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The treatment interventions and targets of cancer cachexia research during the past decade: a systematic review of the literature

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Abstract

Background Cachexia is a detrimental multifactorial syndrome that has been strongly associated with cancer. A growing body of data concerning its management is being generated from the ongoing advances of experimental cancer cachexia research. This study aimed to delineate the broad landscape of cancer cachexia research, by comprehensively presenting the treatment interventions and targets of cancer cachexia during the past decade.

Methods A systematic literature search was performed in Medline and Scopus databases from January to April 2023. Articles were considered eligible if they described any type of intervention in tumor-bearing rodents to study the effect on prevention or treatment of cancer cachexia. The corresponding signaling and metabolic pathways that were targeted by these interventions were documented.

Results A total of 271 articles were considered eligible for our study. Of these, 176 studies pertained to pharmaceutical interventions with 100 corresponding targets, 58 studies pertained to nutritional interventions with 60 corresponding targets, and 37 studies pertained to exercise interventions with 60 corresponding targets.

Conclusions The continuous evolution of cancer cachexia research has provided a plethora of disease targets and corresponding treatment interventions. Moving forward, the available management strategies should be refined and clinical research should efficiently capitalize on the robust experimental evidence.

Keywords Cancer, cachexia, treatment, mechanism, pathway

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Conflict of Interest: None

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Introduction

Cachexia is a multifactorial syndrome, characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass), leading to progressive functional impairment [1]. This condition has been strongly associated with cancer, and has been noted to occur in up to 80% of cases, depending on the cancer type [2]. Cancer cachexia has been described as the main contributor to more than 30% of cancer patients' deaths [3], while this number is predicted to rise in the years to come [4]. Furthermore, cancer cachexia has been associated with negative effects on several aspects of patients' quality of life, including depression, anxiety, physical function, role function, cognition, as well as emotional and social function [5].

The detrimental effects of cancer cachexia have sparked growing enthusiasm in the research community regarding interventions for disease prevention and treatment. Cancer cachexia is defined by a plethora of mediators, signaling and metabolic pathways [6,7]. Understanding these complex mechanisms can facilitate the development of management strategies for this muscle condition.

Currently, the treatment arsenal for cancer cachexia consists of 3 broad categories, including pharmaceutical [8], nutritional [9], and exercise interventions [10]. However, only a limited number of these interventions have been approved as part of the management guidelines [11,12].

The pathways that regulate skeletal muscle homeostasis have been described in detail (Fig. 1) [13]. Experimental research into cancer cachexia has been rapidly evolving with a view to providing novel interventions that target these pathways of interest. Accurate documentation of results is considered of paramount importance, as a prelude to the implementation of innovative treatment strategies in clinical trials, and ultimately their introduction into clinical practice [14]. Therefore, this study aimed to delineate the broad landscape of cancer cachexia research, by comprehensively presenting the treatment interventions and corresponding targets of cancer cachexia during the past decade. Through this work we have attempted to construct a robust scientific base, so as to inform researchers regarding the recent advances in preclinical cachexia treatment, as well as to facilitate the application of this knowledge in refining future research protocols.

Materials and methods

Search strategy

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (Supplementary Table 1) [15]. Prior to the project initiation, a study protocol was drafted to predefine the study aim, as well as the search and data extraction strategies. A systematic literature search was performed in Medline and Scopus databases from January to April 2023. The search string consisted of the following keywords: "cancer", "tumor", "cachexia", "rodents", "rat", "mice". Articles were screened initially by 2 independent investigators (PF, NF), on the basis of title and abstract, and the final decision for inclusion of potentially eligible studies was made after full-text evaluation. Discrepancies were resolved by consensus. The reference lists of included studies and recently published topic-related review articles were screened to minimize the risk of information loss and validate the overall search strategy.

Inclusion criteria

Studies that aimed to prevent or treat cancer cachexia in preclinical tumor models were considered eligible for this review. Eligibility criteria included the following: (a) study population, tumor-bearing rats or mice; (b) intervention, any type of pharmaceutical, nutritional or exercise intervention; and (c) outcome, prevention or treatment of cancer cachexia. Studies that were performed on tumor cells, did not include cancer-induced cachexia models or were not published in the English language were excluded from our review.

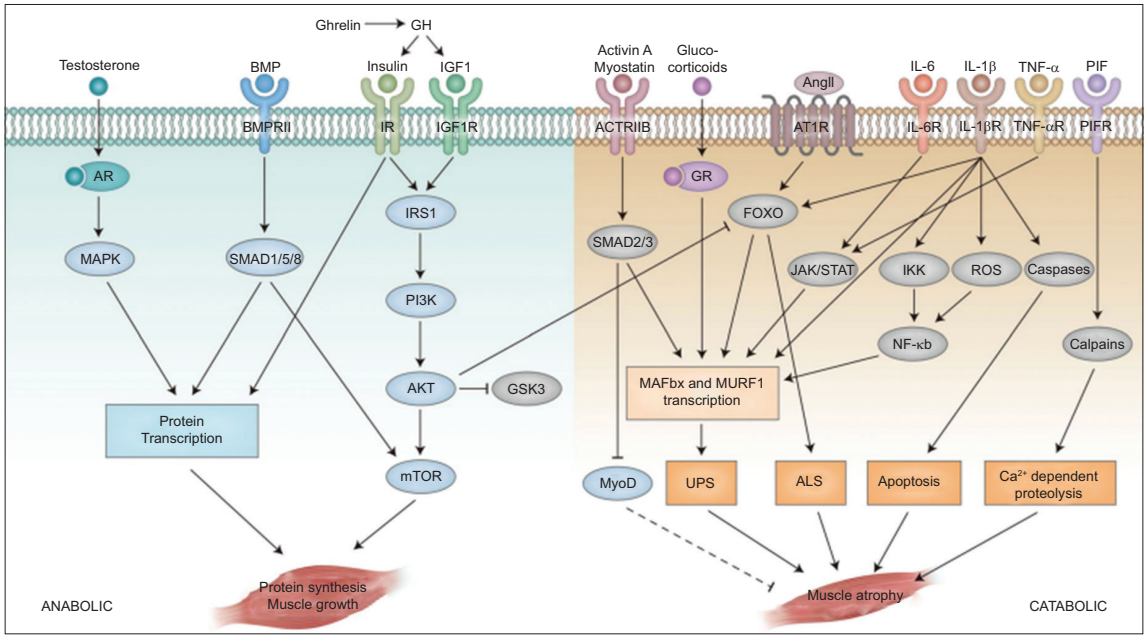

Figure 1 The anabolic and catabolic pathways that regulate skeletal muscle homeostasis. The dashed lines indicate inhibited pathways.
Figure from "Cancer cachexia: molecular mechanisms and treatment strategies", by T. Setiawan et al., J Hematol Oncol, 2023;16:54, https://doi.org/10.1186/s13045-023-01454-0. Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/. No changes were made to the figure
GH, growth hormone; IGF1R, IGF1 receptor; IR, insulin receptor; BMP, bone morphogenetic protein; BMPRII, BMP receptor II; AR, androgen receptor; ActRIIb, activin type II receptor; AngII, angiotensin II; AT1R, type 1 angiotensin II receptors; IL-6R, interleukin 6 receptor; IL1bR, IL1b receptor; TNFaR, tumor necrosis alpha receptor; PIF, proteolysis-inducing factor; PIFR, proteolysis-inducing factor receptor; GR, glucocorticoid receptor; ROS, reactive oxygen species; UPS, ubiquitin (Ub)-proteasome system; ALS, autophagy-lysosome system.

Data extraction

Data extraction was performed by 2 investigators (DS, CZ). The data extraction form contained the following information: first author, year of publication, tumor type, cell line, animal model, intervention, intervention category (pharmaceutical, nutritional, exercise), mechanism through which the intervention affects cachexia, and results of its use in cachexia. A third author (DP) was involved when clarifications regarding the data extraction were required.

Results

The review flow chart is depicted in Fig. 2. A total of 3650 articles were screened in the form of title and abstract, following deduplication of the results that were generated from the Medline (n=1717) and Scopus (n=2710) database searches. After the initial title–abstract screening, a total of 297 articles were retrieved for full-text evaluation. Finally, 271 articles were considered eligible for our study. Details of the included studies classified by type of intervention can be found in Supplementary Table 2.

Of these 271 studies, 176 pertained to pharmaceutical interventions with 100 corresponding targets (Fig. 3), 58 pertained to nutritional interventions with 60 corresponding targets (Fig. 4), and 37 pertained to exercise interventions with 60 corresponding targets (Fig. 5). Table 1 presents the interventions that showed positive results in animal models, organized per targeted pathways, during the last 10 years.

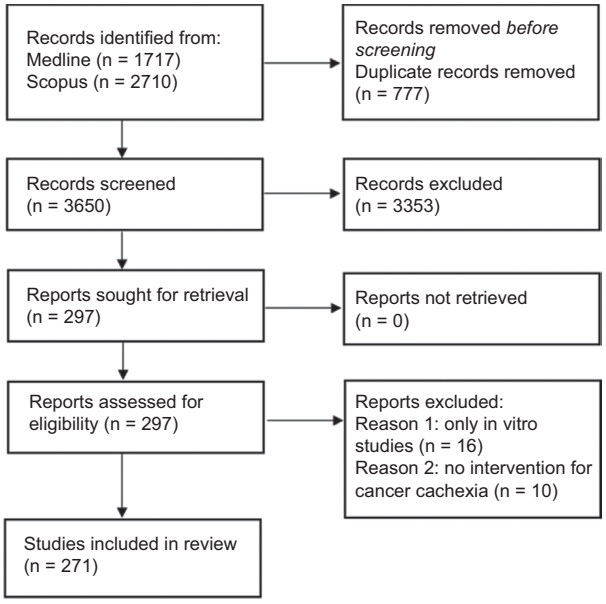

Figure 2 Review flow chart

Discussion

The rapidly evolving landscape of cancer cachexia research has uncovered a plethora of disease targets and corresponding treatment interventions. In this review, a systematic assessment of the literature allowed for a comprehensive presentation of the cancer cachexia advances throughout the past decade. The arsenal of therapeutic strategies consists of pharmaceutical, nutritional and exercise interventions. The knowledge of the available intervention–target couplings can inform evidence-based decision making with a view to the design of future study protocols.

The ubiquitin proteasome system (UPS) has served as one of the most utilized targets for cancer cachexia treatments. The UPS is the main protein degradation system in eukaryotic cells, marking myofibrillar proteins and other short-lived proteins with polyubiquitin chains and transferring them to the 26S proteasome for degradation [16-18]. Activation of the UPS in skeletal muscle leads to the degradation of structural and contractile proteins, resulting in atrophy and decreased muscle function [19]. Accumulating evidence highlights the critical role of dysregulated ubiquitin ligases in processes associated with the initiation and progression of cancer [20], while UPS inhibitors have been continuously gaining ground as a part of the arsenal for cancer therapy. Several studies have now proposed that one of the most essential factors involved in the induction of muscle wasting in cancer cachexia is upregulation of the UPS pathway [21,22].

The function of the UPS is enabled by an enzymatic cascade, which consists of the ubiquitin-activating enzyme (UAE or E1), the ubiquitin-conjugating enzyme (UBC or E2), and the ubiquitin ligase (E3) [18,23]. The E3 ligase muscle-specific RING finger protein-1 (MuRF1) and muscular atrophy fbox-1 protein (MAFbx/Atrogin-1) constitute the 2 key ligases that identify muscle proteins, in order to be degraded by the UPS in skeletal muscle [24]. MuRF1 and Atrogin-1 are regulated by a variety of signaling pathways, including NF-κB, interleukin (IL)-6, and the p38 MAPK pathway [25,26]. Since MURF1 and Atrogin-1 directly control protein degradations that lead to cachexia, it has been suggested that their inhibition has the potential to preserve protein levels and maintain muscle mass without unwanted side-effects [27]. Indeed, through our systematic review of the literature, we have found that MURF1 and Atrogin-1, as well as corresponding regulatory signaling pathways such as IL-6, NF-κB and MAPK, have all been consistently used as targets of therapeutic modalities employed in cancer cachexia research.

Apart from the UPS, another signaling pathway that serves as an essential contributor to skeletal muscle degradation is the autophagy lysosomal pathway. Autophagy is a crucial process, which serves in the selective elimination of damaged organelles and degradation of misfolded proteins [28]. Acting as sensors, mTOR and AMP-activated protein kinase (AMPK) are pivotal regulators of autophagy, crucial for maintaining cellular energy balance [29,30]. The role of autophagy in mediating skeletal muscle wasting and cachexia progression

Pharmaceutical Interventions (n=176 studies)			
↓ UPS pathway	↓ PTHLH	↓ Activin A	↓ BRD4 protein
↓ Autophagy	↓ Hsp70/90	↓ FBXO-40	↑ Androgen receptor
↓ p97-Nploc4	↓ CD8+T cells	↓ TRAF-6	↓ MEK1/2
↓ STATB	↓ Rab27b	↓ PTHLH	↓ HIF-1α
↓ MuRFI	↑ Ghreliri receptor	↓ TLR4/NF-kB	↓ MEK/ERK
↓ Atrogin-1	↓ TGF-β/SMAD	↑ p38 MAPK	↓ Lipolysis
↓ FOXOI	↓ IL-6	↑ mTOR	↓ AMPK
↓ MSTN	↓ Bnip-3	↓ HIF-la	↓ MCP-1
↓ ROS	↓ IL-1	↓ CREB-m1R-373-PHLPP2-Akt	↓ TWEAK
↑ Mitochondria	↓ Socs3	↑ mTORC1	↓ Leukemia inhibitory factor
↓ TGF-β/Smad2	↓ PARP-1/2	↑ Protein synthesis	↑ SREBP-1
↓ HSP90/STAT3/FOXO1	↑ LPAR/ Gαi2	↑ NAD	↓ RAS
↓ TNF-α	↓ Pax-7	↓ ACVR2B	↓ xanthine oxidase
↓ NF-κB	↓ STAT3	↑ Leptin	↑ PPAR-γ
↓ IFN-γ	↓ IL6/STAT3	↓ P selectin	↑ PPAR-α
↑ Neuropeptide Y	↑ PI3K	↑ MyoD	↑ C/EBP-α
↑ Akt	↓ TGF-βl	↑ MAFbx	↓ VEGF
↑ IGF-1	↓ EGFR	↑ ketone body oxidation	↑ GLP-1
↓ GSK-3β	↓ PTHrP	↑ 5-HT1A	↓ Mineralocorticoid receptor
↓ p38/ MAPK	↓ MAPK/ERK	↑ Adiponectin	↑ Insulin sensitivity
↓ TCF4-TWIST1	↓ PERP	↓ FBX032	↓ GDF15-GFRAL
↓ TGF-β1	↓ FOXO3	↑ Akt/mTOR	↓ Oxidative stress
↓ Ly6G+ cells	↑ Myogenin	↑ PI3K/AKT/mTOR	↑ MyHC
↓ MSTN	↓ IL-20	↑ Akt/mTOR/FoxO3α	↓ Pax-7
↑ STAT3/PKM2	↓ IL-6/AMPK/FoxO3	↓ Jak2/STAT3	↓ Ras/Raf/MEK/ERK

Figure 3 Targets of pharmaceutical interventions for cancer cachexia. Data stem from 176 studies on pharmaceutical interventions. Up and down arrows demonstrate upregulation/activation and downregulation/inhibition, respectively

Nutritional/Supplement Interventions (n=58 studies)		
↓ Lipolysis	↓ MuRF-1	↑ STAT-3
↑ Protein synthesis	↑ Akt/F0X03/Atrogin-l	↑ STAT-6
↓ Hepatic gluconeogenesis	↑ p70S6K	↓ NF-κB
↑ Glycolysis	↑ Insulin sensitivity	↓ RPS10
↑ Mitochondria	↑ PGC-1α	↓ miR-135b
↑ Gut microbiota	↑ AKT	↓ Angiopoietins-Tie2
↑ Sirtuin-1	↑ Antioxidant	↑ IL-4
↓ NF-κB/P50	↓ T helper cells	↑ IL-10
↓ F0X03	↑ MLC1	↑ Glucarate
↓ cAMP/PKA/CREB	↑ mTOR	↓ GLP-1
↓ IL-6	↑ Pyruvate synthesis	↓ PYY
↓ TNF-a	↑ Acetyl-CoA synthesis	↓ MCP-1
↓ MSTN	↓ UCP1	↓ Homocysteine
↓ Ubiquitin proteasome system	↑ AMPK	↓ COX-2
↓ Autophagic lysosomal system	↓ NF-κB/MuRF-1	↓ IL-6/STAT3
↓ Atrogin	↓ AMPK/HSL	↓ ATGL
↑ Myogenin	↓ JAK/STAT3	↓ CGI-58
↑ NF-κB/UPSaxis	↓ FoxO	↓ RAG
↓ PI3K/Akt/mTOR	↑ Liver function	↑ 4-EBP1
↓ IL-6/JAK2/STAT3	↑ JNK	↓ E3 ligases

Figure 4 Targets of nutritional interventions for cancer cachexia. Data stem from 58 studies on nutritional/supplement interventions. Up and down arrows demonstrate upregulation/activation and downregulation/inhibition, respectively

Physical activity Interventions (n=37 studies)		
↑ Akt/mTORC1	↑ mTOR	↓ GSH
↓ STAT3	↑ p70S6 kinase	↑ Glut4
↓ IL-6	↑ 4EBP-1	↑ IL-10
↓ Oxidative stress	↓ AMPK	↑ IL-1α
↓ UPS	↑ Akt/mTOR	↑ Ghrelin
↓ Autophagy	↓ IL-6/gpl30	↓ Leptin
↓ AMPK	↓ ACC	↑ IL-10/TNF-α ratio
↓ FOXO3a	↑ mTORC1	↑ IL-15
↑ MFN-1	↓ Proteolysis	↑ IGF-I
↑ DRP-1	↓ TGF-βi	↑ Myogenin
↑ Mitochondria	↑ BNIP3	↓ Pax7
↑ Protein synthesis	↑ PGCIα/musclin/Npr3	↑ 4EBP-1
↑ Adiponectin	↓ ROS	↑ PGC-1α
↑ Akt	↓ Vimentin	↓ Atrogin-1
↑ Vascular endothelial cells	↓ TWEAK/NF-kB	↓ TWEAK
↑ Adipogenic progenitors	↑ Nrf2	↓ TRAF6
↓ NF-κB	↑ Keapl	↓ TAG
↑ Insulin sensitivity	↓ Mitophagy	↓ Autophagy
↓ HIF-1	↓ FOXOI/UPS	↑ COPS2
↓ Murf-1	↑ mTORC1	↓ caspase-3

Figure 5 Targets of physical activity interventions for cancer cachexia. Data stem from 37 studies on exercise interventions. Up and down arrows demonstrate upregulation/activation and downregulation/inhibition, respectively

has garnered increasing interest [21,22]. Accumulating evidence indicates a significant upregulation of autophagy during cancer cachexia [31]. FOXO3, identified as the main transcription factor inducing autophagy, regulates the expression of key autophagy genes such as LC3 and Bnip3 [32]. Activation of FOXO3 stimulates autophagic lysosomal pathways by attenuating the IGF1/PI3K/AKT signaling pathway via mTOR and transcriptional-dependent mechanisms [32]. Additionally, oxidative stress has been linked to the induction of ATG7 expression in the autophagic lysosomal pathway, which was associated with the p38 MAPK pathway in another study [26].

In general, increased oxidative stress contributes to mechanisms that favor protein breakdown over protein synthesis through increased ubiquitin proteasome activity, mitochondrial dysfunction and dysregulation of autophagy, thus making it a potential target for cachexia treatment [33]. Damage to mitochondria by pro-oxidant species triggers a cascade of events, including increased production of reactive oxygen species and induction of mitophagy, ultimately impacting mitochondrial abundance in muscle tissue [34,35]. Given that mitochondria play a crucial role in producing the energy required for muscle contraction, disruptions in their equilibrium detrimentally affect muscle function. Notably, studies have reported alterations in the mitochondrial ultrastructure in the skeletal muscle of Lewis lung carcinoma and colon-26 carcinoma hosts,

Table 1 The interventions used for the most common targets of cancer cachexia throughout the past decade

Targets	List of interventions
Ubiquitin proteasome system	Disulfiram, adalimumab, anti-RANKL antibodies, zoledronic acid, 2-deoxy-D-glucose, Ghrelin, GHSR-1a, rucaparib, Nilotinib, Myomed-205 and -946, Pantoprazole, jianpijiedu (MJPJD), Bortezomib, Erythropoietin, Aliskiren, carfilzomib and z-VAD-fmk, leucine & Ca-β-hydroxy-β-methylbutyrate, bortezomib, MG132 proteasome inhibitor, Curcumin, Creatine, Leucine-rich diet, Resistance training
Autophagy	Ghrelin, GHSR-1a, rucaparib, Nilotinib, Withaferin A, TLR7/8 agonist R848, Myomed-205 and -946, Aliskiren, Megestrol acetate, Creatine, Resistance training, Aerobic running, Moderate exercise training (mild intensity aerobic exercise-increased resistance)
MuRF1	Ginsenoside Rd, Saikosaponin D, alvespimycin, Δ9-tetrahydrocannabinol, EXT418, MAOI (harmine-hydrochloride), Gintonin, MDP, Follistatin mRNA encapsulated in lipid nanoparticles, HMGB1 (glycyrrhizin), 17ß-estradiol, Clodronate liposome, Cryptotanshinone, sActRIIB/Fc, Lithium chloride, Matrine (alkaloid), Calpain inhibitors, jianpijiedu (MJPJD), Baoyuan (BYJD) decoction, AR-42, MG132 proteasome inhibitor, Parthenolide, Quercetin, Coix seed oil
Atrogin-1	Ginsenoside Rd, Saikosaponin D, alvespimycin, Δ9-tetrahydrocannabinol, EXT418, Gintonin, MDP, Follistatin mRNA encapsulated in lipid nanoparticles, HMGB1, Clodronate liposome, Cryptotanshinone, AG and UnAG, sActRIIB/Fc, Lithium chloride, Calpain inhibitors, jianpijiedu (MJPJD), Valproic acid, Baoyuan (BYJD) decoction, AR-42, Acylated and unacylated ghrelin, Quercetin, L-carnitine, Leucine-rich diet, mild exercise training and EPO administration, endurance training
STAT3	Ginsenoside Rd, Saikosaponin D, Cryptotanshinone, adalimumab, Atractylenolide I, Alantolactone, 2-deoxy-D-glucose, Clodronate, liposome, AR-42 plus SARM co-administration, ACVR2B, Leucine-rich diet, Resistance training, Eccentric contractions
ROS	Ginsenoside Rd, Gintonin, Baoyuan Jiedu decoction, Clodronate liposome, Myomed-205 and -946, Formoterol, Aliskiren, Febuxostat, Aerobic training, Moderate exercise training (mild intensity aerobic exercise-likely increased resistance), Resistance exercise training (RET) prior tumor implantation
Mitochondria	Ginsenoside Rd, MitoQ, Ghrelin and GHSR-1a, Baoyuan Jiedu decoction, iNOS inhibitor, 17ß-estradiol, ACVR2B/Fc, SS-31, Myomed-205 and -946, Trimetazidine (TMZ), Vector plasmid for Mfn2 overexpression, B-Carotene, Curcumin, Naringenin (flavonoid) diet, Iron, Eccentric contractions, Aerobic exercise
TNF-α	anti-GDF15 antibody, Gintonin, adalimumab, Alantolactone, HMGB1, Butanolic fraction of V. tucanorum, iNOS inhibitor, olaparib, AG and UnAG, Withaferin A, jianpijiedu (MJPJD), Pterocarpanquinone LQB-118 hybrid, infliximab, MG132, Parthenolide, Coix seed oil, Aerobic interval training and selenium nanoparticles treatment, high-intense Resistance exercise
NF-κB	anti-GDF15 antibody, Gintonin, adalimumab, anti-RANKL antibodies, zoledronic acid, Alantolactone, HMGB1, Withaferin A, MT-102, Bortezomib, Pterocarpanquinone LQB-118 hybrid, Baicalin (flavonoid), sulfasalazine, Compound A, Resveratrol, Curcumin, carnosol, Coix seed oil, Ajoene garlic extract, Morin (3,5,7,2′,4’-pentahydroxyflavone) – flavonoid, endurance training
Akt	ARA 284, adalimumab, S-oxprenolol, Fuzheng Xiaoai Decoction 1, AG and UnAG, MT-102, Matrine (alkaloid), Selumetinib, L-carnitine, carnosol, Morin (3,5,7,2′,4’-pentahydroxyflavone) – flavonoid, Aerobic exercise training
IL-6	EXT418, adalimumab, MDP, Atractylenolide I, Alantolactone, HMGB1, Butanolic fraction of V. tucanorum, iNOS inhibitor, Clodronate, liposome, Withaferin A, Histone deacetylase inhibitor (HDACi) AR-42 plus SARM co-administration, Selumetinib, jianpijiedu (MJPJD), Sipjeondaebo-tang (SJDBT), AR-42, Tocilizumab (MR16-1 rodent analog), MG132, Naringenin (flavonoid) diet, Arctii Fructus, Coix seed oil, Resistance training, Aerobic training
mTOR	Fuzheng Xiaoai Decoction 1 (FZXAD1), iNOS inhibitor, MT-102, Matrine (alkaloid), ACVR2B , Selumetinib , Acylated and unacylated ghrelin, Leucine-rich diet, Aerobic exercise, High-frequency electric stimulation on Tibialis anterior muscle
Protein synthesis	Pyrrolidine dithiocarbamate, iNOS inhibitor, ACVR2B/Fc, soluble myostatin receptor ActRIIB (sActRIIB), Formoterol, L-carnitine, Ajoene garlic extract, Eccentric contractions
FOXO3	Acylated and unacylated ghrelin, Matrine (alkaloid), pan-(BET)-BRD4 protein inhibitor (+)-JQ1, Resveratrol, Curcumin, L-carnitine, Aerobic exercise
RAS	Combination of carfilzomib (CFZ) and z-VAD-fmk, Perindopril (ACE-inhibitor), MEK162/buparlisib (PI3K/Akt inhibitor), Aliskiren (renin inhibitor)
Ghrelin receptor	Anamorelin, ActRIIB-Fc, Z-505 hydrochloride (Z-505), HM01, synthetic Anamorelin HCl (ANAM), Ghrelin
Lipolysis	Insulin and glutamine dipeptide, Atractylenolide I, erythropoietin, B-Carotene, Piceatannol, EPA-enriched phospholipids (EPA-PL)
IL-1	MAOI (harmine-hydrochloride), iNOS inhibitor, Clodronate liposome, jianpijiedu (MJPJD), Aerobic training
MSTN	Ginsenoside Rd, alvespimycin, ARA 284, Gintonin, Peptide-2, sActRIIB/Fc, Curcumin

(*Contd...*)

Table 1(*Continued*)

Targets	List of interventions
Myogenin	Trimetazidine, sulfasalazine, bortezomib, MAPK inhibitors (U0126), Curcumin, 30% caloric restriction, Vitamin D, resistance training
FOXO1	Follistatin mRNA encapsulated in lipid nanoparticles, TLR7/8 agonist R848, MT-102, AR-42
TGF-β1	SB505124, Anti- TGF-β antibody 1D11.16.8, Aerobic exercise training
PPAR-γ	Pioglitazone, L-carnitine, etomoxir, GW9662, Rosiglitazone, imidapril alone
TGF-β/Smad2	MID-35 (myostatin inhibitory D-peptide-35), Anamorelin, ActRIIB-Fc , Adalimumab
IFN-γ	anti-GDF15 antibody, Withaferin A
Sirt1/AMPK	Atractylodin, 17ß-estradiol
p38/MAPK	ARA 284 (EPO derived peptide), Omeprazol
CD8+T cells	Δ9-tetrahydrocannabinol, TLR7/8 agonist R848
PARP-1/2	Rucaparib. Olaparib
IL6/STAT3	Histone deacetylase inhibitor (HDACi) AR-42+SARM co-administration, Adalimumab, Alantolactone, Quercetin
PI3K	Adalimumab, MT-102 (β-adrenergic receptor action), MEK162/buparlisib
EGFR	erlotinib
MAPK/ERK	Erlotinib, Fuzheng Xiaoai Decoction 1 (FZXAD1) (mixture of traditional chinese medicines), MAPK (U0126) inhibitor
Glycolysis	Amiloride, Atractylenolide I, 2-deoxy-D-glucose
Ketone body oxidation	Amiloride, 2-deoxy-D-glucose
p38 MAPK	p38a MAPK inhibitors, Nilotinib, Trimetazidine (TMZ)
mTORC1	17ß-estradiol, Aerobic exercise training, Eccentric contractions
MyoD	Withaferin A, Trimetazidine (TMZ)
IL-6/AMPK/FoxO3	pan-(BET)-BRD4 protein inhibitor (+)-JQ1, Acylated (AG) and unacylated (UnAG) ghrelin
JAK2/STAT3	pantoprazole (orally), Jak2 inhibitor AG490, Ajoene garlic extract
MEK/ERK	MEK162/buparlisib, Selumetinib
AMPK	Ampk-stabilizing peptide (ACIP), Arctii Fructus (AF)
TWEAK	Anti-Fn14 antibodies, Endurance training
Adiponectin	Pioglitazone (PGZ), Aerobic exercise (treadmill running), Progressive aerobic training
GLP-1	Exendin-4, Sipjeondaebo-tang (SJDBT)

which can be attributed to mitochondrial dysfunction [36]. Furthermore, there is evidence of heightened mitophagy activity in cachectic skeletal muscle [37]. These structural changes often coincide with reductions in oxidative capacity, as indicated by alterations in the activity of key enzymes such as succinate dehydrogenase and pyruvate dehydrogenase, both vital for the tricarboxylic acid cycle. Additionally, the modulation of pyruvate dehydrogenase kinase-4, which is involved in regulating cellular energy metabolism, contributes to these metabolic shifts [38]. Collectively, these alterations drive a transition from oxidative to glycolytic muscle fiber composition in cachectic tumor hosts compared to healthy controls, playing a role in the accumulation of intramuscular fat observed in cachectic mice [39].

Aside from these catabolic mechanisms, the anabolic pathways that are responsible for muscle growth stimulation, as well as the accumulation of proteins and organelles in the cytoplasm, should not be neglected. The mechanistic target of rapamycin (mTOR) serves as a pivotal factor in growth regulation and functions as a key regulator of nutrient and stress responses [40]. It comprises mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2): mTORC1 primarily oversees anabolic processes, including protein synthesis, ribosomal and mitochondrial biogenesis, while mTORC2 is involved in maintaining glucose and lipid homeostasis [40]. mTORC1 plays a critical role in metabolic balance by activating 4E-BP1, which subsequently triggers the expression of FGF21 and enhances the translation of peroxisome proliferator-activated receptor γ coactivator-1α

(PGC-1α), thus promoting mitochondrial biogenesis and oxidative function [40,41]. Studies indicate that in cancer cachexia, increased IL-6 levels suppress mTORC1 activation by stimulating AMPK [42]. Additionally, activation of the mTOR pathway via insulin-like growth factor-1 (IGF1) is diminished in tumor-bearing mice with cancer cachexia [43]. Insulin and IGF1 initiate a phosphorylation cascade involving key regulators crucial for skeletal muscle growth, differentiation and homeostasis [44]. In the context of cancer cachexia, insulin resistance is associated with reduced glucose tolerance and insulin sensitivity, leading to decreased glucose uptake [45]. Insulin resistance correlates with diminished phosphorylation of P13K and Akt, which normally inhibits the release of FoxO and caspase-3, thus allowing for increased proteolytic activity [46].

Through this review, we additionally demonstrate the potential of nonpharmacological interventions to regulate a plethora of signaling pathways for cancer cachexia, highlighting that interest in these targets should not be monopolized by drug treatments. Exercise interventions have already been reported to positively affect and control systemic inflammation, induce protein synthesis when Akt/mTORC1 signaling is disrupted, or during systemic IL-6 overexpression, by improving mTORC1 signaling, promote the expression of several mitochondrial proteins, such as PGC-1α, mitochondrial transcription factor A and nuclear respiratory factor. This can lead to improved muscle oxidative capacity, and can also regulate hypogonadism by influencing circulating sex hormones and promoting androgen receptor expression [42,47]. Nutritional support in cancer cachexia targets the restoration of energy balance and prevention of net protein breakdown, all while avoiding stimulation of tumor growth or interference with anti-tumor treatments [48]. Achieving a net positive protein balance involves selecting nutrients that counteract catabolic signals and promote anabolic pathways [49]. Towards fostering an anabolic environment, it is essential to ensure adequate caloric intake and nutrient composition, since without sufficient nutrient availability, even the most potent anabolic signals may fail to maintain muscle mass or induce muscle growth [50].

The main drawback of this study was the broad scope of the review, which resulted in a high number of screened and consequently included articles. We attempted to solve this matter by limiting our search to include only studies from the last decade. To avoid critical loss of information, we also screened the reference lists of included studies, as well as the reference list of cachexia-related recently published reviews. Moreover, in view of the large number quantity of data, we chose to focus specifically on presenting intervention–target relationships.

In this study, we presented the therapeutic interventions and targets of cancer cachexia research throughout the last decade. Moving forward, research should aim towards refining the already available treatment strategies, while also attempting to address the gaps in the literature. Utilization and assessment of combined treatment strategies, as well as comparative research protocols, are essential requirements for future studies.

Summary Box

What is already known:

- Cachexia is a detrimental multifactorial syndrome, which has been strongly associated with cancer
- Experimental research into cancer cachexia is continuously evolving in order to provide novel therapeutic approaches
- A systematic documentation of treatment interventions and corresponding targets of cancer cachexia research would serve as an essential addition in the literature

What the new findings are:

- Over the past decade, a grand total of 271 research articles exploring interventions for treating cancer cachexia have been published
- A total of 176 studies focused on pharmaceutical interventions, encompassing 100 corresponding targets; 58 studies delved into nutritional interventions, targeting 60 pathways; and 37 studies centered on exercise interventions, also targeting 60 pathways
- A thorough exploration of the advances in cancer cachexia research holds the potential to refine existing treatment interventions and address critical gaps in our understanding

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Supplementary material

Supplementary Table 1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	P1
Title	1	Identify the report as a systematic review.	
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	na
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	na
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	na
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	na
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	na
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	na
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	na

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	na
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	na
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	na
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P6-7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P6-7
Study characteristics	17	Cite each included study and present its characteristics.	P6-7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	na
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	na
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Sup Table 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	na
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	na
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	na
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	na
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	na
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P7
	23b	Discuss any limitations of the evidence included in the review.	P11
	23c	Discuss any limitations of the review processes used.	P11
	23d	Discuss implications of the results for practice, policy, and future research.	P8-11
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P1
Competing interests	26	Declare any competing interests of review authors.	P1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2 Characteristics of the included studies for pharmaceutical,nutritional and physical activity interventions in cancer cachexia

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Re Cecconi, 2022		C26	mice	sc	Disulfiram	Inhibition p97-Nploc4 complex, UPS pathway	Prevent muscle atrophy, BW loss, increase CSA	10.1002/jcsm. 13011
Wijaya, 2022		C26 and LLC1	mice	sc	Ginsenoside Rd	Suppression STAT3, MuRF1, Atrogin-1, MSTN, reduce ROS, mitochondrial integrity protection	Improve muscle mass and function increase CSA	10.1002/jcsm. 13084
Chen, 2023		CT26	mice	sc	Saikosaponin D (component of Radix Plueri)	Inhibition STAT3, MuRF1, Atrogin-1	Improve muscle atrophy, BW loss, CSA	10.1002/ptr. 7676
Hanada, 2022		LLC	mice	sc	MID-35 (myostatin inhibitory D-peptide-35)	Inhibition TGF-β/Smad2 signaling	Improve muscle and fat atrophy, increase strength, CSA	10.1111/cas. 15491
Niu, 2021		C26	mice	sc	HSP90 inhibitor (alvespimycin)	Disruption HSP90/STAT3/FOXO1 axis, down regulation MSTN, MuRF-1, Atrogin-1 signaling,	Increase body and muscle mass, strength, iWAT, CSA	10.1111/bph. 15625
Kim-Muller, 2023		TOV21G	immunodeficient mice	sc	anti-GDF15 antibody	Modulation TNF-α/NF-κB and IFN-γ pathways	Increase lean and fat mass, physical performace, food intake, CSA	10.1016/j.celrep. 2022.111947
Yu, 2022		CACS colitis associated colorectal cancer mice			Atractylodin	Antiinflammatory effect, Increase NPY through Sirt1/ AMPK-regulated autophagy	Increase BW, muscle and fat weight, reduce tumor weight	10.1016/j.bbrc. 2022.08.011
Palus, 2022		AH-130	rats	ip	ARA 284 (EPO derived peptide)	Activation anabolic pathways (Akt), downregulation catabolic pathways (GSK-3β, MSTN, p38/ MAPK)	Alleviate loss of BW, lean and fat mass, increase spontaneous activity, prolong survival	10.1002/jcsm. 13009
Fang, 2022		A549	nude mice	sc	Emodin	Inhibition TCF4–TWIST1 interaction and consequent suppresion TGF-β1-induced PTHLH expression, suppression atrophy-associated genes	Alleviate muscle loss and down regulation fat browing	10.3390/ nu14071508
Deyhle, 2022		KPC	mice	pancreas	anti-Ly6G antibody	Immunomodulation by depletion of Ly6G+ cells, (gMDSCs and neutrophils) in tumor and muscle, modification of tumor microenvironment	Reduce muscle wasting, BW, protection fast twitch muscle fibers	10.3390/ cells11121893

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Liu, 2023		LLC	mice	sc	Omeprazol	Inhibition release of Hsp70/90-carrying Evs by increasing intracellular vacuolar pH and suppressing Rab27b expression. Inhibition p38/MAPK related catabolic pathways (UPS, ALS)	Prevents loss of muscle mass and function, increase fat mass, CSA and survival	10.1002/jcsm.12851
Ng, 2023		AOM/DSS model of CAC	mice		Δ9-tetrahydrocannabinol	Reduce serum cytokines and CD8+ T cells infiltration in muscle, reduce myotube atrophy and apoptosis via activation of CB2 in CD8+ T cells, suppression Atrogin-1, MuRF-1	Reverse negative effect on body, heart and muscle weight, no effect on tumor size	10.1016/j.biopha.2023.114467
Queiroz, 2022		GEMM of lung cancer (KL: KrasLSL-G12D/ +;Lkb1flox/flox	mice		Anamorelin and ActRIIB-Fc	Activation ghrelin receptor, inhibitionTGF-β/SMAD pathway	Increase food intake (anamorelin), Increase lean mass and spontaneous activity (ActRIIB-Fc), increase fat mass and survival (anamorelin/ActRIIB-Fc only in female mice)	10.1038/s41467-022-32135-0
Kerr, 2023		LLC	mice	sc	EXT418 (ghrelin analog)	Prevent increase of Atrogin-1, Murf1 and IL-6 levels, decrease mitophagy marker Bnip-3	Attenuation muscle weight loss and strength	10.1002/jcsm.13211
Schmich, 2023		GEMM of PDAC (Trp53, Kras, Pdx-1-Cre)	mice		MAOI (harmine-hydrochloride)	Inhibition inflammation (IL-1, Socs3) and proteolysis (MuRF1 and FBX032) but adverse prooxidative effects (depletion GSH, mitochondrial damage, centronucleation)	Promotes muscle wasting, mainly 'white' glycolitic fibers	10.3390/biomedicines11030912
Pérez-Peiró, 2022		LP07	mice	sc	PARP-1/2 inhibitor (rucaparib)	Attenuation UPS and ALS	Improve BW, physical activity, reduce tumor burden, no effect on muscle weight, CSA and strength	10.3390/cancers14122894
Wijaya, 2023		LLC	mice	sc	Gintonin	Reduction oxidative stress, activation of the LPAR/Gαi2 signaling pathway and inhibition of TNF-a, MSTN, MuRF-1 atrogin-1	Increase tumor-free body weight, muscle weights, grip strength, CSA	10.1016/j.neo.2021.11.008

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Kang, 2022		C26 mice sc	mice	sc	adalimumab	Block TNF-α receptor, antiinflammatory action, modulation of multiple pathways involved in muscle cell catabolism, apoptosis, regeneration (UPS, Pax-7, TGF-β/SMAD, IL-6/ STAT3 inhibition and PI3K, AKT/ mTOR activation)	Improves muscle atrophy, fat and weight loss, prolong survival	10.3164/ JCBN.21-21
Wang, 2021		LLC	mice	sc	SB505124	Inhibition TGFβ type I receptor ser/ thr kinase/	Cachexia associated anemia: increase erythropoiesis and attenuates deterioration hematopoietic stem cells niche in bone marrow	10.1186/ s13287-020-02120-9
Weber, 2022		LLC	mice	sc	erlotinib	EGFR inhibition and suppression of PTHrP, inhibition MAPK/ERK pathway	Increase muscle and fat mass, strength, physical activity, reduce thermogenic activity in tumor	10.1002/jcsm. 12985
Pin, 2022		ES-2	immunodeficient mice	ip	anti-RANKL antibodies or zoledronic acid	Modulation of inflammatory and atrophic pathways (NF-Kb, UPS etc)	Reduce myotube atrophy, improve muscle mass and strength, block bone loss	10.1002/jbmr. 4480
Zhong, 2022		GEMM of PDAC (Trp53, Kras, Pdx-1-Cre)	mice		ACVR2B/Fc	Modulation metabolic and atrophy pathways mainly or esxclusively in males	Protect muscle and fat mass only in male mice (estradiol-regulated production of endogenous activin inhibitors in females at early stages), no effect on tumor growth and survival,	10.1002/jcsm. 12998
Dasgupta, 2022ic		KPC	mice	pancreas	3-methyladenine	Reduction PERP expression, decrease atrophy related genes expression	Preserve lean mass, improve survival, decrease tumor growth	10.1172/jci.insight. 153842
Zhou, 2021		CT-26 and LLC	mice	sc	Amiloride	Inhibition tumor-derived exosome release, attenuation hypercatabolism (transcriptomic profile), improve glycolysis and ketone body oxidation in muscle	Prevention BW, muscle and fat loss, no effect on tumor growth	10.1186/ s13395-021 -00274-5

(*Contd...*)

Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Wu, 2022		C26	mice	sc	MDP	Antiiflammatory properties (reduction IL-6), regulation of gene exression involved in muscle homeostasis (i.e. MuRF-1, Atrogin-1 etc)	Protection muscle atrophy, BW loss, strength, CSA, no effect on food and water intake, no effect on tumour burden	10.1002/jcsm.13028
Fan, 2022		C26	mice	sc	Atractylenolide I	Inhibition IL-6 and STAT3/PKM2 pathway, inhibition of biogenesis and secretion of Evs, suppression aerobic glycolysis and lipolysis.	Increase food intake, BW, WAT, CSA, slight effect on muscle weight, no effect on tumor burden	10.1002/jcsm.13079
Shen, 2022		C26	mice	sc	Alantolactone	Inhibition IL-6/STAT3, weak inhibition TNF-a, NF- κB	Attenuation muscle loss, weight, slight amelioration fat loss	10.1016/j.phymed.2021.153858
Wei, 2022		C26	mice	sc	2-deoxy-D-glucose	Glycolysis suppression , biochemical pathways modulation (increase liver ketogenesis, increase ketone utilization in muscle and ATP generation, block Cori cycle), inhibition STAT3, UPS and autophagy)	Alleviation BW loss, muscle atrophy	10.3390/cells11192987
Pin, 2022		C26	mice	sc	MitoQ (mitochondria-targeting antioxidant)	Inhibition E3 ligases but no effect on anabolic pathways (Akt and mTOR), improve oxidative mitochondria metabolism, reduce fat accumulation and induce β-oxidation in muscle.	Reduse weight loss, improve muscle mass and strength, no effect on tumor size	10.3389/fcell.2022.861622
Korzun, 2022		ES-2	Immunodeficient nude mice	ip	Follistatin mRNA encapsulated in lipid nanoparticles	Reduce Activin A and atrophy related genes (MuRF-1, Atrogin-1, FOXO1)	Reverse muscle loss, increase CSA, reduce tumor burden, Reduce chemotherapy associated muscle atrophy (cisplatin)	10.1002/smll.202204436
Liu, 2021		LCC	mice	sc	Ghrelin and GHSR-1a	a) Modulation autophagy-lysosome pathway, mitophagy and mitochondrial respiration (GHSR-1a dependent), b) Prevention UPS activation c) No effect on protein synthesis	a Attenuation muscle weakness, improve food intake and increase BW (GHSR-1a dependent) b) Prevention muscle mass loss (independently of GHSR-1a), no effect on tumor size	10.1002/jcsm.12743

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Yuan, 2023		AH-130 and LLC	rats mice	ip im	S-oxprenolol	non-selective β1-adrenoceptor blocker and central 5HT1α, preservation anabolic (IGF-1, Akt) and inhibition catabolic pathways (FBXO-40, TRAF-6)	Improve food intake, BW loss, lean and fat mass and survival (Yoshida), muscle mass protection and grip strength (LLC)	10.1002/jcsm.13116
Fang, 2023		LLC	mice	sc	Streptonigrin	InhibitionTCF4/TWIST1-induced PTHLH expression, increase expression of proteolysis related genes in muscle and browning related genes in fat	Improve muscle atrophy and adipose tissue	10.21873/anticanres. 16260
Li, 2021		C26	mice	sc	HMGB1 (glycyrrhizin)	Down-regulation TLR4/NF-κB pathway, inflammatory cytokines (IL-6, TNF) and expression atrophy related genes (MuRF-1, Atrogin)	Alleviation weight mass loss, restoration muscle and fat mass loss	10.3389/fphar.2021.731386
Morgan, 2021		Ehrlich cells	mice	sc	Butanolic fraction of V. tucanorum (Fr-BuVt),	Prevention catabolic state, anti-inflammatory activity (TNF-a, IL-6)	Preservation BW, lean mass and WAT, anti-tumor effect	10.1016/j.molmet.2022.101612
Zhao, 2022		Pan02	mice	pancreas	p38a MAPK inhibitors	Downregulation UCP1 and p38	Prevention weight loss, reduce the WAT browing, improve survival	10.3390/nu14153013
Cheng, 2023		C26	mice	sc	Fuzheng Xiaoai Decoction 1 (FZXAD1) (mixture of traditional chinese medicines)	Activation AKT1, mTOR, inhibition MAPK/ERK, HIF-1a	Alleviation muscle atrophy, kidney atrophy, increase BW	10.1016/j.jep.2022.115944
Zhang, 2022		GEMM CC ApcMin/+	mice		Baoyuan Jiedu decoction	Improve mitocondria structure and function, modulation oxidative stress	Alleviation weight loss, muscle mass	10.3389/fphar.2022.914597
Shi, 2022		Human PDAC cell lines	athymic nude mice	pancreas	Circular RNA ANAPC7	Suppression of CREB–miR-373–PHLPP2-Akt axis, leading to down regulation of Cyclin D1 and TGF-β	Improve muscle wasting, grip strength, CSA and survival, inhibition tumor growth	10.1053/j.gastro.2022.02.017
Sadek, 2021		C26	mice	sc	iNOS inhibitor	Inhibition IL-6, TNF-a, and IL-1b, prevention loss of mitochondrial integrity and ATP production, inhibition AMPK restore mTOR suppresion and increase protein synthesis	Prevention muscle mass and function loss, no protective effect on adipose tissue wasting	10.15252/emmm.202013591

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Counts, 2019		GEMM for CC ApcMin/+	mice		17ß-estradiol	Suppresion AMPK , enhance mTORC1 signaling, improve mitochondrial respiration, induction of MuRF-1 (not Atrogin-1) protein expression	Prevention loss of weight, muscle mass, physical inactivity and strength, increase food intake	10.3389/fendo. 2019.00720
Sin, 2021		LLC	mice	sc	Nilotinib (selective at low doses inhibitor of p38β MAPK)	Inactivation of p300 – C/EBPβ pathway, down-regulation UPS and ALS	Alleviation muscle wasting, increase CSA, prolong survival	10.1158/0008-5472. CAN-19-3219
Hulmi, 2023		C26	mice	sc	ACVR2B/Fc	Increase mitochondria oxidative phosphorylation, restore NAD depletion, increase protein synthesis	Increase BW, rescue muscle mass loss, no effect on tumor growth	10.1016/j.molmet. 2020.101046
Martins, 2020		Walker 256	rats	sc	Euphorbia tirucalli latex	Immunomodulation (increased phagocytic capacity and inhibition tumor cell proliferation)	Amelioration cachectic parameters (BW, Glucose and triacylglycerol serum levels), antitumor potential	10.1016/j.jep. 2020.112722
Shukla, 2020		KPC	mice	pancreas	Clodronate liposome	Macrophage depletion, suppression IL-6 and IL-1α levels, decrease ROS, inhibition STAT3, Atrogin-1 and MuRF1, and restored MyHC	Increase fat and muscle mass, strength, restore CSA, reduce tumor burden	10.1016/j.canlet. 2020.04.017
Ojima, 2020	lung	LLC	mice		Peptide-2	Specific inhibition of myostatin (MSTN) & slightly GDF-11 signaling pathways	Prevent muscle wasting, increase gastrocnemius muscle weight and muscle area, enhance grip strength, prolonge survival	10.1111/cas. 14520
Huot, 2020	metastatic colorectal ca	HCT116 human CRC cells (mHCT116)	NSG male mice		ACVR2B/Fc (synthetic peptide inhibitor of ACVR2B	Activin receptor type 2B (ACVR2B) signalling blockade	Preserve adipose tissue, bone, and SKM, maintain muscle and cardiac functions.	10.1002/jcsm. 12642
Smuder, 2020	colon adeno carcinoma	C26	mice	sc	SS-31 mitochondria-targeting peptide	targeting of mitochondrial function and ROS production : binds to cardiolipin and improves mitochondrial function through facilitation of electron transfer, inhibition of cytochrome c peroxidase activity and reduction of proton leak in mitochondrial matrix	Prevent cardiorespiratory muscle weakness (heart and diaphragm):, Preserve cardiac function, Muscle mass, Diaphragm and ventilatory function, increase diaphragm muscle fiber CSA, reduce mit.ROS production	10.18632/ oncotarget. 27748

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Ballarò, 2021		C26	mice	sc	SS-31	Interaction with mitochondrial cardiolipin, improve mitochondrial activity (increase SDH, intracellular ATP) but ineffective to rescue protein anabolism	Partial anticachectic effects (partial relieve of BW loss and preservation of glycolytic muscle fibers-no effect on muscle mass and strength), no effect on tumor growth	10.3390/cancers13040850
Freitas, 2020		LLC	mice	sc	FFA1 agonist	Increase leptin, restore brain glucose metabolism	Restore cachexia-associated parameters (BW, WAT, behavioral impairment, locomotor activity), splenomegaly, no effect on muscle atrophy, decrease tumor mass	10.1152/ajpendo.00509.2019
Straughn, 2021		A2780	immunodeficient mice	ip	Withaferin A	Pax7-dependent increase of MyoD, induction of adaptive UPR response, down-regulation ALS	Improve muscle mass and strength, CSA, activation and differentiation satellite cells, anti-tumorigenic properties,	10.3389/fcell.2021.636498
Straughn, 2019		A2780	immunodeficient mice	ip	Withaferin A	Modulation NF-κB pathway and related proinflammatory cytokines in muscle and in tumor	Attenuation loss of lean mass, increase CSA and abolishes the slow-to-fast myofiber-type conversion, improve strength, reduce mortality rate, anti-tumorigenic properties	10.1186/s13048-019-0586-1
Zhu, 2020		MCA	rats	tissue implantation sc	TCMCB07 melanocortin-4 receptor antagonist hypothalamus	Suppression inflammatory and P selectin gene expression in hypothalamus	Preservation BW, lean and fat mass, reduction anorexia	10.1172/JCI138392
Michaelis, 2019		KPC	mice	pancreas and ip	TLR7/8 agonist R848	Anti-tumor immune response (increase CD8+T-cell infiltration, decrease regulatory T cells), improve muscle molecular physiology (E3, Foxo1, autophagy transcripts)	Protection cardiac and lean mass, increase food intake, reduce weight loss, increase locomotion and survival, antitumor effect	10.1038/s41467-019-12657-w

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Ghonim, 2021		GEMM for CC ApcMin/+	mice		Partial PARP-1 inhibition (olaparib moderate dose)	Antitumor immune response and modification of intratumoral microenvironment, modulation systemic inflammation (MCP-1, TNF-α)	Increase BW, reduce spleen size and tumor burden	10.1136/jitc-2020-001643
Chen, 2020		C26	mice	sc	Cryptotanshinone	Inhibition STAT3 activation and suppression E3 ubiquitin ligases (MuRF1, Atrogin-1)-	Improve weight loss and muscle wasting, inhibition tumor growth	10.1016/j.jep.2020.113066
Zeng, 2020		C26	mice	sc	AG and UnAG	Inhibition calpain activity, reduce Atrogin-1, increase Akt, reduce TNF-a, (Murf-1 not affected)	Improve tumor-free body weight, muscle and fat atrophy, grip strength and nutritional status, no effect on tumor growth	10.4103/CJP.CJP_59_20
Adams, 2020		B16-F10	mice	sc	Myomed-205 and -946	Attenuation metabolic signatures related to ER and ROS stress, UPS and autophagosome activity. Improve mitochondrial enzymatic activity.	Allevation BW and fat loss, preserve muscle weight and strength	10.3390/cells9102272
Pötsch, 2020		AH-130	rats	ip	MT-102 (β-adrenergic receptor action)	Induction anabolic signaling (PI3K/AKT/mTOR pathway), reduction catabolic signaling (caspases and proteasome, NF-κB, FoxOs, LC3), MuRF-1 (not affected), increase MAFbx	Improve food intake, BW, fat and lean mass, spontaneous activity , survival	10.1002/jcsm.12537
Kelm, 2020		A2780	immunodeficient mice	ip	Withaferin A	Reduction serum Ang-II and cytokines (IL-6, TNF-α, IFN-γ) through AT1 pathway, prevents shift of adult MHCα to the embryonic MHCβ isoform, increase Troponin-I levels	Rescue body and heart weight loss, improve systolic (and in a lesser extent) diastolic function, reduce cardiac fibrosis, preserve cardiomyocyte CSA, reduction tumor burden	10.1371/journal.pone. 0236680
Zhong, 2019		KPC	mice	pancreas	sActRIIB/Fc	Blockade circulating activins, reduction Atrogin-1, MuRF-1, MSTN	Attenuation heart, skeletal muscle and fat loss, prolong survival, antitumor effect	10.1002/jcsm.12461
Lee, 2021		C26	mice	sc	Lithium chloride	Enhance myogenic differentiation and preservation myotube wasting (Increase MHC, down regulation Pax-7, MuRF-1, Atrogin-1), inhibition IL-6	Increase muscle mass and strength, CSA, no effect on fat mass and tumor growth	10.3390/cells10051017

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Liva, 2020	colon adenocarcinoma	C26	mice	sc	Histone deacetylase inhibitor (HDACi) AR-42 + SARM co-administration	Combined Anabolic and anti-catabolic action AR-42/SARM: WNT/β-catenin signaling pathway regulation, IL-6/ STAT3 downregulation in skeletal muscle.	Anabolic androgen monotherapy with SARM ineffective preventing muscle and body weight loss. SARM+AR42 improved survival, total body weight, hindlimb skeletal muscle mass, and grip strength	10.15252/emmm.201809910
Suriben, 2020	gastric, ovarian, liver (PDX)/ RENCA, B16Bl6 (syngeneic)	PDX, syngeneic , HT1080	mice		3p10 monoclonal antibody	Targeting GDF15-GFRAL, inhibition of RET protooncogene/ GFRAL interaction on cell surface (peripheral sympathetic axis), peripheral chemical sympathectomy, loss of adipose triglyceride lipase	Reverse excessive lipid oxidation. Prevent weight loss. Inhibition of GDF15–GFRAL activity reverses cancer cachexia even under calorie-restricted conditions	10.1038/s41591-020-0945-x
Chen, 2019	colon adenocarcinoma	C26	mice	sc	Matrine (alkaloid)	Decrease E3 ubiquitin ligases expression in skeletal muscle, activate Akt/mTOR/FoxO3α signaling pathway, downregulate MuRF1, MAFb xexpression	Preserve mass and CSA of myofibers, ameliorate cachexia by increasing body, fat and organ weights	10.3892/or.2019.7205
Lautaoja, 2019	colon adenocarcinoma	C26	mice	sc	ACVR2B (activin receptor type 2B)	Dysregulated muscle and serum metabolomics	Metabolomes dysregulation in tumor-bearing mice despite amelioration of cachexia with ACVR2 ligand blockade. free phenylalanine as a promising biomarker of muscle atrophy or cachexia	10.1152/ajpendo.00526.2018
Nissinen, 2018	colon	C26	mice		sol. ACVR2B (before/after tumour formation)	reduce increased protein synthesis and Stat3 phosphorylation, partially restore colocalization of mTOR with the lysosomes/ late-endosomes	Improve survival, restore diaphragm-skeletal mass (only in after tumor formation tretment), prevented liver and spleen responses (indepedent treatment protocol)	10.1002/jcsm.12310

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Molinari, 2017	colon	C26	mice	ip	Trimetazidine (TMZ)	Mitochondrial oxidative metabolism reprogramming, activate MAPK-dependent signal transduction pathways, phosphorylated p38MAPK activates PGC1α (major mediator of exercise phenotypic adaptation, mainly expressed in slow muscles and slow fibre specification)	'Exercise mimetic'-like action: Enhance Grip strength, fast-to slow metabolic and contractile myofibre phenotype shift, mitochondrial biogenesis, oxidative metabolism up-regulation, partially restores myofibre CSA, reduce glycaemia	10.1002/jcsm.12226
Chacon-Cabrera, 2017	lung	Parp-1-deficient Parp-1−/− and Parp-2−/−	immunodeficient mice		Potential PARP-inhibitors	PARP inhibition improve mitochondrial function, down-regulation NF-κB and E3 ligases. Activation of PARP-1 or -2 is likely to play a role in muscle protein catabolism via oxidative stress, NF-κB signaling and enhanced proteasomal degradation in cachexia	Attenuate muscle wasting, protein oxidation, tyrosine release, ubiquitin-proteasome system, reduction in contractile myosin and atrophy of the fibers, Therapeutic potential of PARP activity inhibition	10.1002/jcp.25851
Segatto, 2017	colon	C26	mice	sc	pan-(BET)-BRD4 protein inhibitor (+)-JQ1	BRD4 protein blockade by (+)-JQ1, dual control on genes expression involved in muscle atrophy, by impairing BRD4 and BRD2 direct occupancy at catabolic genes and by restraining the IL-6/AMPK/FoxO3 axis activation	Protect from body weight loss, muscle and adipose tissue wasting, prolongs survival. BET proteins as promising therapeutic target	10.1038/s41467-017-01645-7
Morimoto, 2017		castrated male rats/ TNFα-induced cachexia mice/G361 cancer cachexia rats/ C26 mice	rats/mice	sc	SARM-2f (selective androgen receptor modulator)	Activation of androgen receptors in muscles or CNS, inflammation suppression	Anabolic effects, prevention of body weight loss and sarcopenia (without excessively stimulating sex accessory organs), improvment of anorexia	10.3892/ol.2017.7200
Lin, 2017	colon	C26	mice	sc	Calpain inhibitors i.p. (different types)	Reduce calpain activity and expression of MuRF-1 and atrogin-1, increase level cleaved caspase-3 and BAX and lowering level of BCL-2 in some groups	Ameliorate muscle wasting, metabolic profiles and increase survival time	10.3892/or.2017.5396

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Guo, 2017	colon	C26	mice	sc	Pantoprazole (orally)	Inhibiting inflammatory response and blocking JAK2/STAT3 or ubiquitin proteasome pathway	Alleviate body weight reduction and inhibit skeletal muscle wasting in dose-dependent manner.	10.18632/oncotarget. 17387
Yoshimura, 2017	colon	C26	mice	sc	Z-505 hydrochloride (Z-505)	Strong agonistic activity similar to that of human ghrelin, increased anabolic hormone levels stimulated by activation of ghrelin receptor, GHSR1a.	Increase food intake, inhibit weight loss, attenuate muscle wasting and fat loss, increase circulating anabolic factors (insulin and IGF-1), but not catabolic factors (IL-6 and corticosterone)	10.1016/j.ejphar.2017.05.036
Hu, 2017	pancreatic	MiaPaCa2 cells	athymic mice	sc	Emodin and rhein	Inhibit HIF-1α expression	Attenuated high hepatic gluconeogenesis and skeletal-muscle proteolysis (two pathological constituents of cancer cachexia)	10.18632/oncotarget. 21330
Talbert, 2017	colon	C26/C-26R (MEK162-resistant)	mice	sc	MEK162/buparlisib (PI3K/Akt inhibitor)	MEK1/2 and Ras/Raf/MEK/ERK pathway inhibition,/PI3K/Akt pathway inhibition	Tumor-extrinsic effect that preserves skeletal muscle (MEK162) and tumor-intrinsic antitumor activity (buparlisib). As monotherapy, MEK inhibition preserves muscle mass, can directly prevent cancer cachexia without affecting tumor growth, combinatorial treatment with PI3K/Akt inhibitor exhibits antitumor activity.(preclinical data)	10.1158/1535-7163.MCT-16-0337
Yang, 2017	colon	C26	mice	sc	Selumetinib (MEK inhibitor)	MEK/ERK inhibition , AKT & mTOR activation	Attenuating muscle wasting	10.1158/1535-7163.MCT-16-0324

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Gatta, 2017	colon	C26	mice	sc	Trimetazidine (TMZ)	metabolic reprogramming, inhibit mitochondrial FFA β-oxidation, enhance glucose oxidation, overexpression of MyoD, Myogenin, Desmin and slow isoforms of troponin C&I, stimulate AMPKphosphorylation	Enhance myoblast differentiation and promote myogenesis	10.18632/oncotarget. 23044
de Morais, 2017	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats	sc	Insulin (INS) and glutamine dipeptide (GDP)	Suppression of lipolysis, reduction of lipases expression (ATGL and LHS)	INS and INS+GDP prevent retroperitoneal fat wasting and BW loss, anorexia and hyperlactatemia BUT accentuate loss of muscle mass. GDP treatment DID NOT show beneficial effects.	10.1016/j.ejphar. 2017.03.010
Salazar-Degracia, 2017	ascites hepatoma	Yoshida AH-130	rats	i.p.	Formoterol	Beta2-adrenoceptor-selective agonist. Decrease protein oxidation and inflammation	Attenuation of rise in oxidative stress in limb muscles, inflammatory cell infiltration, and loss of myosin content in both respiratory and limb muscles, NO effects observed in the MRC complex activities	10.7717/peerj. 4109
Sun, 2016	ascites-induced hepatic ca (xenograft tumor)	H22 cells	mice	abd.	jianpijiedu (MJPJD)	Reduction in IL-lα, IL-6, TNF-α levels, MU-RF1m, atrogin 1 proteins and inhibiting activation of ubiquitin proteosome pathway	Reduce consumption of gastrocnemius, inhibit increase in body weight and ascites volume, enhance food intake	10.3892/mmr. 2016.5602
Rohm, 2016		C26 , LLC, SW480	mice	sc	Ampk-stabilizing peptide (ACIP)	Inhibit Ampk interaction with Cidea protein, preserve Ampk integrity, lipid homeostasis of WAT	Ameliorate WAT wasting, ACIP-dependent preservation of Ampk integrity in WAT as concept in future therapies for cachexia	10.1038/nm. 4171
Saitoh, 2016	hepatoma	Yoshida hepatoma AH-130	rats	i.p.	Erythropoietin	reduce proteasome activity, improve anemia, multiple tissue-protective efficacy (inhibition of apoptosis, attenuation of inflammatory responses)	Improve cardiac wasting, ameliorate loss of BW, wasting of lean mass, fat mass and reduced physical activity	10.1016/j.ijcard. 2016.05.008

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Wang, 2016	colon	C26	mice	sc	Aliskiren (renin inhibitor)	Antagonize cachexia-induced RAS activation, systematic & muscular inflammation, oxidative stress, autophagy-lysosome pathway, ubiquitin-proteasome pathway.	Alleviate significantly BW loss, tumor burden, muscle wasting, muscular dysfunction, shortened survival.	10.3892/or. 2016.5118
Toledo, 2016		LLC	mice	intramusc.	Combination of soluble myostatin receptor ActRIIB (sActRIIB) and β2-agonist formoterol	Additive effect, formoterol reduced protein degradation rate, sActRIIB increased protein synthesis	Complete reversal of muscle wasting, recover muscle weight, grip strength, increase food intake	10.1002/ijc. 29930
Xi, 2016	xenograft	HCT116 cells	mice	sc	Vector plasmid for Mfn2 overexpression	Downregulation of Mfn2 in skeletal muscle cells may lead to mitochondrial dysfunction and thereby muscle wasting	Mfn2 protects against cachexia-induced muscle loss, re-introduction/ overexpression of Mfn2 ameliorate muscle wasting	10.3892/ol. 2016.5191
Musolino, 2016	ascites hepatoma	Yoshida AH-130	rats	i.p.	Megestrol acetate (MA)	Downregulation of autophagy, in both skeletal and heart muscle	Attenuate BW loss, lean and fat mass wasting, improvement of cardiac function	10.1002/jcsm. 12116
Sun, 2016	colon, lung	C26 , LLC	mice	sc	Valproic acid (VPA)	Histone deacetylase (HDAC) inhibitor, Reduction of C/EBPB binding to atrogin1 promoter locus in myotubes, atrogin1 downregulation	Increase mass and CSA of skeletal muscles, eventual alleviation of muscle wasting and myotube atrophy	10.1152/ajpcell. 00344.2015
Salustiano, 2016	carcinoma, melanoma	Ehrlich ascites carcinoma (EAC) , B16F10 melanoma	mice	sc/ip	Pterocarpanquinone LQB-118 hybrid	Pro-inflammatory cytokines downregulation, counteract with TNF-α liberation and translocation of NF-κB to the nucleus	Ameliorate cachexia, more effective in B16F10-mice than EAC. Antineoplastic effect, minimal immunotoxicity	10.1007/ s10637-016-0359-2
Greco, 2015	Pancreatic ductal adenocarcinoma (PDA)	syngeneic metastatic model (Pan02 murine PDA cell line, FC1242 PDA tumor cells)	mice	i.p.	Anti- TGF-β antibody 1D11.16.8	TGF-β inhibition, decrease metabolic changes	Validation of a simplified useful model of pancreatic cancer cachexia to investigate immunologic treatment strategies. TGF-β inhibition improve mortality, weight loss, fat mass, body mass, bone mineral density, skeletal muscle proteolysis	10.1371/journal. pone. 0132786

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Narsale, 2016		ApcMin/+	mice		Pyrrolidine dithiocarbamate (PDTC) , short term administration	Anti-inflammatory and antioxidant properties, In muscles suppress inflammatory signaling, attenuate protein degradation and activate protein synthesis. In liver increase glycogen and lipid content independent to alterations in inflammatory signaling.	Attenuate ca-induced disruptions to muscle and liver signaling, independently to altered tumor burden and circulating IL-6.	10.18632/ oncotarget. 10699
Borner, 2016	hepatoma	McA-RH7777 (Morris hepatoma 7777 cells)	rats	sc	Ghrelin receptor agonist HM01, synthetic	HM01 mimick ghrelin action, upregulation of lipogenic enzymes and reduction of lipid export in adipose tissue, reduction of metabolic rate.	Protect against BW loss, higher FI, higher muscle and fat mass, by attenuating anorexia and by reducing energy expenditure	10.1152/ajpregu. 00044.2016
Johnston, 2015	?	hFn14-expressing MEF tumor cell line , C26	syngeneic mice		Anti-Fn14 antibodies	Inhibit cytokine TWEAK and its cognate receptor Fn14 pathway (members of TNF/TNFR superfamily)	Protect from tumor-induced inflammation and loss of fat, muscle mass &strength.	10.1016/j.cell. 2015.08.031
Tseng, 2015	colon, lung	C26 , LLC	mice	sc	AR-42 (HDAC inhibitor)	Suppress changes in inflammatory cytokine production and procachexia drivers (IL-6, IL-6Rα, leukemia inhibitory factor, Foxo1, Atrogin-1, MuRF1, ATGL, uncoupling protein 3, myocyte enhancer factor 2c). Restore glycolysis, glycogen synthesis, and protein degradation	Prevent reductions in muscle and adipose tissue mass, muscle strength, fiber size, preserve body weight, prolong survival	10.1093/jnci/djv274
Seto, 2015	colon	C26	mice	sc	leukemia inhibitory factor (LIF)	Increase in LIF precedes the increase of IL-6	Important role of LIF-JAK2-STAT3 in the initiation and progression of C26 cancer cachexia	10.1074/jbc. M115.638411

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Wang, 2015	colon	C26	mice	sc	Combination of carfilzomib (CFZ) and z-VAD-fmk	CFZ inhibit RAS activity, fCFZ+z-VAD-fmk inhibit apoptosis and ubiquitin-proteolysis pathways. Higher levels of caspase-3, BAX and lower level of BCL-XL in g.m, alter level of proteins in the renin-angiotensin system	Early combined treatment ameliorate weight loss, muscle wasting, reduce tumor burden, restore metabolism (higher levels of glucose, albumin and total proteins, lower levels of triglyceride fatty acids), more spontaneous physical activity, longer survival	10.1007/s12032-015-0538-6
Konishi, 2015	ascites hepatoma	Yoshida hepatoma AH-130	rats	i.p.	Febuxostat	Novel selective xanthine oxidase inhibitor, reduce ROS	Attenuate loss of body weight and wasting of lean/fat mass, improve survival	10.1002/jcsm.12017
Beluzi, 2015	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats	sc	Pioglitazone (PGZ)	Activate PPARγ transcription factor, induce insulin-sensitive genes, reduce insulin resistance and adipose tissue loss, upregulate gene expression of PPAR-γ, adiponectin, LPL and C/EBP-α	Adipogenic and lipogenic effect, prevent BW loss, delay onset of cachexia, increase survival, effective during the early stages of the disease	10.1371/journal.pone.0122660
Xu, 2015	colon	C26	mice		Celecoxib	Downregulation of VEGF expression	Attenuate decline in BW and food intake, improve survival	10.3892/mmr.2014.2730
Jiang, 2015	colon	C26	mice	sc	L-carnitine or etomoxir (i.p.) or pioglitazone hydrochloride (p.o.) or GW9662 (i.p.)	Increased levels of PPAR-α and PPAR-γ in liver, augment phosphorylation of PPAR-γ and attenuate expression of phospho-p65 and (COX)-2, attenuate increased mRNA expression levels of sterol-regulatory element-binding protein-1c (SREBP-1c) and FAS.	Improve cachexia and biochemical parameters via the PPAR-γ signaling pathway, decrease serum concentrations of interleukin (IL)-6 and tumor necrosis factor-α (TNF-α). Ameliorative effects of L-carnitine were lessened by the carnitine palmitoyltransferase I (CPT I) inhibitor, etomoxir	10.1159/000439550
Li, 2014	colon	C26	mice		Baicalin (flavonoid)	Suppress cytokine expression, inhibit activation of NF-κB	Ameliorate anorexia, prevent skeletal muscle atrophy	10.1007/s13277-014-2558-9

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Pietra, 2014	Preclinical pharmacologic profile (no tumors) ???		rats, pigs	rats: orally, pigs: intragastric (catheter)	Anamorelin HCl (ANAM)	Highly specific ghrelin receptor agonist, increase in GH and IGF-1	Appetite-enhancing, increas food intake and BW	10.1007/s13539-014-0159-5
Toledo, 2014	ascites hepatoma	Yoshida AH-130	rats	i.p.	Formoterol	β2-adrenoceptor-selective agonist (muscle growth promoter) , decrease protein degradation, apoptosis, increase protein synthesis, muscle regeneration, reduces oxidative stress	Reduction of muscle weight loss, increase lean body mass and body water, do not negatively alter heart function, improve some cardiac parameters	10.1007/s13539-014-0153-y
Ando, 2014	lung	LLC-IL6, murine model of human lung cancer (Pre-clinical and experimental studies)	human patients, mice	sc	Tocilizumab (MR16-1 rodent analog)	Anti-IL-6 receptor antibody	Attenuate loss of BW, maintain better food and water intake and milder cachectic features in blood, prolong survival, & serum IL-6 is marker for evaluating cachexia and prognosis of patients with chemotherapy resistant metastatic LC	10.1371/journal.pone. 0102436
Tsubouchi, 2014	lung adenocarcinomas	urethane-treated, bronchioalveolar epithelium-specific Pten-deficient	mice	i.p.urethane injection	Ghrelin	Reduction of systemic proinflammatory cytokines, anti-catabolic effect through direct blockade of proteolytic pathways, enhance anabolic pathways	Ameliorate BW loss, reduction of fat mass, and retaine muscle mass and muscle contraction force	10.1016/j.ejphar.2014.09.025
Honors, 2014	ascites sarcoma tumor	Yoshida sarcoma	rats	sc	Exendin-4	GLP-1 agonist and insulin sensitizing agent, potent anti-inflammatory effects	Prevent development of CCA symptoms in animals with small, but not large, tumors, preserved insulin levels	10.1007/s12672-013-0163-9
Mirza, 2014	adenocarcinoma	MAC16	mice	sc	leucine & Ca-β-hydroxy-β-methylbutyrate (Ca-HMB)	Reduce activity of the ubiquitin-proteasome pathway	Both attenuate protein degradation increase and protein synthesis decrease, HMB was more potent, low dose of Ca-HMB (0.25 g/kg) to be 60% more effective than leucine (1 g/kg) in attenuating loss of body weight over a 4-d period	10.1016/j.nut.2013.11.012

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Jiang, 2015	colon	C26	mice	sc	L-carnitine or etomoxir (i.p.) or pioglitazone hydrochloride (p.o.) or GW9662 (i.p.)	Increase levels of PPAR-α and PPAR-γ in liver, augment phosphorylation of PPAR-γ and attenuate expression of phospho-p65 and (COX)-2, attenuate increased mRNA expression levels of sterol-regulatory element-binding protein-1c (SREBP-1c) and FAS.	Improve cachexia and biochemical parameters via the PPAR-γ signaling pathway, decrease serum interleukin (IL)-6 and (TNF-α). Ameliorative effects of L-carnitine were lessened by etomoxir	10.1159/000439550
Chen, 2014	colon	C26	mice	sc	Rosiglitazone (RGZ), imidapril alone or in combination	RGZ: a high-affinity PPARγ -ligand, increase insulin sensitivity, improve abnormal metabolism, suppress ubiquitin–proteasome proteolysis pathway. Imidapril, a ACE inhibitor, inhibit (Ang I) to Ang II conversion	Alleviate muscle and adipose depletion, increase BW, improvements in metabolic and inflammatory markers. (synergistic effects of RGZ+imidapril not observed)	10.1007/ s13277-013-1043-1
Trobec, 2014	ascites hepatoma	Yoshida AH-130	rats	i.p.	Rosiglitazone (RGZ)	Binding to the PPAR in fat cells, an insulin sensitizer	Reduce body wasting, preserve fat and lean mass, improve cardiac function &survival	10.1016/j.nut. 2013.12.005
Gilabert, 2014	pancreatic	Pdx1-cre; LSL-KrasG12D; INK4a/arffl/fl transgenic	mice		Jak2 inhibitor AG490	Jak2/Stat3-dependent intracellular pathway inhibition	Pharmacological inhibition strongly attenuate cachexia progression	10.1002/jcp. 24580
Springer, 2014	ascites hepatoma	Yoshida AH-130	rats	i.p.	Bisoprolol, imidapril, spironolactone	Blockade of the mineralocorticoid receptor or sympathetic blockade, enhancing anabolic signalling in the heart	Bisoprolol (β-blocker) or spironolactone (aldosterone antagonist) prevent body/cardiac wasting, loss of LVmass and heart failure	10.1093/eurheartj/ eht302

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Chacon-Cabrera, 2014	lung	LC (LP07)	BALB/c mice	sc	NF-κB (sulfasalazine), MAPK (U0126), and proteasome (bortezomib) inhibitors	Inhibition of NF-κB and MAPK predominant signaling pathways	Pharmacological inhibition of NF-κB and MAPK, but not proteasome system, induced in CAC animals, substantial restoration of muscle mass and force through a decrease in muscle protein oxidation and catabolism, myostatin, and autophagy, together with a greater content in myogenin and contractile and functional proteins.	10.1002/jcp. 24611
Porporato, 2013	Fasting- and denervation-i nduced atrophy	*Myh6/Ghrl* , *Ghsr–/–* (Tg)	Tg mice	sc	Acylated (AG) and unacylated (UnAG) ghrelin	Activation of mTORC2 pathways, induce phosphorylation of AktS473 and FoxO3aT32, eventually impair Atrogin-1 expression and muscle protein degradation	Both AG and UnAG impair fasting-induced atrophy, exert antiatrophic activity acting directly on skeletal muscle, even in Ghsr–/– mice (mediated by a receptor distinct from GHSR-1a)	10.1172/JCI39920
Penna, 2013	colon, lung/ ascites hepatoma	C26, LLC/ YoshidaAH-130	mice/rats	sc, intramusc./ ip	erythropoietin (EPO)	increase lipogenesis, lipoprotein lipase (LPL) activity ,	Preserve adipose tissue homeostasis and fat stores, counteract anemia	10.1194/jlr. M038406
Miksza, 2013	Walker tumour (carcinosarcoma)	Walker 256	rats	sc	infliximab	anti-(TNFα) monoclonal antibody that blocks binding of TNFα to its receptor with high specificity	Ameliorate reduction of adipose tissue and BW, minimal or no effect on other metabolic parameters	10.1016/S1734-1140 (13) 71077-6
Zhang, 2013	colon	C26	mice	sc	MG132 proteasome inhibitor	Inhibition of ubiquitin-proteasome pathway (decrease activity of NF-κB, reduce levels of TNF-α and IL-6, downregulation of MuRF1 and MAFbx)	Ameliorate CAC, weight loss, muscle atrophy, alter carbohydrate metabolism, increase spontaneous activity and survival time	10.1007/ s00432-013-1412-6
Palus, 2013	ascites hepatoma	Yoshida AH-130	rats	i.p.	Simvastatin (statin)	anti-inflammatory, cytokine-lowering properties and cardioprotective effects.	Attenuate BW, muscle mass loss and improve cardiac function, survival	10.1016/j.ijcard. 2013.04.150

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Murphy, 2013	colon	C26	mice	sc	Perindopril (ACE-inhibitor)	ACE inhibition (Ang I to Ang II conversion), renin-angiotensin system (RAS) inhibition	Improve physiological outcomes, mobility, strength and reduce fatigue of respiratory muscles, in mice with both mild and severe cachexia.(did not enhance body or muscle mass)	10.1002/ijc. 28128
Springer, 2013	ascites hepatoma	Yoshida AH-130	rats	i.p.	Xanthine oxidase (XO) inhibitor oxypurinol	Inhibition of (XO)-metabolizing purines to uric acid, hyperuricaemia	Reduce CAC-cardiomyopathy, heart wasting, preserve cardiac function	10.1016/j.ijcard. 2013.05.063
Quanjun, 2013	colon	C26	mice	sc	Parthenolide	anti-inflammatory, lower serum TNF-α & inhibition of MURF1expression in muscle	Alleviate tumor burden, preserve BW, improve skeletal muscle characteristics	10.1016/j.phymed. 2013.04.020
Fermoselle, 2013	lung	LP07	mice		N-acetylcysteine, bortezomib (proteosome inhib.) and NF-κB (sulfasalazine) and MAP kinases (MAPK, U0126) inhibitors	Influencing mitochondrial respiratory chain (MRC) complexes and oxygen consumption	Respiratory and limb muscles: Blockade of NF-κB and MAPK restore muscle mass/force and correct MRC dysfunction in both muscles, while partly reduce tumour burden. Antioxidants improve mitochondrial oxygen uptake without eliciting significant effects on the loss of muscle mass/force or tumour size. Bortezomib reduce tumour burden without influencing muscle mass/ strength or MRC function	10.1113/expphysiol. 2013.072496
White, 2013		ApcMin/+	mice	intramuscular electroporation	IL-6 overexpression	IL-6 induce suppression of mTORC1 signaling, induction of STAT3 and AMPK phosphorylation	Dose-dependent suppression of mTOR activity by IL-6, suppressed mTOR responsiveness to glucose administration	10.1152/ajpendo. 00410.2012

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Elkina, 2013	ascites hepatoma	Yoshida AH-130	rats	i.p.	Tandospirone	Selective agonist activates 5-HT1A receptors postsynaptically, leading to increase in serotonin levels, reduction of sympathetic tone (plasma noradrenalin)	Preserve muscle mass, BW, increase locomotor activity, FI and improve cardiac function, survival	10.1016/j.ijcard. 2013.10.022
Busquets, 2021	AH-130		rats	ip	Formoterol	Presumed decrease protein degradation (NOT TESTED IN THIS ARTICLE)	Muscle weight gain, increase grip strength and physical activity, no effect on tumour volume	10.2147/OTT. S293834
Levolger, 2019	C26		mice	sc	ALK4/5 receptor blockers	Block MSTN signal transduction pathway, reduce expression Atrogin-1, induce myogenesis	Limits loss of BW, muscle mass and grip strength	10.1038/ s41598-019-46178-9
Salazar-Degracia, 2019	LP07		mice	sc	Monoclonal antibodies	Modification tumor immune microenvironment and tumor burden regression, attenuation UPS and apoptosis in muscle cell fibers	Increase BW, muscle mass, CSA, grip strength	10.1002/jcp. 28437
Geraldelli, 2020	Walker 256		rats	sc	Botryosphaeran	Induction tumor cells apoptosis (increase caspases, bax)	Tumor regression, attenuation BW and muscle mass loss, improve food intake, correction metabolic and hematologic profiles	10.1016/ j.lfs. 2020.117608
Comiran, 2020	Walker 256		rats	sc	Botryosphaeran	Potential anti tumor immune response	No effect on BW, lean and fat mass, improve hematologic and metabolic parameters, inhibition tumor development and decrease cachexia incidence	10.1080/ 01635581. 2020.1789681
Schmidt, 2020	C26		mice	sc	Wnt7a	Activation Akt/mTOR anabolic pathway	Counteracts myofiber atrophy, prevents loss and improves differentiation of muscle stem cells in vivo	10.1016 /j.omto. 2019.12.011

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Liu, 2020	LLC		Ghsr +/+ and Ghsr -/- mice	sc	Ghrelin	Attenuation WAT inflammation and lipolysis (modulation activity of ATGL and HSL via GHSR1a-dependent and independent manner, respectively), no effect on reducing UCP-1	Orexigenic effect (GHSR-1a dependent), prevents BW loss, fat atrophy, no effect on BAT inflammation and thermogenesis, WAT browing and energy expenditure.	10.18632/ONCOTARGET.27705
Zhang, 2020	C26		mice with spleen deficiency	sc	atractylenolide I	Inhibition MuRF-1 (muscle), HSP and UCP-1 (adipose), increase MyoD and myogenin (muscle)	Restoration BW, reduce muscle and fat atrophy, amelioration spleen and thymus atrophy, no effect on tumor growth	10.1038/s41401-019-0275-z
Janice Sánchez, 2019	LLC		mice	sc	Potential HuR pharmacological target	Up-regulation PGC-1α in a KSRP-dependent manner (potentiation oxidative mitochondrial metabolism) decrease E3 ligases	Alleviation BW loss and muscle atrophy, increase CSA, no effect on tumor growth	10.1038/s41467-019-12186-6
Lu, 2020	KPC and LLC		mice	pancreas and sc	Anti-IL-20	Suppression PD-L1 in tumor cells (increased anti-tumor immune response), reduction infiltration of macrophages in WAT and inhibition lipolysis (inhibition HSL, ATGL)	Attenuation BW loss and anorexia, preservation FAT, no effect on muscle wasting, inhibition tumor growth and prolongation survival	10.1038/s41467-020-18244-8
Bae, 2020	LLC and MC38		mice	sc	Radix Paeoniae	Reduction IL-1β, IL-6, TNF-a levels, down-regulation NF-κB and UPS signaling pathways	Increase food intake, muscle mass and function	10.1016/j.jep.2019.112222
Chen, 2020	C26		mice	sc	Imperatorin	Direct STAT3 inhibition, suppression TNF-α, IL-6, IL-1β and E3 ligases	Preservation BW, muscle, fat and kidney, inhibition tumor growth (at high dose)	10.1016/j.phrs.2020.104871
Jung, 2021	MIA PaCa-2		mice	sc	Bergamotiin	Decrease E3 ligases and increase MSTN in muscle, induce adipogenesis (increase C/EBPa and PPARγ)	Recover BW, muscle and fat tissue loss, no effect on food intake	10.3390/cancers13061347
Lee, 2021	C26		mice	sc	Astragalus membranaceus and Paeonia japonica (herbal formula)	Reduction atrofy-related cytokines (TNF-α, TWEAK, IL-6), down-regulation E3 ligases, p38, NF-kB	Alleviation BW, muscle mass and strength loss, no effect on anorexia and tumor growth	10.1016/j.jep.2020.113470

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Zhang, 2021	LLC		mice	sc	Alpinetin	Activation PPRARγ, down-regulation NF-κB, STAT3 and E3 ligases, reduction TNF-a, IL-1β, IL-6	Improve tumor free BW, muscle and fat mass, reduction spleen weight	10.3389/fphar.2021.687491
Quintilhano, 2021	Walker 256		rats	sc	Lixisenatide	No improvement of metabolic parameters (insulinemia, insulin-resistance, triacylglycerol)	Worse BW loss, other parameters not improved	10.1002/cbf. 3588
de Fatima Silva, 2020	Walker 256		rats	sc	Insulin	Activation Akt in myocytes and adipocytes and inhibition HSL in adipocytes	Attenuation loss of BW and fat mass, accentuation loss of muscle mass (?)	10.1002/jcb. 29682
Wang, 2020	C26		mice	sc	Baoyuan Jiedu decoction	Activation p38 MAPK/PGC-1a pathway, increase mitochondrial biogenesis and dynamics, down-regulation Atrogin-1, MuRF-1	Alleviation BW loss and muscle mass atrophy	10.3389/fonc.2020.523577
Bora, 2021	B16-F1		mice	iv	Various antidiabetic drugs (metformin, DPP-4 and SGLT2 inhibitors)	Decrease inflammation markers, regulation carbohydrate and lipid metabolism	Increase feed intake, BW, fat mass, induction skeletal muscle hypertrophy, reduction tumor proliferation rate	10.1016/j.lfs.2021.119329
Han, 2018	C26		mice	sc	Anti-IL-6 receptor ab	Inhibition WAT lipolysis and browning	Preservation WAT wasting, no effect on BAT and muscle mass	10.1186/s12944-018-0657-0
de Fatima Silva, 2017	Walker 256		rats	sc	Pioglitazone	Reduction plasma FFA, triacylglycerol and increase insulin sensitivity	Prevention BW loss and fat wasting (at early stage of tumor); no effect on tumor growth, food intake and muscle mass	10.1016/j.lfs.2016.12.016
Musolino, 2019	AH-130		rats	sc	Spironolactone	Down-regulation aldosterone and NGAL (possible modulation oxidative stress)	Protection lean and fat mass, improve heart contractility	10.1002/ehf2.12372
Hentilä, 2019	C26		mice	sc	SACVR2B-Fc	Increase GSH levels (antioxidant defense), induction of unfolded protein response in a tissue specific manner, no effect on ALS	Restoration BW, muscle mass and WAT, reduction tumor growth	10.3389/fphys.2018.01917
Wu, 2019	LLC		mice	sc	Astragalus membranaceus and Angelica Sinensis	Anticancer activity (antioxidant, anti-inflammatory and immunomodulatory function)	Prevention loss of BW, muscle mass and WAT, inhibition tumor growth	10.1155/2019/9206951

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Murphy, 2019	C26		mice	sc	MasR agonist	Activation of the alternative ACE2/Ang-(1-7)/MasR axis and miR-23a -regulated preservation of glycolytic muscle fibers IIb (increase MHC4)	Orexigenic effect, attenuation BW loss and muscle wasting, improve locomotor activity, inhibition tumor growth	10.1158/0008-5472.CAN-18-1207
Chen, 2017	LLC		mice	sc	Carboxyamidotriazole	Up-regulation SIRT1 and PGC-1a, inhibition NF-kB and FOXO3 pathways, down-regulation proinflammatory serum cytokines (IL-6, TNF-a) and UPS	Alleviation muscle mass and adipose tissue wasting, inhibition tumor growth	10.1007/s00210-017-1345-8
Jin, 2018	C26		mice	sc	β3-AR antagonist	Inhibition lipolysis	Increase BW, reduction tumor volume	10.1016/j.ejmech.2018.03.032
Villars, 2017	C26		mice	sc	Ghrelin receptor agonist HM01	Increase neuronal activation of the hypothalamic arcuate nycleus (control mice); no interference with cytokines or E3 ligases signaling.	Increase food intake, BW, fat mass, muscle mass, bone mineral density; decrease energy expenditure; no effect on tumor size	10.3390/ijms18050986
Goncalves, 2018	GEMM KrasG12D/+;Lkb1f/f		mice		PPARα agonist (fenofibrate)	Up-regulation hepatic PPAR-α, restoration ketone production, decrease corticosterone levels	Prevention loss of BW and muscle mass, increase liver and WAT mass	10.1073/pnas.1714703115
Uzu, 2019	85As2		immunodeficient mice	sc	Xanthine oxidase inhibitor (febuxostat)	High activity of xanthine oxidase in the brain (inability of febuxostat to cross the blood brain barrier)	Ineffective in alleviation of cachectic features	10.1016/j.jphs.2019.04.005
Miao, 2017	C26		mice	sc	Pyrrolidine dithiocarbamate	Inhibition protein catabolism and lipolysis and activation protein synthesis; multiple pathways involved (NF-kB, p38 MAPK, Akt and UPS in muscle; NF-kB, p38 MAPK and AMPK in fat),	Reduction muscle and adipose tissue wasting, no influence on tumor size	10.3389/fphar.2017.00915
de Fatima Silva, 2018	Walker 256		rats	sc	Metformin	No amelioration of insulin-resistance and glucose metabolism	No relief of cachectic symptoms	10.1139/cjpp-2017-0171
Miller, 2017	gp130F/F: KrasG12D		mice		Anti-IL-6R mAb (25F10)	Selective blockade IL-6 trans-signalling but not classical signaling, inhibition IL-6/gp130-mediated STAT3 hyperactivation.	Improve BW loss, muscle and adipose tissue, survival	10.1038/onc.2016.437
Sudo, 2018	85As2		Immunodeficient rats	sc	Rikkunshito	Increase SREBP-1 and fatty acid biosynthesis in WAT	Amelioration food intake	10.3390/ijms19123852

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Calore, 2018	LLC		mice	TAIL INJECTION?	TLR7/8/9 antagonist (IMO-8503)	Inhibition JNK-mediated cell death, impairment cleavage of proapoptotic proteins PARP and caspase-3, down-regulation Pax7	Preservation lean and fat mass, no effect on tumor growth	10.1158/0008-5472.CAN-17-3878
Chen, 2018	LLC		mice	sc	Brucea javanica oil emulsion	Down-regulation IL-6, TNFN, identification of hub genes (i.e. Nmd3, Nhp2l1, Bcl-2) involved in RNA synthesis, processing and cell apoptosis	Improvement food intake, BW, survival, inhibition tumor growth and metastasis	10.1080/1061186X.2017.1354003
Henriques, 2018	LLC		mice	sc	TLR4 antagonist (atorvastatin)	Suppression of serum proinflammatory cytokines; beneficial effects on adipose tissue (reduced macrophage infiltration and recruitment, inhibition lipolysis, reduced p38MAPK dependent browing)	Reduced wasting of BW, lean and fat mass, prolongation survival, inhibition tumor growth	10.1038/s41598-018-36626-3
Pin, 2017	AH-130, C26		rats, mice	ip, sc	Dantrolene, calpastatin	Inhibition Ca2+-dependent proteases (calpains)	No effect on BW, muscle mass, CSA and tumor growth	10.3389/fphys.2017.00213
Ohsawa, 2018	B16BF10		mice	sc	Ninjin'yoeito	Modulation STAT3/SOCSO3 and AMPK/mTOR/4E-BP1 signalling and normalization aminoacid metabolism, increase MHC	Amelioration muscle atrophy, increase fat tissue	10.3389/fphar.2018.01400
Hu, 2018	LLC		mice	sc	Neutral sphingomyelinase inhibitor GW4869	Suppression of exosome generation and release from cancer cells, inhibition lipolysis and WAT browing (p-HSL, UCP-1)	Prevention loss of tumor-free BW and WAT	10.1016/j.bbrc.2018.09.139
Walton, 2019	CHO: ActA cells		nude mice	im	Activin A propeptide	Blockade Activin A activity	Protection of muscle, heart, liver and kidney (no fat) from activin-induced wasting	10.1210/en.2019-00257
Terawaki, 2017	85As2 cells		nude rats	sc	Rikkunshito	Alleviation ghrelin resistance (enhance ghrelin signaling through GHS-R without increasing GHS-R gene expression or affecting elevated ghrelin plasma levels; increased hypothalamic neuropeptide Y gene expression)	Improve food intake and cachexia features (BW, muscle mass), no effect on tumor growth	10.1371/journal.pone. 0173113
Salazar-Degracia, 2018	AH-130		rats	ip	Formoterol	Activation muscle beta2-adrenoceptor, attenuation NF-κB p65 atrophy signaling, reduction autophagy marker LC-3 and apoptotic marker BAX	Increase BW, muscle tissue, CSA, improve muscle structural abnormalities, no effect on tumor growth	10.1016/j.biochi.2018.04.009

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model/Cell line	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Yang, 2019	MiaPaCa2		athymic mice	sc	β-Pentagalloyl-Glucose	Inhibition IR/IGF1R activation and Warburg effect in cancer cells; reduction E3 ligases (proteolysis), down-regulation ATGL (lipolysis), normalization glucose, insulin, TGR and IGF-1 plasma levels, attenuation hepatic gluconeogenesis	Alleviation cachexia symptoms (BW, fat), anticancer activity	10.1142/S019241 5X19500356
Kim, 2018	C26		mice	sc	SGE	Induction apoptosis in cancer cells (MAPK, AMPK activation and ER stress), reduce myotube atrophy (increase MHC), inhibition lipolysis, antiiflammatory properties	Protection BW, skeletal muscle, fat and heart mass, no effect on food intake, suppression tumor growth	10.18632/ oncotarget. 24616
Ricardo de Brito Bello, 2019	Walker 256		rats	sc	Capsaicin	Induction cancer cell apoptosis, correction hypertriglyceridemia and hyperlactacidemia (partially)	Reduction tumor mass, partial reverse BW loss	10.1080/01635581 .2018.1557219
Da Silva, 2019	Ehrlich cells		mice	sc	Synadenium umbellatum	Decrease TNF-α and increase TGF-β1 genes expression	Restoration BW, no antitumor action	10.1097/OP9.00000 00000000009
Hall, 2018	C26		mice	sc	1. AMPK agonist (5-aminoimidazole-4-carboxamide ribonucleotide) 2. Metformin INEFFECTIVE	1. Direct AMPK activation; at early stages of disease prevention of cytokine-induced myotube atrophy and recovery of mitochondrial respiration, induction of protein synthesis, inhibition iNOS/NO pathway 2. Metformin induces AMPK activation (indirectly), no other effect	Restoration BW and muscle mass, increase CSA, no effect on fat mass; anticachectic effect occurs independently of anticancer activity 2. Metformin INEFFECTIVE	10.15252/emmm. 201708307
Tomasin, 2015	Walker 256		rats	sc	Aloe vera and honey	Decrease proteolysis (chymotrypsin, calpain), increase antioxidant capacity in muscle, liver, heart; increase oxidative stress in cancer cells	1.Alleviation decrease in BW, fat content, carcass mass, preservation collagen nitrogen content, reduction tumor size	10.1089/jmf. 2014.0129
Oliveira, 2016	Walker 256		rats	sc	Metformin	Increase muscle protein synthesis, (decrease ratio pAMPK/AMPK, induce Akt activation), inhibition UPS	Improve body parameters (carcass weight, lean mass, nitrogen collagen, muscle weight, muscle protein content) decrease tumor growth,	10.1186/ s12885-016-2424-9
Zhuang, 2016	C26		mice	sc	Zhimu and Huangbai herb pair	Reduction tumor induced myofibers atrophy, reduction elevated levels of proinflammatory cytokines, inhibition FOXO3, MuRF-1, atrogin-1, activation IGF-1/Akt, increase autophagy markers (LC3B, sirt-1)	Alleviation tumor-free BW and muscle mass wasting, increase grip strength, prolongation survival	10.1007/ s00520-015-2892-5

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Kim, 2023		C26	mice	sc	B-Carotene	Inhibition lipolysis and hepatic gluconeogenesis, regulate glycolysis and mitochondrial respiration, composition of gut microbiota, antiinflammatory properties	Improve muscle atrophy and fat,	10.1016/j.jnutbio.2022.109248
Penedo-Vázquez, 2023		LP07	mice	sc	Polyphenolic compounds (curcumin ,resveratrol)	Activation sirtuin-1 and modulation of proteolytic/atrophy signaling pathways (NF-κB/p50, FOXO3)	Increase muscle mass, strength, CSA, improve muscle structure, reduce tumor weight (resveratrol)	10.3390/molecules26164904
Wang, 2023		C26	mice	sc	curcumin	Inhibition cAMP/PKA/CREB signaling pathway in adipose tissue	Improve BW, fat loss	10.1016/j.phymed.2022.154563
Zhang, 2022		4T1	mice	sc	Curcumin	Improve mitochondrial function, decline IL-6, TNF-a, MSTN, increase myogenin, regulation NF-κB/UPS axis	Alleviation BW loss, correction nutritional status, restoration muscle mass and function, increase CSA, antitumoral activity	10.1155/2022/2567150
Sakakida, 2022		C26	mice	sc	Water soluble dietary fiber	Increase gut barrier function-antiinflammatory effect	Alleviation of skeletal muscle wasting	10.1111/cas.15306
Kershaw, 2022		C26	mice	in fat	Piceatannol	Inhibition lipolysis through post-transcriptional degradation of ATGL and CGI-58 (coactivator)	Preservation BW, fat mass, no effect on lean mass, food intake and tumor growth	10.3390/nu14112306
Wei, 2022	colon	CT26	mice	sc	Creatine (intraperitoneal)	Alter dysfunction and morphological abnormalities of mitochondria by inhibiting abnormal	Protect against BW loss and muscle wasting and improve grip strength	10.3389/fphar.2022.1086662

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
						overactivation of ubiquitin proteasome system (UPS) and autophagic lysosomal system (ALS)		
Levolger, 2021		C26	mice	sc	Quercetin	Reduction Atrogin, MuRF-1	Reduce BW loss and muscle atrophy, anti-tumor effect	10.3233/NHA-200084
Wu, 2021		C26	mice	sc	L-carnitine	Regulation Akt/FOXO3/Atrogin-1 and p70S6K pathways, increase protein synthesis and decrease degradation	Improve muscle mass and BW	10.1186/s12986-021-00623-7
Viana, 2021		Walker 256	rats	sc	Leucine diet	Suppression protein degradation (MuRF-1 and 20S)	Increase body, fat, and muscle mass, strength and performance,no effect on CSA	10.3390/cells10123272
Snoke, 2021		C26	mice		Naringenin (flavonoid)diet	Reduction inflammation (IL-6), increase insulin sensitivity, increase PGC-1α (mitochondia biogenesis)	Increase muscle strength, survival, adverse (no increased food intake, no protection against weight loss and CSA, increased fat depletion)	10.1002/mnfr.202100268
Lu, 2021	colon	C26	mice	sc	carnosol, dimethyl-carnosol (DCS) and dimethyl-carnosol-D6 (DCSD)	Inhibit activation of NF-κB pathway and activate AKT pathway, antioxidant & anti-inflammatory properties	Prevent BW loss, attenuate muscle atrophy and fat lipolysis, antioxidant & anti-inflammatory properties	10.1002/jcsm.12710
Wyart, 2022		C26	mice	sc	Iron	Improve mitochondrial metabolism, reduce expression atrophy-related genes	Improve body mass, muscle atrophy, CSA, strength and survival	10.15252/embr.202153746
Jia, 2022		B6.129P2-IL10			Eggshell membrane	Shift in the gut microbiota, attenuation of inflammation in colon, muscle and liver,	Attenuation cachectic features (anorexia, muscle mass and function, fat mass)	10.1002/jcsm.13019

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
						suppression of T helper cells differentiation		
Nukaga, 2020		C26	mice	ip	Combination lauric acid and glucose	Improve cardiomyoblast cell metabolism (mitochondria function, oxidative phosphorylation, ATP production), increase MLC1	Prevention myocardiac atrophy and heart morphological alterations, no effect on tumor weight	10.1111/cas.14656
Cruz, 2020	Walker tumour (carcinosarcoma)	Walker 256 carcinosarcoma cells	rats	sc & intraperitoneal	L- leucine	Modulate pathways of mitochondrial biogenesis in skeletal muscle tissue and cell, stimulate mTOR expression, pyruvate and acetyl-CoA synthesis	Increase mitochondrial catalytic activity, BW gain, preserve muscle weight and lean body mass	10.3390/cancers12071880
Han, 2020	colon adenocarcinoma	CT-26	mice		Arctii Fructus (AF)	Suppress IL-6 expression, reduce UCP1 expression by restoring (AMPK) activation in adipose tissue	Reduce muscle and adipose tissue atrophy, prevent weight loss, improve energy homeostasis by regulating adipocyte differentiation, increase adipogenesis and lipogenesis. Improvement of cachexia induced hepatotoxicity and nephrotoxicity.	10.3390/nu12103195
Liu, 2019		LLC	mice	sc	Coix seed oil	Reduce serum TNF-a, IL-6, inhibition NF-κB/MuRF-1 and AMPK/HSL pathways	Attenuation of BW, muscle and adipose tissue loss, no effect on food intake and tumor size	10.1186/s12906-019-2684-4
Lee, 2019	colon	C26	mice		Ajoene garlic extract	decrease inflammatory myokines secretion JAK/STAT3 & FoxO signaling pathways,	Alleviate muscle degradation, enhanced myogenesis in mouse myoblasts, protect	10.3390/nu11112724

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
						suppression of muscle-specific E3 ligases & NF-κB phosphorylation, promote muscle protein synthesis via MAPK activation	against muscle protein degradation	
Cruz, 2019	Walker tumour (carcinosarcoma)	Walker 256 carcinosarcoma cells	fem-Wistar rats		Leucine-rich diet	Modulation of mTOR pathway by triggering increased activation of RAG and mTOR and maintaining JNK, STAT-3 and STAT-6 levels	Stimulate muscle protein synthesis, reducing degradation during tumour evolution	10.1186/s12885-019-5448-0
Miyaguti, 2018	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats	sc	Maternal nutritional supplementation Omega-3 fish oil(O) and/or leucine(L)	preserve hepatic activity, antioxidant response	Offsprings:reduced cachexia index(WO &WLO), longer survival(WLO), improvement of liver dysfunction	10.1016/j.nutres.2017.12.003
Yoshimura, 2018	lung	LLC	mice	sc	Morin (3,5,7,2′ ,4'-pentahydroxyflavone) - flavonoid)	Downregulate viability of LLC cells by binding to RPS10, suppression of Akt pathway, NFκB signaling pathway and miR-135b,	Prevent muscle wasting, inhibition of cancer growth, lower tumor weight, reduce cell viability and protein synthesis of LLC cells	10.1016/j.bbrc.2018.10.184
Levolger, 2018	colon	C26	mice	sc	30% caloric restriction (CR)	enhanced expression of myogenin may be involved	preservation of muscle strength, no impact on muscle mass	10.18632/aging.101724
Li, 2017	esophagus carcinoma	EC1	mice	sc	All-trans retinoic acid (ATRA)	Suppression of Ang-1,Ang-2 angiopoietins-Tie2 pathway	Prevent body weight loss, suppress xenograft tumor growth	10.1371/journal.pone.0174555
Cruz, 2017	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats		Leucine-rich diet	Increase anti-inflammatory cytokines (IL-4, IL-10), modulation of pro-inflammatory cytokines, proteasomal pathway modulation	Onset of leucine action (14th day), improved body weight, muscle mass, muscle protein	10.1016/j.cyto.2017.04.019

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
						&muscle protein maintenance		
Zhang, 2017	lung	LLC	mice	sc	Baoyuan (BYJD) decoction	Downregulating expression of Atrogin-1 and MuRF-1 protein	Increase BW, gastrocnemii mass and transverse diameter of muscle fiber morphology	10.1155/2017/6268378
Ohbuchi, 2015	ascites hepatoma	Yoshida hepatoma AH-130	rats	i.p.	Rikkunshito (RKT)	Alter levels of 23 metabolites, elevation of Glucarate in plasma have anticarcinogenic anti-inflammatory activity	Glucarate elevation delay weight loss, improve muscle atrophy, reduce ascites content, ikely to be responsible for anti-inflammatory activity of RKT	10.1155/2015/871832
Kim, 2016	colon	C26	mice	sc	Sosiho-tang (SO)	Blockade of systemic inflammatory response	Prevent loss of BW, carcass weight, heart weight, skeletal muscle/fat tissue and increase in serum IL-6 levels	10.3892/or.2015.4527
Choi, 2014	colon	C26	mice	sc	Sipjeondaebo-tang (SJDBT)	SJDBT may regulate cytokines (IL-6 and MCP-1) and hormones (GLP-1 and PYY)	Improves weight loss and anorexia/cachexia, anemia, more effective in treatment model after anorexia and cachexia than in prevention model	10.1155/2014/736563
Camperi, 2017	hepatoma	AH130	rats		Vitamin D	Vitamin D treatment result in VDR overexpression and myogenin down-regulation	Vitamin D-treated myoblasts did not differentiate properly. VDR overexpression contribute to muscle wasting by impairing muscle regenerative program. (Attention be paid when considering vitamin D supplementation to patients with chronic pathologies where	10.18632/oncotarget.15583

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
							muscle regeneration may be involved)	
Martins, 2016	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats	sc	L-glutamine 2%	Restore morphophysiology abnormalities and cell proliferation of the intestinal mucosa of duodenum and jejunum (through restoring number of PAS-positive goblet cells), improves its metabolic function	Prevent loss of body mass, reduction of tumor growth, inhibition of cachectic syndrome	10.1007/s00726-016-2313-1
Jiang, 2016	colon	C26	mice	sc	L-carnitine		Ameliorates the liver inflammatory response	
Deminice, 2016	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats	sc	Creatine (oral. in drinking water)	Effect on hepatic impaired Hcy metabolism	Prevent hyperhomocysteinemia, hepatic oxidative stress, BW loss	10.1007/s00726-016-2172-9
Du, 2015	ascitic tumor	S180	mice	via abd. cav.	EPA-enriched phospholipids (EPA-PL)	Inhibiting lipolysis, partly recover adipogenesis	Ameliorate BW loss, preserving WAT mass	10.1039/c5fo00478k
Bindels, 2015	acute leukemia	Transplanted with Bcr-Abl-transfected proB lymphocytes	mice	inj. tail vein	Peptic oligosaccharides(POS) or inulin (INU)	POS inhibit fatty acid catabolism,induction of adipocyte HSL expression, restore conjugated linoleic acid metabolite. SCFA as mediators of INU effect in cancer cell proliferation control.	POS modulate gut microbiota, blunt adipose fatty acid catabolism,contribute to fat mass sparing, delay anorexia. INU increase portal SCFA	10.1371/journal.pone.0131009
Schiessel, 2015	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats		fish oil (FO) / Oro Inca oil (OI)	Production of eicosanoids and leukotrienes via cyclooxygenase and lipoxygenase pathways, reduce expression COX-2, inflammatory cytokines	OI, rich in ALA, caused same effects on cancer/cachexia as those seen in FO. Avoid hypoglycemia and hypertriacylglycerolemia, preserve body mass, inhibit IL-6 and TNF- plasma levels increment.	10.1080/01635581.2015.1043021

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Leow, 2014	myeloma	J558 cells	mice	sc	Oil palm phenolics (OPP)	Anti-tumour activities via cytostatic mechanism, downregulate inflammatory genes, upregulate cholesterol biosynthesis genes(spleens,liver)	Attenuation of systemic inflammation and cachexia, lower immune response (spleens, liver genes expression profiling)	10.1159/000357948
Ham, 2014	colon	C26	mice	sc	Glycine	Reduce oxidative and inflammatory burden, reduce expression of genes associated with muscle protein breakdown	Attenuate skeletal muscle wasting and loss of function, reduce tumor growth, increase FI	10.1016/j.clnu.2013.06.013
Velázquez, 2014	colon	(Apc)Min/+	mice		Quercetin	Blunt the IL-6/STAT3 inflammatory signaling pathway	Improvements in BW, muscle mass, strength, prevent hypogonadism	10.3945/jn.113.188367
Iagher, 2013	Walker tumour (carcinosarcoma)	Walker 256	Wistar rats	sc	Shark liver oil (SLOil) & fish oil (FOil) comparison	n-3 PUFAs (EPA, DHA) and AKGs lipids in its composition decrease tumor factors involved in cachexia promotion (via increased lipid peroxidation, increased apoptosis, reduced tumor cell proliferative capacity)	Independent chronic ingestion of SLOil equivalent to FOil efficient anti-cachectic properties, combination did not cause additive effect	10.1186/1476-511X-12-146
Yanagihara, 2013	human stomach cancer	h-MKN-45 cell line xenografts (sublines (MKN45cl85 and highly metastatic 85As2mLuc)	mice (immunod.)	sc	Isoflavones	antiproliferative action, inhibition of tumor proliferation, activation of a signal transduction pathway for apoptosis.	3 isoflavones , graded as soy isoflavone aglycone AglyMax > daidzein > genistein, ameliorate cachexia, inhibit tumor growth, prolong survival	10.1080/01635581.2013.776089
Busquets, 2020	AH-130		rats	ip	l-carnitine	Reduction E3 ligases, FOXO3 and oxidative stress in a muscle specific manner (gastrocnemius)	Improve food intake, BW, muscle mass and muscle structrural alterations. Reverse atrophy of both slow	10.1002/jcp.28992

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
							and fast-twich fibers in a muscle specific manner (gastrocnemius particularly), no effect on tumor	
An, 2021	C26		mice	sc	Prebiotic kimchi	Inhibition IL-6/JAK2/STAT3, suppression NF-kB, UPS, activation PI3K/Akt/mTOR, inhibition lipolysis and increase lipogenesis, increase mitochondrial proteins PGC-1a and MFN-2,	Restore BW, muscle mass, increase survival	10.3164/JCBN.19-10
Obermüller, 2020	MHH-NB11		athymic mice	sc	Prebiotic oligosaccharides	Modification composition gut microbiome and fecal volatile organic compound production, no effect on gut permeability. potential anti-inflammatory action	Cachectic parameters not improved, no effect on tumor growth	10.3390/nu12072029
Wang, 2021	LLC		mice	sc	Micronutrient enriched nutrition formula in addition to antineoplastic drugs (especially Iressa)	Inhibition intratumoral Drugs!G126zz and epithelial mesenchimal increase apoptosis cancer cells -Reduction systemic oxidative stress (reduction serum malondialdehyde, NO)	Improve BW loss, muscle, fat mass and splenomegaly, enhance anticancer activity	10.3390/md19050262
Oliveira, 2021	Walker 256		Offspring rats	sc	Maternal fish (omega-3) oil diet (premating/gestation/lactation)	ADULT OFFSPRING: Improve liver function and lipid metabolism, increase mTOR and 4-EBP1 and reduce 20S proteasome protein expression in muscle but no effect on protein synthesis	Preservation fat mass, no effect on lean mass wasting, no effect on tumor development	10.1002/mnfr.202000863

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Martins, 2017	Walker 256		rats	sc	L-glutamine	Increase intestinal gluconeogenesis, plasma glycemia and insulinemia	Improve BW, slower tumor growth	10.1177/1010428317695960
Carnier, 2018	Walker 256		rats	sc	Chia seeds (n-3 fatty acid a-linolenic acid)	No modification of tissue cytokine content except decreased IL-1β, TNF-α (liver), IL6R, IL-10R (adipose) and IL-10 (tumor)	No beneficial effect on BW, food intake; increased tumor growth and accentuation muscle mass loss	10.1080/01635581.2018.1502329
Gonçalves, 2019	Walker 256		rats	sc	Conjugated Linoleic Acid	Negative impact on hepatic lipid metabolism (i.e. fatty acid oxidation, VLDL production and secretion), increase cytokine content in adipose tissue	Aggravation hepatic steatosis and hyperlipidemia	10.1016/j.clnu.2018.09.023
Goncalves, 2018	GEMM KrasG12D/+;Lkb1f/f		mice		PPARα agonist (fenofibrate)	Up-regulation hepatic PPAR-α, restoration ketone production, decrease corticosterone levels	Prevention loss of BW and muscle mass, increase liver and WAT mass	10.1073/pnas.1714703115
Nakamura, 2018	C26		mice	sc	Ketogenic formula	Suppression systemic inflammation (IL-6), increase serum ketone bodies	Maintenance BW and muscle mass, tumor regression	10.3390/nu10020206
Miyaguti, 2019	Walker 256		Offspring rats	sc	Maternal Leucine-Rich Diet (pregnancy/lactation)	ADULT OFFSPRING: Improved muscle protein turnover, modulation proteasome 20S, calpain and cathepsin (lysosome) activity, preservation mTOR pathway	Improve food intake, preservation muscle weight	10.3390/biom9060229
Toneto, 2016	Walker 256		rats	sc	Leucin supplementation diet	Reduced markers of proteolysis (chymotrypsin),	Myocardial protection (attenuation ECG changes suggestive of	10.1002/jcsm.12100

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
						myocardial damage (myeloperoxidase, tissue inhibitor of metalloproteinases, and total plasminogen activator inhibitor 1) and cell apoptosis (caspases 3, 7)	ischemia, heart failure and arrhythmias)	
Ahmadabadi, 2020	4T1		mice	sc	Saffron aqueous extract	Reduction caspase-3, increase ratio of Bcl-2 to Bax in muscle cells	Protection BW,muscle mass and strength, increase food consumption	10.1139/apnm-2019-0352
Chen, 2018	LLC		mice	sc	Luteolin	Reduction Il-6, TNF-a; suppression NF-kB, p38/MAPK, MuRF-1, Atrogin-1 (skeletal muscle), suppression NkB and MuRF-1 (cardiac muscle)	Increase tumor-free BW, skeletal and heart muscle mass	10.3892/or.2018.6453
Chen, 2016** PLUS CHEMO	C26, LLC		mice	sc	Salidroside	Increase m-TOR, pm-TOR, MHC, rescue TNF-a induced down-regulation of m-TOR, pm-TOR, MHC	Preservation tumor-free BW, muscle and fat mass, increase food intake, prolongation survival; anti-tumour activity	10.1002/jcsm.12054
Shukla, 2015	S2-013		athymic nude mice	pancreas	Silibinin	Induction apoptosis cancer cells (down-regulation c-myc, STAT3); reduction MuRF-1, atrogin-1 gene expression in muscle, reduction IL-6, TNF-a m-RNA in tumor	Anticancer effect; increase carcass weight, muscle weight, grip strength and latency of fall, improve muscle fiber morphology and fibrosis	10.18632/oncotarget.5843

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Collao, 2023	Rhabdomyosarcoma (RMS)	M3-9-M RMS cells	mice		Sedentary (SED) or resistance and endurance exercise training (RET) groups	Increase vasc endothelial cells (ECs) and fibro-adipogenic progenitors (FAPs), partial reversal of the inflammatory/ fibrotic transcriptome	RET induce skeletal muscle hypertrophy, improves muscle mass and inflammatory/ fibrotic gene signature	10.1002/jcsm.13185
Pereira, 2022		C2	mice	sc	Aerobic exercise training	Activation Akt/mTORC1 pathway through modulation of eIF2-a	Prevent and revert muscle wasting, CSA	10.3390/cancers14010028
Wood, 2022		C26	mice	sc	Moderate Intensity Endurance and Resistance Exercise		Antiinflammatory effect	10.21873/anticanres.15498
Testa, 2022		Ehrlich cells sc	mice	sc	Resistance training	Prevention of STAT3 activation mediated by IL-6 and muscle oxidative stress, inhibition of UPS and autophagy pathways	Mitigation muscle atrophy, strength	10.3389/fonc.2022.880787
Fix, 2021		ApcMin/+ (MIN) mice (G.E.)	mice		Wheel running	Suppresion of aberrant fasting-induced AMPK activity in pre-cachexia, suppresion of FOXO3a, E3 ligase and autophagy related proteins, regulation of quality control mitochondrial proteins (MFN-1, DRP-1)	increase food intake, muscle mass, seminal vesicle mass, reduce spleen mass	10.14814/phy2.14924
Kitaoka, 2021		C26 mice sc	mice	sc	Voluntary exercise (wheel running)	Improve markers of mitochondria content and dynamics, reduce markers of oxidative stress, attenuation mitochondrial morphological alterations	Attenuation loss of BW and skeletal muscle mass	10.14814/phy2.15016
Morinaga, 2021		C26 mice sc	mice	sc	Aerobic exercise (treadmill running)	Enhance protein synthesis (Increase adiponectin, Akt, mTOR, p70S6 kinase, and 4EBP-1)	No change in total BW, protective effect in fast-type muscle fibers,	10.3390/ijms22063110
Tanaka, 2020		AH130	rats	ip	Pre-exercise (before inducing cachexia)	Suppresion of hypoxia-induced AMPK activation, increase Akt/mTOR and protein synthesis , improve	Improve muscle mass, prevention of capillary regression	10.1096/fj.202001330R

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
						mitochondrial function in fast-twitch muscles , no effect on inflammatory cytokines, no effect on Atrogin-1, Murf1,		
Hardee, 2020		ApcMin/+	mice		Eccentric contractions	High IL-6 levels but suppression IL-6/gp130 downstream signaling (STAT3, AMPK, ACC), increase mTORC1, improve mitochondrial oxidative metabolism and protein synthesis	Attenuation muscle wasting, increase CSA, diminish myofiber types I and II atrophy	10.1152/japplphysiol.00908.2019
Tanaka, 2020	Hepatoma	Ascites hepatoma AH130 cells	Wistar rats		Pre-exercise	Increase in phosphorylated AMPK levels, decrease in Akt/mTOR pathway activity	Inhibit muscle mass loss, hypoxia in plantaris and soleus muscles, rescue protein synthesis, prevent capillary regression. Inhibit mitochondrial dysfunction in the plantaris muscle only while not affecting slow-twitch muscle.	10.1096/fj.202001330R
Fernandes, 2020	colon	C26	mice	sc	Aerobic exercise training (AET)	ReduceTGF-β1 mRNA, increase mitochondrial complex IV protein, partial recovery of BNIP3 mRNA	Significant anti-cardiac remodeling effect: reduce necrosis, inflammation and cardiac collagen deposition, partially reversed left ventricle ejection fraction	10.1016/j.lfs.2020.118392
Re Cecconi, 2019		C26 mice sc	mice	sc	Aerobice exercise (running)	Restoration levels PGC1α/musclin/Npr3 axis, inhibition proteolysis	Protection muscle mass, cell atrophy and CSA	10.3390/cancers11101541
Sato, 2019	lung	Wt , ApcMin/+ (Min)	female mice		High-frequency electric stimulation (HFES) on Tibialis anterior (TA) muscle	Increase mTOR signaling & myofibrillar protein synthesis, attenuate AMPK activity & oxidative capacity decrease in skeletal muscle	HFES can activate muscle protein synthesis, increase muscle weight, mean CSA of type IIa	10.1249/MSS.0000000000001991

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
							and type IIb fibers, attenuate muscle mass loss	
Ballarò, 2019	colon	C26	mice	sc	Moderate exercise training (on motorized wheel, mild intensity aerobic exercise-likely increased resistance)	Alter ROS and GSH levels, increase GSSG/GSH ratio and Nrf2 and Keap1 protein expression, decrease protein carbonylation, down-regulate autophagy & mitophagy	Prevent muscle wasting &strength loss, decrease muscle protein catabolism and oxidative stress, preserve mitochondria	10.3390/cancers11030285
Parry, 2018	mammary gland	MatBIII tumor cells	Fisher 344 rats	sc	Wheel run (Voluntary exercise)	Autophagy regulation supports protein metabolism and anabolism to balance proteolysis via AMPK activation and Glut4 upregulation on muscle membrane, Inflammation reduction through IL-6, IL-10, and IL-1ra upregulation, Protection against heart α- to β-MHC isoform shift	Preserve cardiac function, attenuate autophagic response in heart and tumor tissues. This may be related to reduced tumor growth in aerobically exercised rats,or to improved regulation of autophagy by exercise, or both	10.1249/MSS.0000000000001544
Amani Shalamzari, 2018	breast	MC4L2	mice	sc	Progressive aerobic training	Modification of 3 major cytokines influencing appetite & energy metabolism (increase ghrelin,adiponectin, decrease leptin)	Attenuate tumor growth and cachexia, improve appetite, muscle size and function/fitness	10.5812/ircmj.13305
Molanouri Shamsi, 2017	breast	4T1	mice	sc	Aerobic interval training(treadmill) AND selenium nanoparticles treatment(oral)	Aerobic interval training enhanced anti-inflammatory indices IL-10/TNF-α ratio and IL-15 expression in skeletal muscle	Combined exercise training &antioxidant suppl. prevent cachexia and muscle wasting, decrease tumor volume. Selenium supplementation enhance cachexia (loss of body/fat mass,decreased appetite), Exercise training prevent muscle wasting	10.1016/j.cyto.2016.11.005

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Padilha, 2017	Walker 256	Walker 256 tumor cells	rats	sc	Resistance exercise training (RET) prior tumor implantation	Attenuation of muscle oxidative stress and systemic inflammatory markers.	Mitigate reduced BW and muscle wasting, prevent loss of muscle strength	10.1139/apnm-2016-0436
Jee, 2016	colon	C26	mice	via tail vein	Prehabilitation moderate(ME) /intense(SE) treadmill exercise	Anti-inflammatory effect	SE improve QoL, survival rate, prevent muscle atrophy. Metabolic changes resulting from 90% maxHR exercise should be simulated as prehabilitation.	10.7150/jca.17162
Pigna, 2016	colon	C26			Aerobic Exercise + AICAR or rapamycin	Exercise / AICAR or rapamycin treatment may release the autophagic flux, prevent atrogene induction,and rescue muscle homeostasis	Voluntary exercise prevent loss of muscle mass and function, reduce skel.muscle autophagic flux, increasing survival. Treatment with AICAR or rapamycin,also rescued muscle mass. AICAR, rapamycin and exercise equally affect autophagic system and counteract cachexia, so autophagy-triggering drugs may be exploited to treat cachexia in conditions in which exercise cannot be prescribed.	10.1038/srep26991
Khamoui, 2016	colon	C26	mice		Aerobic(AT, wheel running) and resistance(RT, ladder climbing) training	AT: possibly through activation of mTOR pathway. RT: upregulated expression of myogenin, IGF-I	AT or RT unable to prevent body weight loss. AT may preserve function, reduce inflammatory response of spleen, and marginally rescue muscle mass. RT:damaged skeletal muscle phenotype,	10.1016/j.metabol.2016.01.014

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
							induction of genes associated with muscle damage and repair.	
Coletti, 2016	colon	C26	mice	sc	Voluntary excercise (wheel running)	Downregulate Pax7 expression	Rescue of muscle mass and fiber size	10.1155/2016/6729268
das Neves, 2016	Walker 256	Walker 256 tumor cells	rats	bone marrow (osteotomy)	Resistance exercise training (RET) ,short-term	Increase lactate dehydrogenase protein content, fully restored phosphorylated form of 4EBP-1	RET did not mitigated loss of muscle function, anorexia, tumor growth or mortality rate, only modest effects. Loss of strength capacity is directly associated with mortality in severe cachexia	10.1016/j.lfs.2016.08.025
Pin, 2015	colon / lung	C26 / LLC	mice	sc	mild exercise training(EX) + EPO administration	EPO adm. prevent anemia and boost exercise effectiveness. For skeletal muscle, EPO+moderate EX, inducing PGC-1α expression, promote mitochondrial biogenesis and turnover. Muscle-specific PGC-1α overexpression prevent LLC-induced muscle atrophy and Atrogin-1 hyperexpression.	In C26 mice acute EX does not improve muscle wasting , EX-EPO co-treatment spares oxidative myofibers atrophy and counteracts oxidative to glycolytic shift. LLC-mice are responsive to exercise and treatment with EX-EPO combination prevents loss of muscle strength and onset of mitochondrial ultrastructural alterations, &restore normal heart weight. CONCL: Low intensisty exercise can be effective tool to be included in combined therapeutic approaches against cancer	10.18632/oncotarget.6439

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
							cachexia, provided that anemia is coincidently treated in order to enhance the beneficial action of exercise	
Padrão, 2015	mammary carcinogenesis	MNU administration	rats	ip	endurance training impact on heart	Prevent cardiacTWEAK, NF-κB, TRAF6, atrogin-1, p70S6K activation	Prevent ca-induced cardiac proteolysis and fibrosis but not myostatin-mediated cardiac remodelling.	10.1016/j.abb.2014.12.026
Kryczyk, 2014	Walker 256	Walker 256 tumor cells ex vivo	rats		Exercise (swimming/ jumping training) & shark liver oil supplementation (before inducing cachexia)	Induction of apoptotic process by increasing lipid peroxidation in tumor tissue and modifying pattern of proteins'expression linked to cell death	SLO suppl and exercise alone are able to avoid installation of cachexia and also reduce tumor growth, but the association of both cause further effect only in the tumor growth.	10.4172/1948-5956.1000254
Donatto, 2013	Walker 256 carcinosarcoma	Walker 256 tumor cells	rats	sc	high-intense Resistance exercise (RET)	increase IL-10/Tnf-a ratio, down modulation of chronic inflammation, decrease circulating TAG and modulating lipoprotein metabolism	Positive effect against sarcopenia and muscle glycogen depletion, anti-inflammatory effect upon the adipose tissue. Prevention of systemic consequences ofo CAC similar to that by endurance exercise	10.1016/j.cyto.2012.10.021
Gholamian, 2020	4T-1		mice	sc	Interval aerobic training	Decrease of TGF-β, Twist, and Vimentin gene expressions	Protection muscle mass and function, reduce rate of tumor growth	10.22038/ IJBMS.2019.39535.9375
Vanderveen, 2020	ApcMin/+		mice		Wheel exercise	Increase mitochondria complex II, plasma IL-6 not affected	Increase BW, lean mass, improve grip strength and fatigue resistance, no effect on tumor burden, no effect on volitional (cage) activity	10.1249/ MSS.0000000000002393

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI
Alves, 2020	LLC, B16-F10, Walker-256		mice and rats	sc, intra bone-marrow	Aerobic training	Reduction oxidative stress and increase COPS2 protein expression (corepressor role - decrease DR4 response element activity; involvement in the modulation of F-actin cytoskeleton)	Protection muscle mass, improve running capacity, prolongation survival, no effect on tumor growth	10.1016/j.molmet.2020.101012
Ahmadabadi, 2020	4T1		mice	sc	High-intensity interval training	Reduction caspase-3, increase ratio of Bcl-2 to Bax in muscle cells	Protection BW,muscle mass and strength, increase food consumption	10.1139/apnm-2019-0352
Tanaka, 2019	AH130		rats	sc	Low-intensity endurance exercise	TNF-a levels unaffected, suppression FOXO1/UPS, reduction HIF-1a, modulation AMPK/mTOR	Increase muscle weight, improve muscle capillary regression andhypoxia	10.1096/fj.201802430R
Tatebayashi, 2018	C26		mice	sc	High-intensity eccentric training	Activation mTORC1 signaling and down regulation MuRF-1	Preservation muscle tissue	10.1371/journal.pone.0199050
Padrão, 2017	Chemical mammary carcinogenesis (N-MethylN-nitrosourea)		rats	ip	Long-term endurance training	Prevention TWEAK/NF-κB signalling, improve mitochondrial biogenesis (PGC-1a) and oxidative capacity, no apparent effect on UPS,	Prevention decrease CSA, lower malignant lesions	10.1111/apha.12721
Moreira, 2018	Walker 256		rats	sc	Aerobic exercise	Improve insulin sensitivity and reduction insulin secretion, preservation islet number/area but decrease β-cell mass	Increase tumor-free BW and appetite, inhibition tumor growth, metastasis,	10.3389/fphys.2018.00465
Moreira, 2019	Walker 256		rats	sc	Moderate exercise training (especially in adolescence)	Inhibition cancer cells proliferation, possible involvement of glucose-insulin homeostasis	Reduction muscle wasting and tumor growth	10.1113/JP277645
Ranjbar, 2019	C26		mice	sc	Combined exercise	Modulation autophagy (reduction LC3B-II/I ratio) and increase mitochondria oxidative capacity (SDH),	Positive effect on muscle mass and strength	10.1249/MSS.0000000000001916

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Supplementary Table 2 (*Continued*)

Author, Year	Tumor type	Model	Animal	Inoculation site	Intervention	Mechanism	Result	DOI

sc: subcutaneous; ip: intraperitoneal; UPS pathway: The ubiquitin-proteasome system; p97-Nploc4: p97- Nuclear protein localization protein 4 homolog; STAT3: Signal Transducer and Activator of Transcription 3; MuRF1: Muscle RING Finger 1; FOXO1: Forkhead Box O1; MSTN: Myostatin; ROS: Reactive Oxygen Species; TGF-β/Smad2: Transforming Growth Factor- beta/Mothers against decapentaplegic homolog 2; HSP90/STAT3/FOXO: Heat Shock Protein 90/ Signal Transducer and Activator of Transcription 3/Forkhead Box O1; TNF-α: Tumor Necrosis Factor-α; NF-κB: Nuclear Factor kappa B; IFN-γ: Interferon-γ; Sirt1/ AMPK: Sirtuin 1/ AMP- activated protein kinase ; PKB: Protein Kinase B; IGF-1: Insulin-like Growth Factor-1; GSK-3β: Glycogen synthase kinase; p38/ MAPK: p38 Mitogen-Activated Protein Kinases; TCF4–TWIST1: Transcription Factor 4- Twist-related protein 1; TGF-β1/PTHLH: Transforming Growth Factor- beta1/ Parathyroid Hormone-Like Hormone; Hsp70/90: Heat Shock Protein 70/90; CD8+ T cells: Cluster of Differentiation 8+ T cells; IL-6: Interleukin-6; Bnip-3: BCL2/adenovirus E1B 19kDa interacting protein 3; IL-1: Interleukin-1; Socs3: Suppressor of Cytokine Signaling 3; PARP-1/2: Poly(ADP-ribose) polymerase ½; LPAR/ Gαi2: Lysophosphatidic Acid Receptor/ G alpha i2; Pax-7: Paired Box Protein- 7; STAT3: Signal Transducer and Activator of Transcription 3; IL6/STAT3: Interleukin-6/ Signal Transducer and Activator of Transcription 3; PI3K: Phosphoinositide 3-Kinase; TGF-β1: Transforming Growth Factor- beta 1; EGFR: Epidermal Growth Factor Receptor; PTHrP: Parathyroid hormone-related protein ; MAPK/ERK: Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase; PERP: P53 Apoptosis Effector Related to PMP-22; FOXO3: Forkhead Box O3; FBXO-40: F-Box Protein 40; TRAF-6: Tumor necrosis factor Receptor-Associated Factor 6; TCF4/TWIST1: Transcription Factor 4/ Twist-related protein 1 ; PTHLH: Parathyroid Hormone-Like Hormone; PLA2G7: Phospholipase A2 Group VII; p38 MAPK: p38 Mitogen-Activated Protein Kinase; mTOR: mechanistic Target of Rapamycin; HIF-1a: Hypoxia-inducible factor 1-alpha; CREB–miR-373–PHLPP2-Akt: cAMP Response Element-Binding Protein- microRNA-373- PH domain and leucine-rich repeat protein phosphatase 2- Protein Kinase B; mTORC1: mechanistic Target of Rapamycin Complex; Protein synthesis; NAD: Nicotinamide Adenine Dinucleotide; MHC: Major Histocompatibility Complex; ACVR2B: Activin Receptor Type-2B; MyoD: Myogenic Differentiation 1; MAFbx: Muscle-specific ligases Atrophy F-box protein; WNT/β-catenin: Wingless-related integration site/ β-catenin; 5-HT1A: 5-hydroxytryptamine (serotonin) receptor 1A; BRD4 protein: Bromodomain-containing protein 4; JAK2/STAT3: Janus Kinase 2/ Signal Transducer and Activator of Transcription 3; MEK1/2: Mitogen-Activated Protein Kinase ½; HIF-1a: Hypoxia-inducible factor 1-alpha; MEK/ERK: Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase; AMPK: AMP- activated protein kinase; MCP-1: Monocyte Chemoattractant Protein-1; TWEAK: Tumor Necrosis Factor-like Weak Inducer of Apoptosis; ATGL: Adipose Triglyceride Lipase; RAS: renin-angiotensin system; PPAR-γ: Peroxisome Proliferator-Activated Receptor-gamma; C/EBP-α: CCAAT/enhancer-binding protein alpha; VEGF: Vascular Endothelial Growth Factor; GLP-1: Glucagon-like peptide-1; ACE: Angiotensin- converting enzyme; GDF15-GFRAL: Growth Differentiation Factor 15- GDNF Family Receptor Alpha-Like; IL-6/AMPK/FoxO3: Interleukin-6/ AMP- activated protein kinase/ Forkhead Box O3