice, particularly as anticancer agents. Matrine is an alkaloid extracted from *Sophora flavescens*, a plant found widely in Asia with potent activities against various malignancies, including ovarian cancer, hepatocellular carcinoma, and human non-small-cell lung cancer. Intraperitoneally injected matrine (50 mg/kg for 5 or 11 days from the onset of cachexia) in C26-bearing mice lowered serum levels of TNF α and IL-6 and preserved body and gastrocnemius muscle weights, down regulating the expression of atrogenes in skeletal muscle. Matrine

also restrains C2C12 Myotube atrophy and apoptosis by activating the AKT/mTOR signalling pathway and inhibiting FoxO3-mediated atrogenes expression. Since matrine can influence mitochondrial function and ROS production in diverse cancer cells and in oxidized LDL-stimulated macrophages, it remains to be established whether it can modulate OS also in muscles during Cancer Cachexia.

5.5. Triterpenoids

Triterpenoids are a class of metabolites composed of three terpene units, biosynthesized in plants by the cyclization of squalene, a biochemical precursor of all steroids, widely used as chemo-preventive and anticancer agents, though their exact mechanisms of action have not been elucidated yet (reviewed in). Among the most important tri terpenoids, ursolic acid, a pentacyclic tri terpenoid found in various fruits and vegetables, displays anti-inflammatory, cardio protective, and anti-tumour properties. Ursolic acid exerts anticancer action by restraining various inflammation-related pathways, including STAT3, NF- κ B, and MAPK (reviewed in). As suggested by Shen and collaborators, it can also modulate ROS production, by triggering endoplasmic reticulum stress and autophagy via ROS-dependent pathway, at least in human glioma cells. In muscles, Ebert et al. found that ursolic acid promoted muscle growth through an mTORC1-dependent mechanism and reduced muscle atrophy and weakness in aged mice by repressing atrogenes expression and transcription factor ATF4 activation. In a mouse model of chronic kidney disease, with associated muscle wasting, 3 week treatment with ursolic acid (100 mg/kg/day, by oral gavage) stimulated muscle protein synthesis, suppressed muscle protein degradation, and lowered plasma levels of inflammatory cytokines (TGF- β , IL-6, and TNF α). Similarly, 5 day-treatment with ursolic acid (100 mg/kg/day, by oral gavage) in dexamethasone-treated rats protected them from muscle damage and weakness and reduced MuRF1 expression by limiting the nuclear translocation of Fox O1.¹⁸

6. Conclusion

Over the last two decades, the study of CC has provided new insights that allowed a better understanding of the multiple mechanisms regulating the onset and progression of this metabolic disorder, and paved the way to the development of novel therapeutic strategies. It is a multifactorial infection portrayed by weight reduction through skeletal muscle and fat tissue misfortune, awkwardness in metabolic guideline, and decreased food consumption. It is brought about by components of catabolism delivered by tumours in the fundamental course as well as physiological factors, for example, the imbalanced fiery initiation, proteolysis, autophagy, and lipolysis that may happen with gastric,

pancreatic, oesophageal, cellular breakdown in the lungs, liver, and entrails malignant growth. From this review we conclude that the various treatments which is used in the treatment of cancer cachexia, such as Pharmacological, non-pharmacological, nutraceuticals and investigational new treatments.

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None.

8. Conflict of Interest

The authors declare that there is no conflict of interest.

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Author biography

Pranali S Kalambe, Research Scholar

Shubhada V Mangrulkarb, Assistant Professor

Dhanashri T Jawald, Research Scholar

Mayuri K Sonkusared, Research Scholar

Sudarshan Behered, Research Scholar

Dinesh R Chaplec, Principal

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