Role for Plant-Derived Antioxidants in Attenuating Cancer Cachexia

Subjects: Physiology

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Cancer cachexia describes the cancer-related muscle wasting that contributes to the progression of many cancer types. It is defined as “a multifactorial syndrome exhibiting ongoing loss of skeletal muscle mass, with or without the loss of fat mass, leading to progressive muscle functional impairment”. Typical clinical symptoms include anorexia, involuntary weight loss, weakness, anemia, systemic inflammation, insulin resistance and increased resting energy expenditure (REE). Antioxidants have therapeutic potential to attenuate cancer-related muscle loss, with polyphenols, a group of plant-derived antioxidants, being the most widely investigated.

cancer cachexia oxidative stress

1. Pathogenesis of Cancer Cachexia

Various factors produced by both host and tumor are thought to contribute to the development and progression of cancer cachexia [1]. These multiple factors ultimately disrupt the balance between protein synthesis and protein degradation, leading to a loss of muscle mass [2][3]. Dysfunction of the membrane stabilizing dystrophin-glycoprotein complex (DGC), characterized by reduced dystrophin expression and increased glycosylation of DGC proteins, has been shown in a mouse model of gastrointestinal cancer, indicating that a loss of communication between the muscle cell membrane and the extracellular matrix could be associated with cachexia [4]. Increased metabolic stress, which occurs as a consequence of tumor burden, nutritional deficiency and various medical interventions such as chemotherapy, contributes to the development of cancer cachexia by elevating REE and exacerbating muscle loss [5]. Anti-cancer interventions such as chemotherapy can cause discomfort, nausea and anorexia in some patients, leading to reduced food intake, metabolic changes and muscle loss [6]. Since oxidative stress is a major contributor to the development of cancer cachexia, factors able to mitigate excessive oxidative stress could have therapeutic potential.

2. Polyphenols to Reduce Oxidative Stress in Cancer Cachexia

Despite oxidative stress being a main driver of cancer cachexia, there is a dearth of studies investigating the therapeutic potential of antioxidants for treating cancer-related muscle wasting (**Table 1**). Polyphenols are common phytochemicals with protective effects against oxidative stress-related diseases. They are widely distributed across plants and can be found in various plant-based foods, including fruits, vegetables and whole grains with rich

antioxidant sources [7]. Due to their antioxidative and anti-inflammatory properties, the potential benefits of polyphenols against different cancers have been investigated extensively [8]. The potential for polyphenols to attenuate cancer cachexia has been attributed to a possible preservation of muscle mass through inhibition of NF-κB signaling [7].

2.1. Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is the dominant antioxidant in green and black tea extract, having antioxidant, anti-inflammatory and anti-cancer functions [9]. EGCG suppresses cancer cell proliferation, inducing cell apoptosis and inhibiting cell invasion and migration to attenuate tumor progression [10]. In cell culture, 48 h EGCG treatment suppressed the growth of Lewis lung carcinoma (LLC) cancer cells in a dose-dependent manner, confirming its anti-tumor effects [9]. In the LLC tumor-bearing mouse, 12 days of EGCG treatment reduced tumor mass and volume and attenuated the loss of body weight without altering anorexia [9]. The attenuation of muscle wasting was attributed to inhibition of NF-κB and the downstream E3 ligases, MuRF1 and atrogin-1. Furthermore, ECGC treatment decreased leukocytic infiltration, thus reducing inflammation in skeletal muscles of tumor-bearing mice [9]. In addition to the suppression of tumor growth, high dose EGCG treatment reduced the survival rate of a healthy, baby hamster kidney cells (BHK-21) by 50%, [9], suggesting that higher concentrations of EGCG cause cytotoxicity in normal cells and interrupt healthy cell growth. Given that EGCG treatment in the LLC-injected mice was administrated several days prior to tumor palpability, it remains to be determined whether the protective effect of EGCG on muscle mass was due to its anti-cancer effects or direct effects on the muscle. Moreover, EGCG has a low systemic bioavailability [11], which may reduce the efficacy of EGCG treatment in clinical studies and in vivo animal studies. EGCG treatment for cancer cachexia is a relatively preliminary concept in the field and further investigation is needed to confirm therapeutic potential.

2.2. Resveratrol

Resveratrol is found most abundantly in the skin of grapes, peanuts and pine bark, and has been shown to exert anti-cancer effects in vitro and in vivo [12]. In Yoshida ascites hepatoma (AH-130) cells in vitro and in rats implanted with AH-130 cells, resveratrol administration reduced tumor cell number via induction of AH-130 cell apoptosis [12]. In Ehrlich ascitic carcinoma bearing mice, the combined treatment of resveratrol (10 mg/kg) with the chemotherapeutic drug, doxorubicin (5 mg/kg), twice a week via intraperitoneal injection, exerted the best reduction in tumor size and prolonged survival compared with either treatment alone [13]. These findings demonstrate the potential for resveratrol to enhance the anti-cancer effect of chemotherapies by decreasing inflammation and the oxidative stress associated with chemotherapy [13].

Table 1. Effect of treatment with polyphenols for cancer cachexia.

Types	Experimental Setting	Treatments	Findings	References
EGCG	In vivo 6–8-week-old	Low dose (0.2 mg/kg/day), high dose	↓ NF-κB	[9]

Types	Experimental Setting	Treatments	Findings	References
	male LLC-tumor-bearing mice (C57BL/6)	(0.6 mg/kg/day) via oral gavage;	↓ NF-κB-mediated ubiquitin–proteasome proteolysis	
		12 days pre-treatment or 30 days post-tumor treatment	↓ atrogin-1 and MuRF1 expression	
			↓ tumor-induced muscle atrophy	
Resveratrol	In vivo 6–10-week-old female C-26 tumor-bearing mice (CD2F1)	200 mg/kg/day via oral gavage for 11 days	↓ NF-κB	[14]
			↓ atrogin-1 and MuRF1 expression	
			↓ tumor-induced muscle atrophy	
			No effect on tumor growth	
	In vivo 5-week-old male Wistar AH-130 tumor-bearing rats	1 mg/kg/day via intraperitoneal (i.p.) injection to AH-130 tumor bearing rats for 7 days	No effect on skeletal muscle and whole body mass	[15]
	12-week-old male LLC-tumor-bearing mice (C57BL/6)	5 or 25 mg/kg/day via i.p. injection to LLC-tumor bearing mice for 15 days	Failed to attenuate cancer cachexia in different tumor-bearing rodents	
	In vivo 10-week-old female BALB/c mice	20 mg/kg/day via i.p. injection for 15 days	↓ muscle wasting	[16]
			↑ gastrocnemius and soleus muscle mass	
			↓ tumor growth	
			↑ limb strength gain	
			↑ muscle fiber (I & II) cross-sectional area, ↓ muscle abnormalities	
			↑ sirtuin-1 protein expression	
			↓ atrogin-1 and MuRF1 expression	
			↓ forkhead box O3 (FoxO3)	

Types	Experimental Setting	Treatments	Findings	References
			↓ signaling markers NF-κB and p50	
Curcumin	In vivo 10-week-old female LP07 tumor-bearing BALB/c mice	1 mg/kg/day via i.p. injection for 15 days	↓ muscle wasting	[16]
			↑ gastrocnemius and soleus muscle mass	
			↑ limb strength gain	
			No effect on tumor growth	
			↑ muscle fiber (I & II) cross-sectional area, ↓ muscle abnormalities	
			↑ sirtuin-1 protein expression	
			↓ atrogin-1 and MuRF1 expression	
			↓ FoxO3	
			↓ signaling markers NF-κB and p50	
	In vivo MAC16-colon tumor-bearing mice	Low dose (100 mg/kg/day), high dose (250 mg/kg/day) via oral gavage for 20 days	↓ muscle wasting with low dosage	[17]
			↑ body weight, muscle hypertrophy with high dosage	
			↓ proteasome complex activity	
	In vivo Male Wistar AH-130 tumor-bearing rats	20 µg/kg body weight via i.p. injection for 6 days	Inhibited NF-κB pathway	[18]
			↓ tumor growth	
			Failed to attenuate cancer cachexia	
Carnosol	In vitro C2C12 myotube	3.125 µM to 25 µM concentration of carnosol incubated with C-26 cancer medium for 48 h in C2C12 myotubes;	In vitro: High dose (25 µM) had no toxic effect to C2C12 myotubes;	[19]
			↓ C-26 tumor-induced muscle wasting in C2C12 myotubes in	

Types	Experimental Setting	Treatments	Findings	References
			dose-dependent manner	
			↑ MyoD, p-Akt at high dose of carnosol	
			↓ MuRF1, p-p65/p65 at high dose of carnosol	
	In vivo 6–8-week-old male C-26 tumor-bearing, BALB/c mice	10 mg/kg/day via i.p. injection from the day after tumor injection for 16 days	In vivo: ↑ body weight	
			No effect on tumor growth	
			↑ MyoD, myosin heavy chain	
			↓ p-p65/p65 ratio	
Quercetin	In vivo 15-week-old $Apc^{Min/+}$mice	25 mg/kg/day via oral gavage for 3 weeks	Attenuated ↓ body mass	[20]
			↑ gastrocnemius and quadriceps muscle mass	
			No change in soleus muscle mass	
			No improvement in muscle function	
			↓ plasma IL-6	
	In vivo 9-week-old C-26 tumor-bearing male CD2F1 mice	250 mg/kg added to daily chow diet for 20 days	↑ body weight	[21]
			↑ food intake	
			No change grip strength	
			Prevented tumor-induced ↓ muscle volume	
			No change in tumor weight	
			↑ gastrocnemius and tibialis anterior muscle mass	
Rutin	In vivo 6-week-old K14-HPV16 mice	413 mg/kg/day to daily diet for 24 weeks	↑ survival	[22]
			No change in body weight	

Types	Experimental Setting	Treatments	Findings	References
			↑ gastrocnemius muscle weight	
			↓ NF-κB signaling pathway	
Genistein and daidzein	In vivo 8-week-old male C57BL/6 mice with LLC tumors	Normal diet mixed with 40.74% of soyaflavone HG (containing high genistein and daidzein contents) for 3 weeks	No change in food intake or body mass	[23]
			↑ gastrocnemius muscle weight and myofiber size	
			No change in tumor mass	
			No change in plasma IL-6 or TNF-α	
			↓ atrogin-1 and MuRF1 expression	
		[16]	↓ phosphorylation of extracellular signal-regulated kinase (ERK)	
Morin	In vitro LLC cells and C2C12 myotubes [16]	In vitro: 10, 50, 100, 200 μM treated to LLC cells and C2C12 myotubes for 48 h	[28] In vitro: ↓ cell viability of LLC cells with 100 and 200 μM	[24]
			↑ cell viability of C2C12 myotubes with 10 μM; no cell death at high dose (100 and 200 μM)	
			[15] ↓ protein synthesis shown in LLC cells using SUnSET method; no significant changes were found with C2C12 myotubes.	
	In vivo 6-week-old male C57BL/6 mice with LLC tumors	In vivo: Morin-rich (0.1% *w/w*) diet for 3 weeks	In vivo: Attenuated↓muscle mass and gastrocnemius muscle myofiber size	[17][18]
			↓ tumor mass	

↓—decreased and ↑—increased.

Resveratrol has been studied as an anti-cachectic treatment to attenuate muscle atrophy. Daily administration of resveratrol (200 mg/kg/day) via oral gavage attenuated the loss of lean body and fat mass, and gastrocnemius

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suppression of NF-κB activity [18][30]. In MAC16 tumor-bearing mice, curcumin prevented muscle wasting and reversed existing muscle loss [17]. Treatment with curcumin c3 complex has been used in human clinical trials [31], where it protected skeletal muscle from wasting when orally administered a low dose (100 mg/kg/day) for 20 days, and induced weight gain relative to the control tumor-bearing group when administered at a higher dose (250 mg/kg/day) [17]. In MAC16 colon tumor-bearing mice, curcumin treatment attenuated the PIF-induced increase of the 20S proteasome, and decreased expression of NF-κB, atrogin-1 and MuRF1, indicating that protection from

[illegible] [18]. The disparity in these reports may arise from differences in dose, route of administration and treatment duration in different animal models, as well as the low systemic bioavailability of curcumin [32].

While studies investigating curcumin efficacy in cancer cachexia did not measure oxidative stress directly, the role of curcumin for attenuating oxidative stress in skeletal muscle is well established. Curcumin reduced exercise-induced oxidative stress, evidenced by decreased levels of serum lactate and muscle MDA [33]. Oral curcumin treatment (100 mg/kg/day) for 14 days reduced hypobaric hypoxia-induced oxidative stress and increased muscle fiber number in Sprague Dawley rats [34]. The antioxidative effect of curcumin was linked with reduced activity of NF-κB and activation of Nrf2 signaling [33], effects that reflect regulation of redox balancing, protein synthesis and protein degradation. Thus, regulating redox balance may be one mechanism by which curcumin attenuates cancer cachexia.

The therapeutic potential of curcumin has also been explored in clinical trials. Based on the limited data available, curcumin reduced expression of NF-κB in some patients with pancreatic cancer [30]. Due to its poor oral absorption and weak bioavailability, curcumin supplementation had only limited benefit for these pancreatic cancer patients [30]. However, the difficulty in accurately determining redox status in skeletal muscle [35], may explain why evaluating the efficacy of antioxidant supplements like curcumin has proved challenging, especially when assessments in trials rely on measures of antioxidant levels in the blood. Improvements in the accuracy of these outcome measures are required to better evaluate the therapeutic potential of curcumin for cancer cachexia.

2.4. Carnosol

Carnosol is a bioactive diterpene compound present in rosemary, with antioxidant, anti-inflammatory and anti-cancer properties [19]. The antioxidative function of carnosol has been well characterized and includes protection from lipid peroxidation [36], suppression of nitric oxide production and gene expression of inducible nitric oxide synthase [37] and amelioration of the damage caused by UVB-induced ROS [38]. Carnosol can inhibit the activities of NF-κB signaling to protect against free radical damage [37] and it has been shown to reduce tumor growth in mouse models of intestinal cancer [39], breast cancer [40] and skin cancer [38].

Carnosol can protect against cancer-induced muscle wasting in in vitro and in vivo models [19]. Carnosol supplementation attenuated C2C12 myotube atrophy after exposure to C-26 cell conditioned media and ameliorated the loss of body mass in C-26 tumor-bearing mice [19]. These effects were associated with downregulation of MuRF1 expression and upregulation of Akt phosphorylation and MyoD expression, indicating suppressed protein degradation and increased protein synthesis [19]. Both in vitro and in vivo models showed reduced phosphorylation of p65, implicating a role for carnosol in suppressing NF-κB signaling in cancer cachexia [19]. While carnosol had a protective role in C-26 tumor-bearing mice by maintaining body mass and adipose tissue mass, skeletal muscle mass was not improved. This suggested the increase in body mass resulted from an attenuation of fat lipolysis rather than direct effects on the regulation of skeletal muscle mass [19]. These interesting findings warrant further investigation of the therapeutic potential of carnosol for cancer cachexia. Moreover, a recent study revealed the synergistic effect of carnosol and a chemotherapeutic drug, cisplatin, where combined therapy induced the highest rates of apoptosis in MCF-7 and MDA-MB-231 breast cancer cell lines [41]. Therefore, carnosol has potential to become part of a combination therapy in the treatment of cancer and cancer-induced muscle wasting.

2.5. Quercetin and Rutin

Quercetin is an abundant flavonoid and prominent dietary antioxidant in various fruits and vegetables, such as onions, tomatoes and apples [42]. Quercetin has antioxidative and anti-inflammatory functions, and hence therapeutic potential for treating cancer [43][44]. Supplementation with quercetin (0.05% (*w/w*) in food) for nine weeks protected against TNF-α-induced skeletal muscle atrophy via activation of Nrf-2 signaling and inactivation of the NF-κB signaling pathway to overcome oxidative stress in the C57BL/6 mouse model of high fat diet-induced obesity, confirming the antioxidant and anti-inflammatory properties of quercetin [42]. Quercetin has significant bioavailability compared with other polyphenols, with detection in plasma 12 h after oral intake [21]. The high absorption in plasma was associated with whole body accumulation of quercetin since it was detected in different tissues such as the liver, skeletal muscle, heart and brain, resulting in the slow clearance of quercetin metabolites from the body [21].

Quercetin has been shown to protect against cancer-induced muscle wasting in vivo [20][21]. Oral administration of quercetin (25 mg/kg/day) to $Apc^{Min/+}$ mice for three weeks attenuated the loss of whole body mass and increased gastrocnemius and quadriceps muscle mass [20]. These effects may have resulted from reduced inflammation, based on the decrease in plasma IL-6 levels [20]. However, treatment failed to improve muscle function in the $Apc^{Min/+}$ mouse model of cancer cachexia [20]. Supplementation of 250 mg/kg quercetin to a daily chow diet for 20 days attenuated both the loss of body mass and the reduction in gastrocnemius and tibialis anterior muscle mass in C-26 tumor bearing mice, but did not improve grip strength [21]. Micro-CT analysis of the hindlimb revealed that quercetin supplementation completely prevented the tumor-induced reduction in muscle volume [21]. A substantial (albeit a non-statistically significant) decrease was detected in the expression of E3 ubiquitin ligases, atrogin-1 and MuRF1, in treated mice, indicating an attenuation of protein degradation. While these studies suggest a positive outcome of quercetin with a potential anti-cachectic function, the underlying mechanism remains undetermined. Interestingly, tumor mass was not significantly decreased with quercetin. Furthermore, the experiment did not

control for the increase in food intake in the quercetin supplemented group [21]. While quercetin has proposed anti-cachectic benefits, a mechanism for these effects has not been established at the cellular level, and this diminishes the significance of these outcomes. Moreover, oral quercetin (50 mg/kg/day) for 1 h prior and during 15-day doxorubicin exposure, reduced chemotherapy-induced oxidative stress in the spleen via suppression of apoptosis, reducing inflammation and increasing the antioxidant response in Sprague–Dawley rats [45]. The protective effect of quercetin against chemotherapy-induced cytotoxicity indicates its potential for attenuating chemotherapy associated muscle atrophy in cancer cachexia. Future studies using pair-fed groups to control for potential treatment-related changes in food intake, as well as additional clinically relevant end-point analyses such as survival, are warranted in order to fully investigate the therapeutic potential of quercetin in cancer cachexia.

Similar to quercetin, rutin, a quercetin glycoside more commonly seen in edible plants, has similar high bioavailability, making it a suitable candidate for nutritional therapy [46]. Supplementation with rutin (413 mg/kg/day) for 24 weeks increased survival in HPV16-tumor bearing mice and increased gastrocnemius muscle mass, which was associated with inhibition of NF-κB signaling [22]. Rutin also alleviated carcinogenesis via suppression of cyclo-oxygenase-2 in K14-HPV16 mice [47]. Studies have demonstrated the synergistic benefit of rutin in combination with chemotherapeutic drugs to further reduce cell proliferation in different cancer cell lines via activation of apoptosis, thereby enhancing the anti-cancer effect of chemotherapy [48]. Thus, rutin has significant potential in combination therapies to attenuate cancer cachexia.

2.6. Genistein, Daidzein and Morin

Genistein and daidzein are isoflavones abundant in soy products, with anti-inflammatory and antioxidative properties [23]. Supplementation with soy isoflavones (mainly genistein and daidzein) for three weeks attenuated LLC tumor-induced muscle wasting by increasing both the overall muscle mass and size of individual muscle fibers within the gastrocnemius. These effects were associated with decreased expression of the ubiquitin-related E3 ligases, atrogin-1 and MuRF1, and likely mediated by ERK signaling to exert muscle-protecting function against cancer cachexia [23]. Soy isoflavones have also been widely discussed in the context of breast cancer, since they are plant-derived substances that activate signaling via estrogen receptors [49]. However, the benefit of soy isoflavones for breast cancer patients has been controversial [50]. In the MCF-7 breast cancer cell line, high dose (100 μM) of genistein combined with the chemotherapeutic agent, cisplatin, suppressed breast cancer cell growth and proliferation, whereas 10 μM of genistein antagonized the action of cisplatin to induce cancer cell apoptosis [49]. Further investigation confirmed that oral genistein supplementation (5 mg/kg/day) for three weeks counteracted cisplatin chemotherapy in breast cancer-bearing mice [51]. The anti-cancer effect of these soy isoflavones (genistein in particular) therefore remains controversial due to insufficient evidence. Such conflict raises doubt about the potential of these soy isoflavones to attenuate cancer-induced muscle atrophy. Future investigation is warranted to address these concerns.

Morin is a type of flavonoid, found in plants including Moraceae, Malpighiaceae, Myrtaceae, almond hulls and seaweeds [24]. Supplementation with a morin-rich diet for three weeks reduced tumor weight and progression in LLC-tumor bearing mice, demonstrating a powerful anti-cancer effect [24]. In addition, morin has been shown to

have anti-cachectic potential, by attenuating cancer-induced muscle wasting in these same mice [24]. In vitro studies revealed that morin suppressed cancer cell growth via decreasing protein synthesis [24]. In contrast, morin (10 μM) increased protein synthesis in C2C12 myotubes, and this was associated with increased cell viability [24]. Moreover, oral morin treatment (50 mg/kg/day) for 30 days reduced the damage caused by a single injection of cisplatin in Sprague–Dawley rats by ameliorating chemotherapeutic drug-induced oxidative stress and activating antioxidant signaling cascades in isolated renal mitochondria [52]. These findings suggest a benefit for morin supplementation in reducing chemotherapy-induced cytotoxicity, which may also have positive effect on ameliorating chemotherapy-related oxidative stress in skeletal muscle. Further investigation is needed to evaluate the potential for morin to attenuate cancer cachexia.

References

1. Powers, S.K.; Lynch, G.S.; Murphy, K.T.; Reid, M.B.; Zijdewind, I. Disease-Induced Skeletal Muscle Atrophy and Fatigue. Med. Sci. Sports Exerc. 2016, 48, 2307–2319.
2. Eley, H.L.; Tisdale, M.J. Skeletal muscle atrophy, a link between depression of protein synthesis and increase in degradation. J. Biol. Chem. 2007, 282, 7087–7097.
3. O'Keefe, S.J.; Ogden, J.; Ramjee, G.; Rund, J. Contribution of elevated protein turnover and anorexia to cachexia in patients with hepatocellular carcinoma. Cancer Res. 1990, 50, 1226–1230.
4. Acharyya, S.; Butchbach, M.E.; Sahenk, Z.; Wang, H.; Saji, M.; Carathers, M.; Ringel, M.D.; Skipworth, R.J.; Fearon, K.C.; Hollingsworth, M.A.; et al. Dystrophin glycoprotein complex dysfunction: A regulatory link between muscular dystrophy and cancer cachexia. Cancer Cell 2005, 8, 421–432.
5. Fearon, K.; Arends, J.; Baracos, V. Understanding the mechanisms and treatment options in cancer cachexia. Nat. Rev. Clin. Oncol. 2013, 10, 90–99.
6. Damrauer, J.S.; Stadler, M.E.; Acharyya, S.; Baldwin, A.S.; Couch, M.E.; Guttridge, D.C. Chemotherapy-induced muscle wasting: Association with NF-kappaB and cancer cachexia. Eur. J. Transl. Myol. 2018, 28, 7590.
7. Salucci, S.; Falcieri, E. Polyphenols and their potential role in preventing skeletal muscle atrophy. Nutr. Res. 2020, 74, 10–22.
8. Zhou, Y.; Zheng, J.; Li, Y.; Xu, D.-P.; Li, S.; Chen, Y.-M.; Li, H.-B. Natural Polyphenols for Prevention and Treatment of Cancer. Nutrients 2016, 8, 515.
9. Wang, H.; Lai, Y.J.; Chan, Y.L.; Li, T.L.; Wu, C.J. Epigallocatechin-3-gallate effectively attenuates skeletal muscle atrophy caused by cancer cachexia. Cancer Lett. 2011, 305, 40–49.
10. Yang, C.S.; Wang, X. Green tea and cancer prevention. Nutr. Cancer 2010, 62, 931–937.

11. Yang, C.S.; Lambert, J.D.; Hou, Z.; Ju, J.; Lu, G.; Hao, X. Molecular targets for the cancer preventive activity of tea polyphenols. Mol. Carcinog. 2006, 45, 431–435.
12. Carbo, N.; Costelli, P.; Baccino, F.M.; Lopez-Soriano, F.J.; Argiles, J.M. Resveratrol, a natural product present in wine, decreases tumour growth in a rat tumour model. Biochem. Biophys. Res. Commun. 1999, 254, 739–743.
13. Rai, G.; Mishra, S.; Suman, S.; Shukla, Y. Resveratrol improves the anticancer effects of doxorubicin in vitro and in vivo models: A mechanistic insight. Phytomedicine 2016, 23, 233–242.
14. Shadfar, S.; Couch, M.E.; McKinney, K.A.; Weinstein, L.J.; Yin, X.; Rodriguez, J.E.; Guttridge, D.C.; Willis, M. Oral resveratrol therapy inhibits cancer-induced skeletal muscle and cardiac atrophy in vivo. Nutr. Cancer 2011, 63, 749–762.
15. Busquets, S.; Fuster, G.; Ametller, E.; Olivan, M.; Figueras, M.; Costelli, P.; Carbo, N.; Argiles, J.M.; Lopez-Soriano, F.J. Resveratrol does not ameliorate muscle wasting in different types of cancer cachexia models. Clin. Nutr. 2007, 26, 239–244.
16. Penedo-Vázquez, A.; Duran, X.; Mateu, J.; López-Postigo, A.; Barreiro, E. Curcumin and Resveratrol Improve Muscle Function and Structure through Attenuation of Proteolytic Markers in Experimental Cancer-Induced Cachexia. Molecules 2021, 26, 4904.
17. Siddiqui, R.A.; Hassan, S.; Harvey, K.A.; Rasool, T.; Das, T.; Mukerji, P.; DeMichele, S. Attenuation of proteolysis and muscle wasting by curcumin c3 complex in MAC16 colon tumour-bearing mice. Br. J. Nutr. 2009, 102, 967–975.
18. Busquets, S.l.; Carbó, N.; Almendro, V.; Quiles, M.a.T.; López-Soriano, F.J.; Argilés, J.M. Curcumin, a natural product present in turmeric, decreases tumor growth but does not behave as an anticachectic compound in a rat model. Cancer Lett. 2001, 167, 33–38.
19. Lu, S.; Li, Y.; Shen, Q.; Zhang, W.; Gu, X.; Ma, M.; Li, Y.; Zhang, L.; Liu, X.; Zhang, X. Carnosol and its analogues attenuate muscle atrophy and fat lipolysis induced by cancer cachexia. J. Cachexia Sarcopenia Muscle 2021, 12, 779–795.
20. Velázquez, K.T.; Enos, R.T.; Narsale, A.A.; Puppa, M.J.; Davis, J.M.; Murphy, E.A.; Carson, J.A. Quercetin Supplementation Attenuates the Progression of Cancer Cachexia in ApcMin/+Mice. J. Nutr. 2014, 144, 868–875.
21. Levolger, S.; van den Engel, S.; Ambagtsheer, G.; Ijzermans, J.N.M.; de Bruin, R.W.F. Quercetin supplementation attenuates muscle wasting in cancer-associated cachexia in mice. Nutr. Healthy Aging 2021, 6, 35–47.
22. Gil da Costa, R.M.; Aragão, S.; Moutinho, M.; Alvarado, A.; Carmo, D.; Casaca, F.; Silva, S.; Ribeiro, J.; Sousa, H.; Ferreira, R.; et al. HPV16 induces a wasting syndrome in transgenic mice: Amelioration by dietary polyphenols via NF-κB inhibition. Life Sci. 2017, 169, 11–19.

23. Hirasaka, K.; Saito, S.; Yamaguchi, S.; Miyazaki, R.; Wang, Y.; Haruna, M.; Taniyama, S.; Higashitani, A.; Terao, J.; Nikawa, T.; et al. Dietary Supplementation with Isoflavones Prevents Muscle Wasting in Tumor-Bearing Mice. J. Nutr. Sci. Vitaminol. 2016, 62, 178–184.
24. Yoshimura, T.; Saitoh, K.; Sun, L.; Wang, Y.; Taniyama, S.; Yamaguchi, K.; Uchida, T.; Ohkubo, T.; Higashitani, A.; Nikawa, T.; et al. Morin suppresses cachexia-induced muscle wasti.ing by binding to ribosomal protein S10 in carcinoma cells. Biochem. Biophys. Res. Commun. 2018, 506, 773–779.
25. Schmid, H.H. Reasons for low incidence of peptic ulcer in pregnancy. Zent. Gynakol. 1950, 72, 1839–1840.
26. Wang, D.T.; Yin, Y.; Yang, Y.J.; Lv, P.J.; Shi, Y.; Lu, L.; Wei, L.B. Resveratrol prevents TNF-alpha-induced muscle atrophy via regulation of Akt/mTOR/FoxO1 signaling in C2C12 myotubes. Int. Immunopharmacol. 2014, 19, 206–213.
27. Menzies, K.J.; Singh, K.; Saleem, A.; Hood, D.A. Sirtuin 1-mediated effects of exercise and resveratrol on mitochondrial biogenesis. J. Biol. Chem. 2013, 288, 6968–6979.
28. Sanchez, A.M.; Candau, R.B.; Bernardi, H. FoxO transcription factors: Their roles in the maintenance of skeletal muscle homeostasis. Cell Mol. Life Sci. 2014, 71, 1657–1671.
29. Quan-Jun, Y.; Jun, B.; Li-Li, W.; Yong-Long, H.; Bin, L.; Qi, Y.; Yan, L.; Cheng, G.; Gen-Jin, Y. NMR-based metabolomics reveals distinct pathways mediated by curcumin in cachexia mice bearing CT26 tumor. RSC Adv. 2015, 5, 11766–11775.
30. Dhillon, N.; Aggarwal, B.B.; Newman, R.A.; Wolff, R.A.; Kunnumakkara, A.B.; Abbruzzese, J.L.; Ng, C.S.; Badmaev, V.; Kurzrock, R. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin. Cancer Res. 2008, 14, 4491–4499.
31. Sharma, R.A.; Euden, S.A.; Platton, S.L.; Cooke, D.N.; Shafayat, A.; Hewitt, H.R.; Marczylo, T.H.; Morgan, B.; Hemingway, D.; Plummer, S.M.; et al. Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance. Clin. Cancer Res. 2004, 10, 6847–6854.
32. Shehzad, A.; Wahid, F.; Lee, Y.S. Curcumin in cancer chemoprevention: Molecular targets, pharmacokinetics, bioavailability, and clinical trials. Arch. Pharm. 2010, 343, 489–499.
33. Sahin, K.; Pala, R.; Tuzcu, M.; Ozdemir, O.; Orhan, C.; Sahin, N.; Juturu, V. Curcumin prevents muscle damage by regulating NF-kappaB and Nrf2 pathways and improves performance: An in vivo model. J. Inflamm. Res. 2016, 9, 147–154.
34. Chaudhary, P.; Sharma, Y.K.; Sharma, S.; Singh, S.N.; Suryakumar, G. High altitude mediated skeletal muscle atrophy: Protective role of curcumin. Biochimie 2019, 156, 138–147.
35. Assi, M.; Rebillard, A. The Janus-Faced Role of Antioxidants in Cancer Cachexia: New Insights on the Established Concepts. Oxid. Med. Cell Longev. 2016, 2016, 9579868.

36. Loussouarn, M.; Krieger-Liszkay, A.; Svilar, L.; Bily, A.; Birtic, S.; Havaux, M. Carnosic Acid and Carnosol, Two Major Antioxidants of Rosemary, Act through Different Mechanisms. Plant. Physiol. 2017, 175, 1381–1394.

37. Lo, A.H.; Liang, Y.C.; Lin-Shiau, S.Y.; Ho, C.T.; Lin, J.K. Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through down-regulating nuclear factor-kappaB in mouse macrophages. Carcinogenesis 2002, 23, 983–991.

38. Tong, L.; Wu, S. The Mechanisms of Carnosol in Chemoprevention of Ultraviolet B-Light-Induced Non-Melanoma Skin Cancer Formation. Sci. Rep. 2018, 8, 3574.

39. Moran, A.E.; Carothers, A.M.; Weyant, M.J.; Redston, M.; Bertagnolli, M.M. Carnosol inhibits β-catenin tyrosine phosphorylation and prevents adenoma formation in the C57BL/6J/Min/+(Min/+) mouse. Cancer Res. 2005, 65, 1097–1104.

40. Alsamri, H.; El Hasasna, H.; Al Dhaheri, Y.; Eid, A.H.; Attoub, S.; Iratni, R. Carnosol, a Natural Polyphenol, Inhibits Migration, Metastasis, and Tumor Growth of Breast Cancer via a RO.OS-Dependent Proteasome Degradation of STAT3. Front. Oncol. 2019, 9, 743.

41. Huang, Y.; Yu, L.; Lu, P.; Wei, Y.; Wang, X.; Chen, L. Evaluate the inhibition of cytochrome P450 1A1 for enhancing breast cancer chemotherapy with a turn-on fluorescent probe. Sens. Actuators B Chem. 2021, 344, 130233.

42. Quercetin Reduces Tumor Necrosis Factor Alpha-Induced Muscle Atrophy by Upregulation of Heme Oxygenase-1. J. Med. Food 2018, 21, 551–559.

43. Camargo, C.A.; da Silva, M.E.F.; da Silva, R.A.; Justo, G.Z.; Gomes-Marcondes, M.C.C.; Aoyama, H. Inhibition of tumor growth by quercetin with increase of survival and prevention of cachexia in Walker 256 tumor-bearing rats. Biochem. Biophys. Res. Commun. 2011, 406, 638–642.

44. Reyes-Farias, M.; Carrasco-Pozo, C. The Anti-Cancer Effect of Quercetin: Molecular Implications in Cancer Metabolism. Int. J. Mol. Sci. 2019, 20, 3177.

45. Farag, M.R.; Moselhy, A.A.A.; El-Mleeh, A.; Aljuaydi, S.H.; Ismail, T.A.; Di Cerbo, A.; Crescenzo, G.; Abou-Zeid, S.M. Quercetin Alleviates the Immunotoxic Impact Mediated by Oxidative Stress and Inflammation Induced by Doxorubicin Exposure in Rats. Antioxidants 2021, 10, 1906.

46. Manach, C.; Morand, C.; Demigné, C.; Texier, O.; Régérat, F.; Rémésy, C. Bioavailability of rutin and quercetin in rats. FEBS Lett. 1997, 409, 12–16.

47. Moutinho, M.S.S.; Aragão, S.; Carmo, D.; Casaca, F.; Silva, S.; Ribeiro, J.; Sousa, H.; Pires, I.; Queiroga, F.; Colaço, B.; et al. Curcumin and Rutin Down-regulate Cyclooxygenase-2 and Reduce Tumor-associated Inflammation in HPV16-Transgenic Mice. Anticancer Res. 2018, 38, 1461–1466.

48. Satari, A.; Ghasemi, S.; Habtemariam, S.; Asgharian, S.; Lorigooini, Z. Rutin: A Flavonoid as an Effective Sensitizer for Anticancer Therapy; Insights into Multifaceted Mechanisms and Applicability for Combination Therapy. Evid. -Based Complementary Altern. Med. 2021, 2021.
49. Hu, X.-J.; Xie, M.-Y.; Kluxen, F.M.; Diel, P. Genistein modulates the anti-tumor activity of cisplatin in MCF-7 breast and HT-29 colon cancer cells. Arch. Toxicol. 2014, 88, 625–635.
50. Qiu, S.; Jiang, C. Soy and isoflavones consumption and breast cancer survival and recurrence: A systematic review and meta-analysis. Eur. J. Nutr. 2019, 58, 3079–3090.
51. Ma, X.; Yu, X.; Min, J.; Chen, X.; Liu, R.; Cui, X.; Cheng, J.; Xie, M.; Diel, P.; Hu, X. Genistein interferes with antitumor effects of cisplatin in an ovariectomized breast cancer xenograft tumor model. Toxicol. Lett. 2022, 355, 106–115.
52. Ijaz, M.U.; Shahzadi, S.; Zahra, Z.; Samad, A.; Ehsan, N.; Afsar, T.; Almajwal, A.; Al-disi, D.; Abulmeaty, M.; Razak, S. Ameliorative effects of morin on cisplatin-induced toxicity in renal mitochondria isolated from rats. J. King Saud Univ. Sci. 2021, 33, 101655.