Multi-ingredient supplementation for combating sarcopenia and polymorbidity

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Purpose of review
We discuss the premise and potential of multi-ingredient supplements (MIS) in the treatment of complex skeletal muscle (SkM) pathologies, and provide an updated review of literature on nutraceuticals in sarcopenia and sarcopenic obesity (SO) management, with an emphasis on single- vs. multi-ingredient protein-based formulations.

Recent findings
Several meta-analyses have confirmed the synergistic benefits of combining resistance training (RT) with dietary protein supplementation in older adults with sarcopenia or physical frailty, with a potential ceiling effect at 1.5–1.7 g PRO/kg BW/day.
Single-ingredient supplements with proven synergism with RT and clinical relevance for sarcopenia treatment include the major milk proteins (whey and/or casein) and creatine monohydrate. Vitamin D_3, calcium, and/or *n*-3 polyunsaturated fatty acids are also recommended for mitigating concurrent micronutrient deficiencies, bone loss, and inflammation. More evidence is needed to justify monotherapy with leucine or leucine metabolites over high-quality protein sources.
RCTs have demonstrated superiority of whey-based MIS compared to isocaloric and isonitrogenous placebo for enhancing SkM growth in both younger and older persons, including obese and nonobese sarcopenic subgroups, as confirmed by *in vivo* body composition and/or biopsy sampling.
Multi-ingredient formulations containing high-quality milk proteins, creatine monohydrate, vitamin D_3, calcium, and *n*-3 polyunsaturated fatty acids may therefore be recommended in the multimodal treatment of sarcopenia and sarcopenic obesity.

Summary
Resistance training is the first-line treatment for musculoskeletal conditions and improves lean body mass, strength, and function in sarcopenia patients. Increased protein intake augments RT-induced muscle anabolism across clinical subpopulations, with recent evidence suggesting superiority of multi vs. single-ingredient protein-based supplements.

Keywords
aging, multi-ingredient, muscle, nutrition, obesity, protein, sarcopenia, sarcopenic obesity

INTRODUCTION

As global demographics shift toward an aging population, society confronts mounting challenges in preserving optimal body composition and functional capacity throughout the lifespan. The definition of sarcopenia has evolved considerably from its initial characterization as age-related skeletal muscle mass (SkM) loss with functional decline [1] to the current comprehensive diagnostic frameworks that assess lean body mass (LBM), strength, and function [2]. Current estimates of sarcopenia prevalence are ~10–16% in older adults, escalating to ~30% among adults aged >65 years and 50–60% in octogenarians [3].

Sarcopenic obesity (SO), a related and complex health condition, is characterized by concurrent SkM loss and body fat gain, representing a growing concern in older adults due to associated comorbidities, including dyslipidemia, insulin resistance, and heart disease [4]. Sarcopenic obesity has a ~10% prevalence in older adults [5] and represents an ~twofold risk of frailty and associated health outcomes [6]. Obesity

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KEY POINTS

- Resistance training (RT) is the first-line treatment for improving lean body mass (LBM), strength, and function in nonobese and obese sarcopenia patients.
- High-quality protein intake potentiates RT-induced LBM and strength gains, with a potential ceiling effect at 1.5–1.7 g PRO/kg BW/day.
- Proven nutraceuticals for treating sarcopenia include milk proteins (whey and/or casein) and creatine monohydrate. Vitamin D_3, calcium, and *n*-3 polyunsaturated fatty acids are also recommended, especially in comorbid states.
- Large-scale and well controlled trials that compare single- vs. multi-ingredient protein-based supplements (w/wo exercise therapy) are currently limited. Recent trials have shown superiority of whey/casein-based multi-ingredient supplements vs. isoenergetic and/or isonitrogenous placebo (maltodextrin or collagen peptides) in both younger and older adults, including sarcopenic subgroups w/wo obesity.
- Multi-ingredient supplements allow for better targeting of interconnected organ systems and pathways that contribute to complex disease states (i.e., sarcopenia), with specific utility for management of polymorbid conditions (i.e., sarcopenic obesity).

alone threatens to cost ~ $4 trillion annua lly by 2035 [7], with sarcopenia imposing further financial burdens on healthcare systems across the world [8].

Therapeutic options remain limited, with no approved pharmaceutical interventions despite extensive research efforts [9,10]. The complexity of age-related muscle pathophysiology necessitates multitarget approaches, as traditional mono-drug strategies [11–13] inadequately address the full constellation of contributing factors to these diseases. Exercise and physical activity represent the sole interventions demonstrating efficacy across multiple pathophysiological pathways [14]. Developing cost-effective, safe treatments targeting the multifaceted contributors to age-associated muscle loss requires enhanced mechanistic understanding to address this escalating global health crisis.

ETIOLOGY

Age-related muscle loss is a complex pathophysiological process driven by concurrent deterioration of interconnected organs systems (e.g., musculoskeletal, nervous, endocrine, vascular, reproductive, and digestive) and disruption of hallmark cell signaling pathways that ultimately lead to disability, loss of independence, and increased mortality risk [15,16]. The pathophysiology is characterized by universal hallmarks of aging, including mitochondrial dysfunction, oxidative damage, autophagic impairment, and chronic inflammation (termed 'inflammaging'). Sarcopenia is associated with a decrease in anabolic hormones combined with increased pro-inflammatory cytokines, a reduction in muscle blood flow and muscle satellite cell content. Muscle growth/maintenance is ultimately governed by the balance of several growth-regulatory processes, mainly protein synthesis (MPS) and protein breakdown (MPB), with current evidence pointing to impaired anabolism driving age-related SkM loss. Specifically, it manifests as impaired anabolic responses to protein-containing meals, exercise, and/or growth factors, effectively producing the 'anabolic resistance' phenomenon that typically emerges with aging [17,18]. Metabolic alterations affecting muscle preservation may also be exacerbated by obesity, malnutrition (overnutrition or undernutrition), and physical inactivity/immobility, insulin resistance, contributing to SkM anabolic resistance with aging.

Episodic disuse represents a critical precipitating event in the development and progression of sarcopenia, characterized by discrete periods of physical inactivity that can rapidly accelerate muscle loss beyond the gradual decline typically associated with normal aging [19]. These episodes occur with increasing frequency in older adults due to hospitalizations, periods of recovery following acute illness, osteoarthritis, and progressive reductions in habitual physical activity levels [20]. The clinical significance of these events lies in their creation of a stepwise deterioration in muscle mass and function, where each episode pushes individuals towards a steeper downward trajectory. Episodic disuse is also relevant for muscle health across the lifespan, with middle-aged adults losing SkM during disuse similar to that seen in older adult populations [21,22]. Of critical note for aging muscle, however, is the finding that two weeks of disuse may results in decreased MPS rates and impaired glucose regulation in overweight, prediabetic older adults, with these effects persisting even after returning to normal activity levels [23] - in contrast to the full recovery seen in younger individuals. These findings, paired with an attenuated ability for older adults to gain meaningful muscle volume following retraining after disuse [24], highlight the impact of episodic disuse on the progression of age-associated muscle wasting.

Sarcopenic obesity has been recently redefined as a concurrent decline in muscle mass and function along with increased adipose tissue, representing a growing concern in older adults due to significant health consequences impacting mortality and

comorbidities [25]. The pathophysiology of this condition involves a complex interplay between muscle and adipose tissue, hormonal changes, inflammation, mitochondrial impairment, reduced bioenergetic potential, oxidative stress and lifestyle factors, creating a multifaceted syndrome that poses diagnostic and management challenges in clinical settings [26]. Obesity has a deleterious effect on SkM mitochondria by disrupting biogenesis and dynamics, leading to decreased content and compromised function [27,28] – but improving mitochondrial capacity in the muscle may drive successful body re-composition [28].

Given the multifactorial pathogenesis of sarcopenic obesity and sarcopenia alike, multi-ingredient supplements targeting multiple pathophysiological mechanisms should be superior to single nutrient approaches, as first proposed in the treatment of neurological disorders by Tarnopolsky & Beal in 2001 [29]. The notion of using multi-ingredient supplementation mainly rests on the simultaneous targeting of interconnected organ systems and signaling pathways to potentiate LBM/muscle gains in both nonobese and obese populations at increased risk for muscle loss. Single-agent or pathway-redundant ingredients addressing only one aspect of sarcopenia (e.g., exclusively supplementing protein to address anabolic resistance) are less likely to succeed than multi-ingredient strategies targeting anabolic resistance, mitochondrial dysfunction, oxidative stress, impaired autophagy, and dysbiosis simultaneously.

CURRENT MANAGEMENT STRATEGIES

International clinical practice guidelines for sarcopenia recommend combined treatment plans focused on resistance training (RT), higher protein intake, and nutrition education [30]. RT is the most effective exercise mode for improving SkM mass, strength, and function, and is the first-line strategy to prevent and manage sarcopenia [31]. Two full-body RT sessions per week at a relatively high exercise intensity may be sufficient for mitigating age-related muscle loss [32]. Aerobic training (AT) also has merits for attenuating the hallmarks of aging (e.g., mitochondrial dysfunction, oxidative stress, impaired autophagy, and inflammation) and delay muscle wasting [33,34]. A combination of RT and AT can provide both neuromuscular and cardiorespiratory benefits and does not result in interference effects in healthy older adults [31]. Although current exercise guidelines are generally effective for attenuating sarcopenia risk, they need to be adjusted for patients who are immobilized, limited to low-intensity physical therapy or otherwise unable to perform enough exercise. A stronger emphasis may be placed on adjunctive treatments (such as nutritional interventions) in physically frail individuals, comorbid states, and during periods of illness, disuse, and immobilization (Fig. 1).

Nutritional recommendations include a healthy diet (as reviewed by Calvani *et al.*[35]), adequate hydration, and increased daily protein intake (1.2–1.5 g PRO/kg BW/day) to avoid protein-energy malnutrition (PEM) [35,36]. A recent network meta-analysis of 42 RCTs with 3728 participants confirmed that RT with or without nutritional intervention (e.g., protein supplementation) and the combination of RT and balance training or aerobic training (AT) are effective for improving strength, function, and quality of life in older adults with sarcopenia [37]. The investigators also reported synergistic benefits of exercise/nutrition therapy on certain strength outcomes, which is largely consistent with the meta-analysis by Liao *et al.* demonstrating that protein supplementation improves RT-induced adaptations in older adults [38]. This synergism was recently confirmed in sarcopenic and/or physically frail individuals in meta-analyses by Cuyul-Vasques *et al.* [39▪] and Yoshimura *et al.* [40▪]. Morton and Phillips have previously demonstrated that dietary protein supplementation enhances RT-induced changes in fat free mass (FFM), muscle fiber cross-sectional area (CSA), and mid-femur CSA in healthy adults, but that the synergistic benefits may be blunted in older persons [41]. This adaptive impairment is likely attributed to SkM anabolic resistance and a higher total daily protein requirement (1.2–1.5 g PRO/kg BW), protein dosing per meal (~0.4–0.6 g PRO/kg BW), and post RT protein dose (~35–40 g PRO) to maintain and/or potentiate muscle growth at old age [42]. A recent meta-analysis by Nunes and Phillips [43] suggests that a daily protein intake of 1.2–1.59 g/kg BW/day is necessary to enhance RT-induced LBM and strength gains in older adults though meta-analysis has reported a potential upper threshold for FFM improvement at 1.6 g PRO/kg BW/day [41]. In terms of protein quality, both animal- and plant-based protein sources are recommended in a healthy diet, while animal-based options are more efficiently digested/utilized by the body (PDCAAS ~1.0), have higher anabolic potential (EAA, BCAA, and leucine content), and promote greater muscle gains vs. plant proteins [44]. As single-ingredient supplements (i.e., monotherapy), the major milk proteins, whey and casein, are therefore more effective for maintaining LBM in older adults, and have repeatedly been shown in meta-analysis to enhance RT-induced muscle gains in sarcopenia patients [39▪,45▪,46,47,48▪].

The potential therapeutic benefits of other nutraceuticals in sarcopenia management (beyond milk proteins) must be evaluated on a case-by-case basis

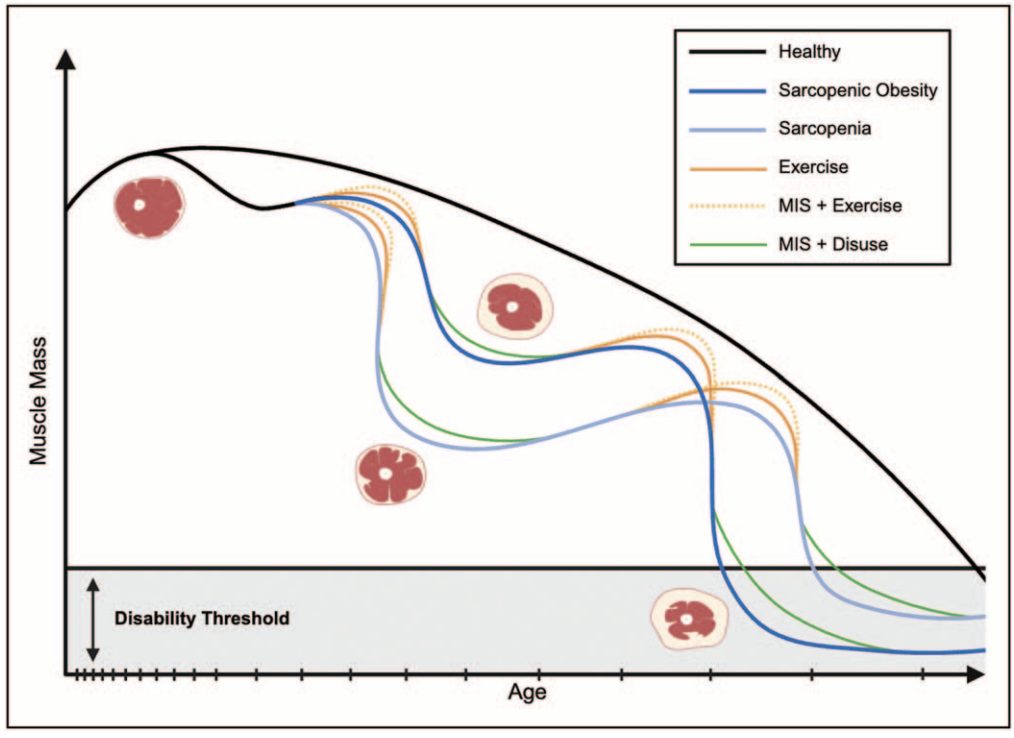

FIGURE 1. Age-related sarcopenia involves progressive muscle mass and strength decline, contributing to increased fall risk, fractures, and reduced mobility. Episodic disuse events create steeper downward trajectories that compound the effects of healthy aging (which would feature lifelong physical activity and sufficient nutrition). These episodes occur more frequently in older adults and often result in incomplete recovery despite rehabilitation, causing rapid transitions between progressively worse functional states. Sarcopenic obesity presents a complex paradox where increased total weight may predispose to higher comorbidities but also temporarily preserve bone and muscle mass. MIS may limit the impact of disuse on muscle loss and amplify the impact of exercise on muscle gain in both sarcopenic and sarcopenic obesity conditions.

and supported by evidence from placebo-controlled, double-blind RCTs or meta-analytic data using studies that are similar enough that their results can be meaningfully combined to produce a more precise estimate of the overall effect. Creatine monohydrate (CrM) has been extensively studied as a monotherapy during exercise training in older adults, with meta-analytic data supporting the use of creatine monohydrate (3–5 g/day) for improving SkM mass, strength, and power in older adults [49,50]. The effects of *n*-3 (omega-3) polyunsaturated fatty acids (*n*-3-PUFAs) were recently reviewed by Nunes *et al.*, who concluded that *n*-3-PUFA monotherapy has no benefits on LBM, muscle strength and physical function in healthy young or older adults [51▪▪], which is in line with current meta-analyses [52,53]. However, the inclusion of *n*-3-PUFAs (EPA and DHA; 1 - 2 g/day) in sarcopenia treatment may be justified by their general health benefits, including improvements in systemic inflammation [54,55], blood lipid levels [56], and cardiovascular mortality risk [57]. Of particular interest for periods of immobility contributing to the pathogenesis of sarcopenia over time was the finding that *n*-3-PUFA supplementation attenuated disuse atrophy [58], likely by improving mitochondrial function [59]. Further high-quality research is needed to elucidate the extent and mechanisms of *n*-3-PUFA uptake into skeletal muscle and other relevant tissues. Currently, there is insufficient evidence to support vitamin D_3 monotherapy in sarcopenia treatment [60,61]; however, vitamin D_3 supplementation (~1000–2000 IU/d w/wo calcium) is recommended for the prevention of low bone mass and vitamin D insufficiency [62,63]. A meta-analysis by Nasimi *et al.* further suggested that vitamin D_3 may synergize with whey protein to improve muscle mass, strength, and function in older adults, potentially attributed to correction of vitamin D insufficiency [45▪]. Ultimately, low bone mass is strongly associated with sarcopenia and any intervention that supports bone health (i.e., vitamin D_3 + calcium) likely will benefit muscle health in sarcopenic patients. Although leucine is a recognized rate-limiting factor for MPS (~2.8–4 g/meal in older adults), the evidence for leucine monotherapy in sarcopenia treatment is limited [64]. Meta-analyses on β-hydroxy-β-methylbutyrate (HMB; a leucine metabolite) also demonstrate minimal benefits in sarcopenic populations

[65,66]. Together, a well designed supplementation plan for sarcopenia should include high-quality proteins (whey and/or casein) and creatine monohydrate for direct musculoskeletal benefits, with vitamin D_3, calcium, and *n*-3-PUFAs as optional (whilst strongly recommended) for improved bone health, anti-inflammatory benefits, and metabolic synergism.

Strategies for treating sarcopenic obesity are multimodal and aim to induce a net negative energy balance for reducing fat mass (FM; white adipose tissue (WAT)), ectopic lipid deposition, and inflammation, concurrent with maintenance of FFM, specifically SkM and bone [67]. Thus, a significant challenge for SO management is to balance 'pro-anabolic' (e.g., muscle gain) and 'pro-metabolic' (e.g., WAT loss) signals to optimize body re-composition and improve the SkM/WAT ratio. Current recommendations include hypocaloric diets (−200 to −700 kcal/day; ~0.5 kg BW/week), increased protein intake (1.2–1.5 g/kg BW/day), and regular exercise training, such as RT (2–3 times/week), AT (150 min/week), or combined RT/AT [67,68]. More extreme weight loss methods may be merited in some cases, including bariatric surgery, pharmacotherapy (e.g., GLP-1 receptor agonists), and/or very low-calorie diets (VLCDs), but will also lead to substantial LBM deterioration (~20–40% of total weight loss), as recently reviewed by others [69,70]. While the clinical significance of LBM loss is a topic of considerable debate [71,72], maintenance of LBM is undeniably important at old age and weight cycling (i.e., weight loss followed by unintentional weight gain) may predispose individuals to sarcopenia or sarcopenic obesity [73].

Although interventional RCTs are currently limited in this population, an umbrella review of meta-analyses by Reiter *et al.* demonstrated that all exercise modes (RT, AT, or RT/AT) reduce fat mass and/or body fat (%) in SO patients, while RT may be more effective in improving gait speed and leg strength (in a nonenergy restricted conditions) [74]. A meta-analysis by Eglseer *et al.* confirmed that RT effectively improves body fat, lean mass, strength, and gait speed, and that combining exercise with protein intake may add synergism in SO patients [75▪▪]. A recent topical review by Prado *et al.* stressed the importance of combining high-quality proteins with *n*-3-PUFAs, calcium, vitamin D_3, and antioxidants for targeting the underlying aspects of SO etiology (e.g., oxidative stress and inflammation) [67]. Single-ingredient supplements with known metabolic benefits include polyphenols (e.g., green coffee bean, green tea, and forskolin), mitochondrial antioxidants (e.g., α-lipoic acid, CoQ10, and vitamin E), and conjugated linoleic acid (CLA) [76▪,77]. Thus, nutraceuticals with proven pro-anabolic or pro-metabolic effects have clinical utility for improving body re-composition and underlying SkM pathology in SO patients (Fig. 2), though further research in this area is needed.

MULTI-INGREDIENT SUPPLEMENTS – PREMISE AND POTENTIAL

The underlying mechanisms that drive biological aging are similar across organ systems and cell populations in humans [16]; however, there is no universal treatment that can be applied to all age-related conditions, except exercise therapy [31]. This principle holds true for both single- and multi-ingredient supplements (MIS) although the application of MIS leverages the ability to simultaneously target many interconnected organ systems and intracellular pathways that drive primary and secondary pathoetiologies.

Given the complex pathoetiology, an idealized MIS formulation for sarcopenia (Table 1) should seek to ameliorate the hallmarks of aging (e.g., mitochondrial dysfunction, oxidative stress, impaired autophagy, and inflammation) and stimulate SkM growth-regulatory processes, thereby more effectively overcome age-related anabolic resistance and muscle loss vs. single-ingredient supplements. The inclusion of nutraceuticals that promote SkM anabolism and weight gain is generally desirable over those that induce weight loss and fat oxidation considering that protein-energy malnutrition and an underweight body mass index (<~18.5–20 kg/m^2) are strongly associated with sarcopenia. However, MIS that are designed to attenuate the universal hallmarks of aging and/or activate pro-longevity pathways still hold therapeutic promise for optimizing SkM function, body composition, and overall health. Thus, nutraceuticals that can target mitochondria and/or other organelles and cell mechanisms involved in quality control, repair, and recycling are potential therapeutic options for attenuating myocellular aging [33].

The use of idealized MIS has even greater therapeutic potential in the treatment of polymorbid conditions, such as sarcopenic obesity, where both intrinsic and extrinsic pathways converge and contribute significantly to SkM anabolic resistance and deterioration. A combination of nutraceuticals that can safely aid in alleviating peripheral insulin resistance, adipose tissue expansion, and ectopic lipid deposition, while maintaining LBM and/or muscle, may be an ideal treatment strategy for sarcopenic obesity, especially during acute periods of stress and disuse (e.g., illness, immobilization, and/or energy restriction) (Table 1). While milk proteins are evolutionary designed to optimize growth and satiety (for

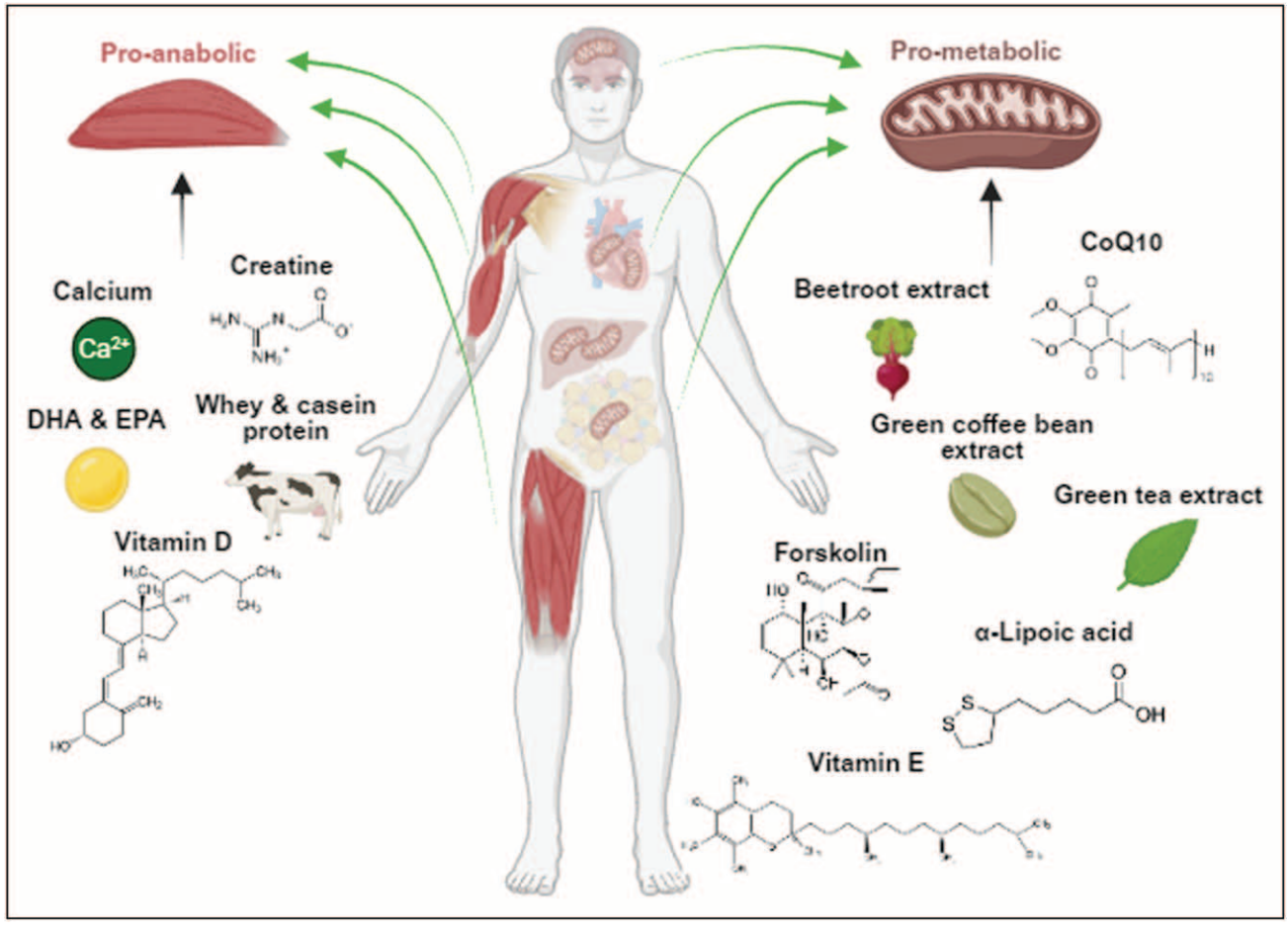

FIGURE 2. Rationale for the treatment of sarcopenia or sarcopenic obesity with a multi-ingredient supplement targeting pro-metabolic and pro-anabolic outcomes.

example, the 60:40 whey/casein ratio in humans [78]), it is not known whether they maintain lean mass and/or interfere with fat loss in extreme weight management, such as bariatric surgery, GLP-1 RA therapy, or VLCDs. Thus, nutraceuticals that promote SkM anabolism and satiety signaling (e.g., whey/casein and CrM) may be combined with those that induce body re-composition and pro-longevity pathways (e.g., polyphenols and mitochondrial antioxidants) to counteract both myocellular aging and overnutrition to optimize the results of weight management. The development of novel protein and amino acid (AA) blends that target a balanced activation of pro-anabolic (muscle gain) vs. pro-metabolic (loss of adiposity) signaling pathways therefore also have relevance for the treatment of SO. Recent

Table 1. Idealized multi-ingredient supplementation as a treatment strategy for sarcopenia and sarcopenic obesity

Category	Sarcopenia	Sarcopenic obesity
Anabolic activators	Whey, casein, CrM	Whey, casein, CrM
Metabolic enhancers	*n*-3-PUFAs	Polyphenols, *n*-3-PUFAs, CLA
Vitamins & minerals	Vitamin D_3, calcium	Vitamin D_3, calcium
Mitochondrial antioxidants	CoQ10, α-LA, vitamin E	CoQ10, α-LA, vitamin E
Other	Pro-anabolic protein/AA blends	Pro-metabolic protein/AA blends

CLA, conjugated linoleic acid; CrM, creatine monohydrate; PUFA, polyunsaturated fatty acid.

advancements in nutritional biochemistry and food technology have enabled the precise formulation of bespoke and novel amino acid compositions. Predominately, this may be particularly beneficial for plant-based diets that typically lack enough levels of essential amino acids (EAAs) compared to animal-derived sources. Supplemental free-form amino acids, including branched-chain amino acids (BCAAs) and EAAs, have demonstrated clinical utility in mitigating muscle loss, especially under conditions of compromised gastrointestinal function, dysregulated appetite or anabolic resistance, features that are often associated with older age or disordered eating [93]. While BCAAs – with leucine often in focus - serve as a potent anabolic signal to upregulate MPS, they are insufficient to maintain muscle mass when other dietary protein intake is limited. Evidence indicates that nonessential amino acids (NEAAs), particularly L-glutamine and L-arginine, exert pleiotropic effects through multiple signaling pathways that can contribute to maintenance of muscle mass [94,95]. Strategic inclusion of specific NEAAs in novel amino acid formulations, alongside leucine enrichment may reduce muscle atrophy and deleterious body composition changes [96,97] during periods of disuse.

Emerging evidence also suggests that supplementation that focuses exclusively on excessive BCAA intake may have adverse metabolic consequences. Studies indicate a correlation between blood levels of BCAAs and obesity and insulin resistance [98]. Recently, Yu *et al*. (2021) demonstrated that the detrimental effects of BCAA overconsumption are primarily mediated by isoleucine and valine, rather than leucine, in a mouse model. Specifically, diets low in isoleucine were shown to reprogram hepatic and adipose tissue metabolism, improving insulin sensitivity, enhancing ketogenesis, and increasing energy expenditure [99]. Beyond BCAA restriction, Olsen *et al*. (2024) demonstrated the restriction of dietary methionine and cysteine (essential and semi-essential sulfur amino acids, respectively) lead to a significantly greater loss of fat free mass in participants with overweight or obesity during weight loss, suggesting benefit in carefully selecting amino acids included in therapeutic interventions [100].

Given these insights, tailored amino acid compositions represent a promising avenue for future therapeutics – if provided alongside other critical components of a MIS. By leveraging improved production methods and clinical evidence, it is possible to create novel formulations that optimize metabolic health while minimizing potential adverse effects associated with indiscriminate amino acid supplementation.

MULTI-INGREDIENT SUPPLEMENTS – CLINICAL EVIDENCE

Based on previous meta-analytic data, protein supplementation (single- and/or multi-ingredient) improves RT-stimulated gains in FFM and strength in both younger and older adults [41,47,79,80], with an upper threshold for improvement at ~1.5–1.7 g PRO/kg BW/day [41,81]. Several meta-analyses conducted 2023–2025 have reported similar findings in sarcopenic individuals [39▪,40▪,45▪,82,83▪], while the benefits of multi vs. single-ingredient protein supplements remain unclear in all (sub)populations.

O'Bryan *et al*. [80] conducted a systematic review and meta-analysis of 35 trials with 1387 participants and reported that multi-ingredient protein supplements (MIPs) were superior to non-MIP supplements for lean mass and maximal strength gains in healthy adults undergoing long-term resistance exercise training (RET; 6–78 weeks). Subgroup analyses showed that the benefits were greater in untrained vs. trained individuals, and that MIP supplementation resulted in analogous gains in lean mass and improved upper body strength gains in older vs. younger adults. Although MIP supplements were not statistically superior to protein alone (PRO), the mean differences favored MIP over PRO for all study outcomes. These findings support the use of MIPs over non-MIPs and PRO alone for maximizing lean mass and strength gains across age groups, but with more pronounced benefits in sedentary and older adults.

In contrast, the meta-analysis by Puente-Fernandez *et al*. found no benefits of multi-ingredient supplementation vs. calorie-matched placebo (PLA) on FFM and strength gains in middle-aged and older healthy participants engaging in ≥6 weeks of AT or RT [84]. The authors attributed these differences in findings (vs. O'Bryan *et al*. and Liao *et al*. [38,80]) to removing RCTs that included clinical populations (i.e., obesity and sarcopenia) and those with no isocaloric comparator group. Conversely, this research team also reported superiority of a multi-ingredient postworkout supplement (i.e., carbohydrates, leucine-enriched whey, vitamin D_3, CrM, and β-HMB) vs. isocaloric placebo for improving body composition in aging, physically active individuals following a 6-week RT training program [85].

Wageh *et al*. [86,87▪▪] examined the effects of whey-based MIS (whey protein isolate 20 g, CrM 2.5 g, leucine 2 g, calcium citrate 300 mg, and vitamin D 1000 IU) vs. isonitrogenous and isoenergetic PLA (collagen peptides 20 g, alanine 1.4 g, glycine 0.6 g) in healthy young adults undergoing a 10-week progressive RT program. The intervention improved LBM significantly in both groups, but the gains were superior in the whey-based MIS cohort attributed to a

greater increase in muscle fiber CSA [87▪▪]. Muscle biopsies were also taken before and after a damaging bout of exercise in the untrained (pre intervention) and trained (post intervention) states and were suggestive of greater acute satellite cell activation in the whey-based MIS group following the intervention [86]. These results clearly suggest that whey-based MIS may be superior to isocaloric/isonitrogenous collagen PLA in augmenting muscle growth in healthy young males and females, as confirmed by both body composition analysis (DXA) and muscle biopsy sampling.

Several RCTs have previously reported superiority of a similar high-quality protein-based MIS (e.g., whey and/or casein, CrM, vitamin D_3, calcium, and *n*-3-PUFAs) vs. calorie- and/or isonitrogenous placebo (i.e., maltodextrin or collagen peptides) in both younger and older adults [87▪▪,88–90], including a sarcopenic subgroup [91]. In a recent retrospective analysis [92▪], Nilsson *et al.* analyzed baseline predictors of the adaptive response to home-based exercise/nutrition therapy in older adults, and confirmed that obesity/MetS is key driver of anabolic resistance and that a high-quality whey/casein-based MIS may be more effective than a collagen-based alternative for improving body composition in older adults at risk for sarcopenic obesity. Notably, total protein intake exceeded current treatment guidelines in both MIS and PLA groups in this study (i.e., 1.26 vs. 1.43 g PRO/kg BW/day, respectively). With relevance to obesity and weight management, Nederveen *et al.* [76▪] has shown that a polyphenol-based MIS (containing green coffee bean, green tea, forskolin, beetroot, CoQ10, α-LA, and vitamin E) may promote significant body weight and FM loss vs. isocaloric placebo in overweight and/or obese individuals. Furthermore, Alblaji *et al.* recently demonstrated the therapeutic potential of krill oil (which contains *n*-3-PUFAs, choline, and astaxanthin) for maintaining FFM during weight management [101].

In summary, recent RCTs have shown superiority of whey/casein-based MIS vs. isoenergetic and/or isonitrogenous placebo in both younger and older adults, including sarcopenic subgroups with obesity as a comorbidity. While a systematic review of the literature reveals significant discrepancies between current meta-analyses, a key limitation of the meta-analytical approach is that it combines highly heterogeneous RCTs into supposedly homogeneous groups, potentially obscuring the superior efficacy of specific nutraceutical MIS combinations.

FUTURE DIRECTIONS

Overall, there is a need for more large-scale RCTs with appropriate control groups (isocaloric and/or isonitrogenous placebo) to assess the therapeutic potential of multi vs. single-ingredient protein supplements with or without exercise therapy across all subpopulations. The development of novel protein and/or AA blends may further enhance the clinical efficacy of MIS and allow for more precise targeting of complex pathoetiologies and polymorbid disease states. A tailored nutraceutical approach for sarcopenic obesity must strike a balance between pro-anabolic (muscle gain) and pro-metabolic (loss of adiposity) signals for optimizing body composition, with specific relevance to extreme weight management.

CONCLUSION

A nutraceutical strategy that includes multi-ingredient supplements is advantageous for targeting interconnected organ systems and cell pathways that drive complex musculoskeletal diseases, such as sarcopenia, with specific utility for management of polymorbid disease states (i.e., sarcopenic obesity). Overall, the 'no one-size-fits-all' principle holds true for both single- and multi-ingredient supplements and it is imperative to identify and promote idealized, nutraceutical combinations that are supported by high-quality clinical evidence, mechanistic plausibility, and standardized manufacturing practices.

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Conflicts of interest

M.A.T. is the founder, C.E.O., and C.S.O. of Exerkine Corporation. M.I.N receives salary support as a senior research scientist for Exerkine. M.A.T. and M.I.N. are shareholders in the company. Exerkine Corporation has filed patents on the use of multi-ingredient supplementation for muscle loss and weight management. All authors warrant that these COIs did not impact on the decision to publish the manuscript or its contents.

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- ▪ of special interest
- ▪▪ of outstanding interest

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