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REVIEW ARTICLE

Sarcopenia: Current treatments and new regenerative therapeutic approaches

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ABSTRACT

Sarcopenia is characterized by loss of muscle and reduction in muscle strength that contributes to higher mortality rate and increased incidence of fall and hospitalization in the elderly. Mitochondria dysfunction and age-associated inflammation in muscle are two of the main attributors to sarcopenia progression. Recent clinical trials on sarcopenia therapies such as physical exercise, nutraceutical, and pharmaceutical interventions have revealed that exercise is the only effective strategy shown to alleviate sarcopenia. Unlike nutraceutical and pharmaceutical interventions that showed controversial results in sarcopenia alleviation, exercise was found to restore mitochondria homeostasis and dampen inflammatory responses via a complex exchange of myokines and osteokines signalling between muscle and bone. However, as exercise have limited benefit to immobile patients, the use of stem cells and their secretome are being suggested to be novel therapeutics that can be catered to a larger patient population owing to their mitochondria restoration effects and immune modulatory abilities. As such, we reviewed the potential pros and cons associated with various stem cell types/secretome in sarcopenia treatment and the regulatory and production barriers that need to be overcome to translate such novel therapeutic agents into bedside application.

Translational potential: This review summarizes the causes underlying sarcopenia from the perspective of mitochondria dysfunction and age-associated inflammation, and the progress of clinical trials for the treatment of sarcopenia. We also propose therapeutic potential of stem cell therapy and bioactive secretome for sarcopenia.

Introduction- sarcopenia definition and aetiology

According to the United Nation's World Population Ageing 2015 report, the global number of people aged 60 years or above has increased substantially in recent years and is projected to accelerate in the coming decades, doubling the number in 2015 by the year 2050 to an astonishing 2.1 billion people [1]. Ageing is a multifactorial process that is associated with numerous changes in body composition including bone mass, muscle mass, and adipose tissue composition. Muscle, being the largest organ in the body that makes up 40% of the body mass shows an apparent and progressive reduction in the size and number of muscle fibres (up to 30%) in an age-dependent way from 25 to 80 years of age [2]. This loss in muscle mass and consequently its strength results in sarcopenia, a term that describes a prevalent age-associated decline in muscle mass, strength, and function, first introduced by Irwin Rosenberg [3]. Sarcopenia affects 10% (95% confidence interval [CI]: 8–12%) in men and 10% (95% CI: 8–13%) in women, respectively. Meta-analysis indicated that sarcopenia is associated with higher rate of mortality (pooled odds ratio [OR] of 3.596, 95% CI: 2.96–4.37), muscle functional decline (pooled OR of 3.03, 95% CI: 1.80–5.12), higher rate of falls and higher incidence of hospitalization [4]. Epidemiological studies indicated that muscle ageing is associated with a number of degenerative disorders such as osteoporosis, type II diabetes, and cancer [5,6].

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It is known that sarcopenia is a multifactorial condition with varying outcomes and can be observed in both older and younger adults, as is likewise the case for dementia and osteoporosis, sarcopenia can be clinically considered "primary" (or age-related) or "secondary" (when one or more other causes are evident) (Supplementary Table 1). Sarcopenia has been underdiagnosed in the past owing to the lack of consensus on clinical definition. The European Working Group on Sarcopenia in Older People defined specific clinical parameters for sarcopenia based on low muscle mass and low muscle function. Thereafter, International Working Group on Sarcopenia published an US guideline in 2011, and Asian Working Group for Sarcopenia provided guidelines for Asian population in 2014. These guidelines (which have been reviewed extensively elsewhere are not included in this review) with ethnic-based modified parameters set the stage for further intensive investigation on the etiopathogenesis and intervention.

In accordance to the European Working Group on Sarcopenia in Older People, sarcopenia is further subgrouped based on the presence of both low muscle mass, low muscle strength, and low physical performance, which dependent on the results and characteristics, was further defined into conceptual stages as "presarcopenia", "sarcopenia" and "severe sarcopenia" (Supplementary Table 2). The "presarcopenia" stage is characterized by low muscle mass without significant impact on muscle strength or physical performance. This stage can only be identified by techniques that measure muscle mass accurately and in reference to standard populations. The "sarcopenia" stage is characterized by low muscle mass, plus low muscle strength or low physical performance. "Severe sarcopenia" is the stage identified when all three criteria of the definition are met (low muscle mass, low muscle strength, and low physical performance) [7,8]. Recognizing stages of sarcopenia may help in selecting treatments and setting appropriate recovery goals. Staging may also support design of research studies that focus on a particular stage or on-stage changes over time. However, staging of sarcopenia can be complicated by other medical conditions that are associated with prominent muscle wasting such as cachexia, frailty, and sarcopenic obesity. As such, it is important to distinguish such medical conditions from age-related sarcopenia to guide targeted and appropriate therapy for each sarcopenia type [9].

Though the biological mechanism underlying sarcopenia is not clearly understood [10], there is a growing scientific and public interest to develop effective approaches to counteract the effects of sarcopenia to maintain functional independence or known as "active ageing". In this review, we summarize the definition and consequences of sarcopenia, reviewed how ageing-associated factors, including mitochondria and energy homeostasis dysfunction [11,12], reactive oxygen species (ROS) accumulation [13,14] and inflammation [15] play important roles in the aetiology of age-related sarcopenia. Secondly, we looked into the pros and cons of the currently available therapeutic options, including exercise, pharmaceutical and nutraceutical interventions, for sarcopenia with focus on how exercise alleviates sarcopenia by targeting the mentioned sarcopenia attributing factors and the therapeutic limitation associated with physical exercise. Finally, we reviewed the potential therapeutic effects, pros and cons of administering stem cell and stem cell secretome as novel therapeutic options for sarcopenia and the associated technical and regulatory barriers that need to be overcome.

Causes of sarcopenia

Mitochondria dysfunction and sarcopenia

Muscle, being the largest organ in the body, is mainly made up of highly contractile and energy-dependent myocytes. To carry out its contractile function, muscle cells receive neurotransmitters such as acetylcholine and dopamine from motor neurons at the motor plates. It is well established that both the muscle and neurons are high energy consuming cells which are greatly addicted to adenosine triphosphate (ATP) supply for them to function and are hence highly dependent on the proper functioning of mitochondria, the powerhouse and ATP supply organelle of the cell.

As age takes toll, mitochondria dysfunction in the muscle started to occur resulting in an increase in levels of apoptosis [16] and reduced capabilities for muscle regeneration [17] that were commonly observed in sarcopenic patients [18]. In addition to the muscular changes, age-related mitochondria deregulation also results in motor neuronal cell death [19], that ultimately resulted in innervation impairment [20] and an ~27% reduction in the motor unit pool that possibly accounts for the muscular atrophy [20–22] and loss in muscular contractile force in sarcopenic aged humans and rodents [23].

The mitochondria are double membrane bound organelles that contain their own genetic material, the mitochondria DNA (mtDNA) and produces ATP through the electron transport chain process which consists of a series of oxphos reactions [24,25]. The oxphos reactions in mitochondria produces high levels of ROS which are damaging for mtDNA, creating mutations, and deletion in them [26,27]. Hence, mitochondria fission and fusion are in place to maintain mitochondria homeostasis in the cell [25]. Mitochondria fusion and fission are two different processes with fusion being to process that mitigates stress by mixing contents of partially damaged mitochondria as a form of complementation while the latter being the process necessary to create new mitochondria and contribute to quality control of mitochondria via removal of damaged mitochondria [28].

However, as age progresses, mitochondria homeostasis is no longer maintained due to numerous processes, namely the building up of ROS [29] which can be attributed to the reduction in antioxidant enzyme levels in both muscle and neuron cells [30] (Fig. 1). This accumulation of ROS results in mtDNA deletion or mutation causing mitochondrial dysfunction [31,32]. To further add on to the already dire situation, mitophagy–proteosome–induced mitochondria clearance function also deteriorates with age [17,33,34]. As the number of damaged mitochondria accumulates, not only does the mitochondria not able to produce sufficient ATP to sustain cellular function in muscle and neurons, there will also not be enough normal functional mitochondria to act as complementary partners for mitochondria fusion to take place to restore mitochondria homeostasis. These events ultimately lead to damaged mitochondria membrane potential and leakage of mitochondria content to the cell cytosol that initiates apoptosis in both muscle and neurons, leading to muscular atrophy and muscle dennervation in sarcopenia (Fig. 2) [28].

Inflammation in sarcopenia

In normal physiological conditions, the immune system plays an important role in protecting the body from pathogens. Inflammation is a response elicited by immune cells such as macrophages, dendritic cells, and Th cells in the event of infection to allow the body to clear off pathogens from the body. However, as the body ages, hormonal changes such as decrement in testosterone, growth hormones, androgens, oestrogen occur, and this tips the balance of the body towards a state of chronic inflammation with increased plasma levels of proinflammatory mediators, such as tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP) (Table 1) [35]. This chronic inflammation status causes an increased number of cells to leave cell cycle, enter the state of cellular senescence, and acquire a senescence-associated secretory phenotype (SASP), further inducing the production of proinflammatory cytokines such as TNF-α, IL-6, and NF-κB [35,36] (Fig. 2).

The upregulation of inflammatory cytokines, particularly in the microenvironment of muscle contributes to the upregulation of apoptosis and senescence of myocytes (Fig. 2). Inflammatory cytokines such as IL-6 and TNF-α mainly function as signalling molecules that recruit inflammatory cells into site of infection while concurrently enhance their antipathogen clearance functions such as phagocytosis. However, in the ageing scenario, IL-6 and TNF-α recruit inflammatory cells to the muscle and this initiates the vicious cycle of inducing cellular senescence,

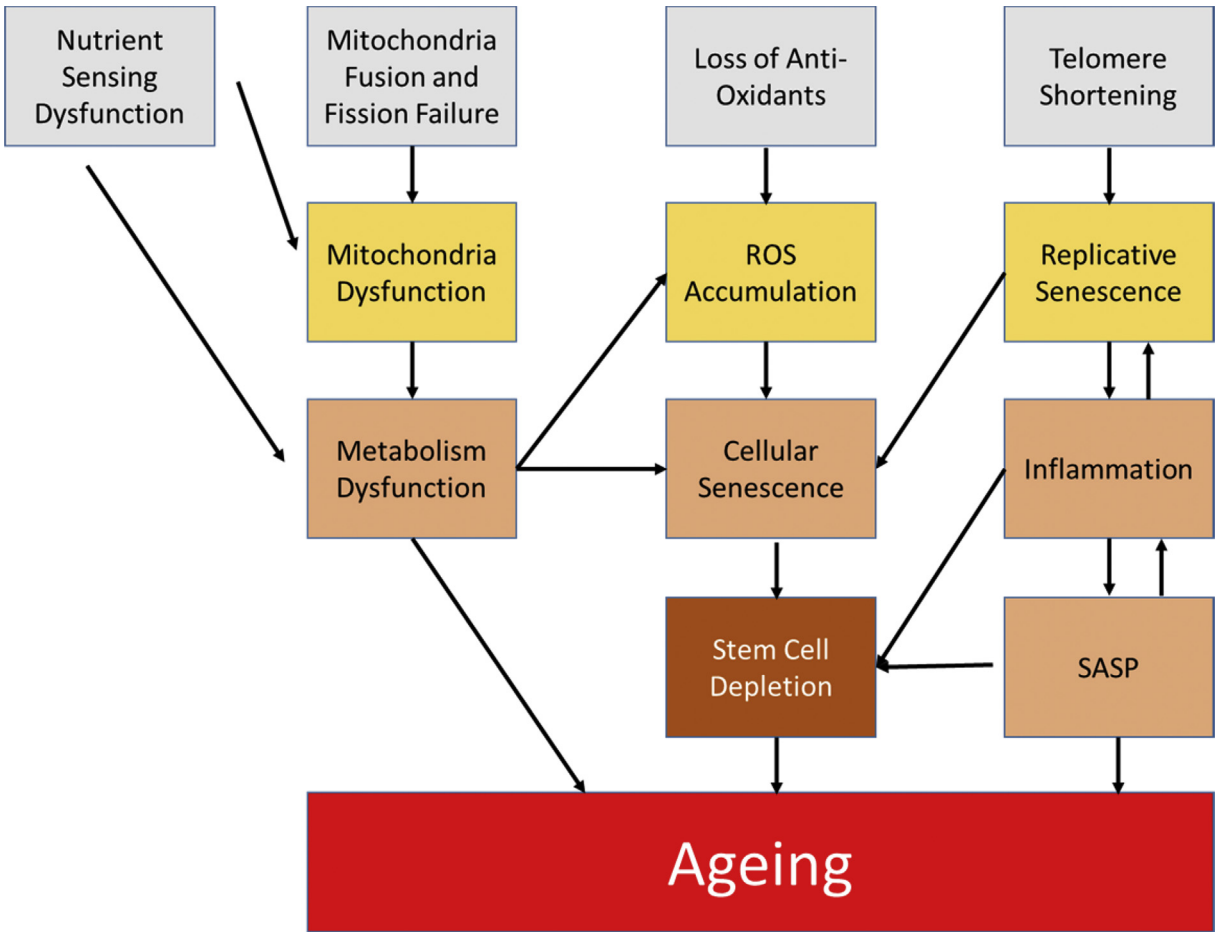

Figure 1. Factors contributing to ageing include mitochondrial fusion/fission failure, replicative senescence, unresponsive to changes in microenvironment, telomere shortening, ROS accumulation and loss of antioxidants. Mitochondria fusion/fission failure gives rise to the gradual build up in mitochondria DNA mutation owing to the inability of the cells to minimize the mutation ratio of mitochondria DNA via mitochondria fusion and the inability of the cells to produce new mitochondria to replace the dysfunctional ones. With the build up of defective mitochondria, prolonged division of cells and the build up of ROS, cellular senescence take place that ultimately results in stem cell depletion.

production of SASP, further inflammatory cells recruitment and as a result aged muscle will be overwhelmed by vast amount of inflammatory cytokine, particularly TNF-α [37,38] (Fig. 2). TNF-α functions by binding to receptors on cell surface, initiating the recruitment of adaptor proteins, eventually resulting in a death-induced caspase cascade. This was confirmed by previous findings by Dirks and Leeuwenburgh in 2002 that indicated an elevation in apoptosis (+50%) (measured by nucleosome fragmentation) was observed in 24 months old rats compared with 6 months old young rats [39]. The same group has also reported the higher susceptibility of aged type II muscle fibres to TNF-α stimulated apoptotic signalling, partially attributing to the greater loss of fast twitch muscle fibre with ageing, a phenotype frequently presented in sarcopenia patients [40].

In addition to the apoptotic effects of inflammatory cytokines on myocytes, inflammatory cytokines also affect the muscle regeneration capabilities 41]. Under normal conditions, satellite cells remain in a quiescent state. Upon muscle damage, satellite cells will regenerate damaged muscle by re-entering into cell cycle [42]. However, as the muscle ages, the pool of Pax7 expressing satellite cells decrease resulting in the inability of satellite cells in aged muscle to drive the expression of myogenic differentiation genes such as Myf5 and MyoD [43,44]. The decrement in Pax7 expressing satellite cells along with altered notch signalling, deprivation of growth differentiation factor 11 (GDF11), Igf-1, and increased inflammation and proinflammatory cytokines in age muscle causes deterioration in satellite cell function(s) [45–47] (Fig. 2). As such, inflammation-mediated myocyte apoptosis and loss of satellite cells' muscle regenerating capabilities are few of the many sarcopenia mediating factors that are targeted by numerous pharmaceutical companies as potential candidates for therapeutic development in addition to nutritional intervention.

Therapeutic intervention for sarcopenia

Based on the current understanding on the possible underlying causes of sarcopenia that includes malnutrition, chronic inflammation and lack of exercises, several clinical trials have been conducted to evaluate the feasibility and potential efficacy of using exercise, especially resistant training, commercial nutraceuticals (amino acid, vitamins supplements or mixed compounds), and drug for muscle mass and strength building. A literature search was performed to have a better understanding on the landscape of sarcopenia related clinical studies over the past ten years. In clinicaltrials.gov, a search with the keywords of "sarcopenia" AND "treatment" and inclusion criteria of "10 years" results in 23 registered trials including those with an "Unknown" and "Recruiting" status (Table 2). A PubMed clinical search with "sarcopenia AND intervention" showed 115 clinical trials (excluding 81 irrelevant reports) published over the past ten years. At the time of writing, a total of 34 relevant clinical trials were selected for reporting (Table 2). It appears that exercise and nutraceuticals administration account for about 76% of main treatment strategy for sarcopenia clinical trials; while drugs administration such as testosterone and metformin and whole body electrical myostimulation (WB-EMS) were less frequently adopted therapeutic

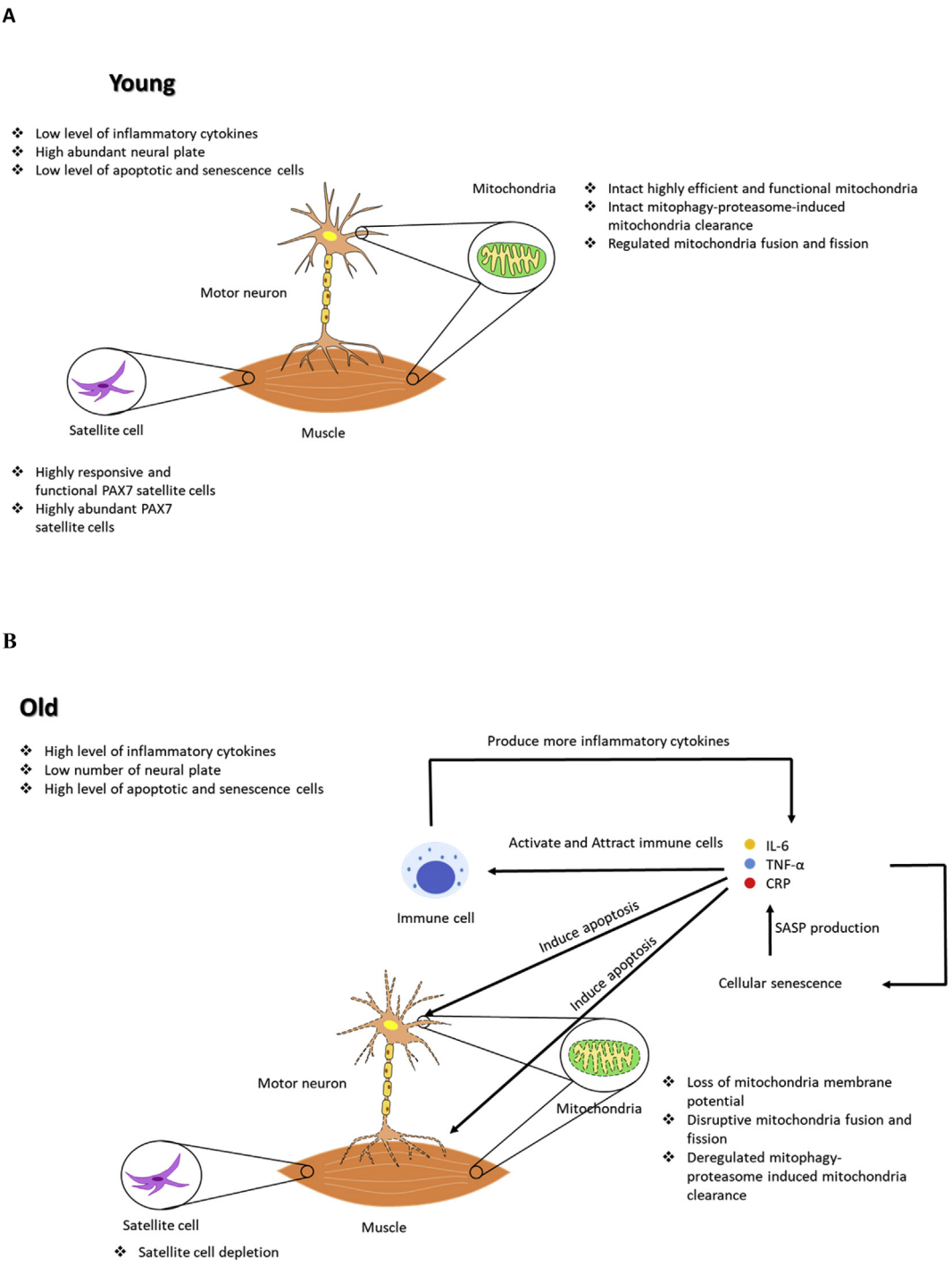

Figure 2. Schematic diagram illustrating the microenvironmental and intracellular changes in young and old muscular microenvironment. (A) In the physiological microenvironment of young individual, low level of inflammatory cytokines is present with highly abundant neural plates and low level of apoptotic and senescence cells in the muscle. Pax 7 satellite cells are abundant and responsive to external stimulation such as physical activities and nutritional stimulation that facilitate muscle building. The mitochondria within the muscle cells, neurons and satellite cells are intact and highly functional and efficient in energy (ATP) production. Proper clearance of dysfunctional mitochondria and properly regulated mitochondria fusion and fission are in place to ensure mitochondria homeostasis in the cells. This ensures cellular viability and function that are essential in muscular function and muscle building. (B) In the physiological microenvironment of aged/old individual, dysfunction mitochondria are in high abundance owing to deregulated mitophagy–proteasome–induced mitochondria clearance and disruptive mitochondria fusion and fission. This results in the accumulation of ROS the trigger cellular senescence in muscle cells, neurons and satellite cells. Senescent cells will release SASP that will initiate an inflammatory cascade that causes more cells to undergo senescence and apoptosis that ultimately results in denervation of muscle and muscle loss in sarcopenia. SASP, senescence-associated secretory phenotype.

approaches (Fig. 3). Of note, WB-EMS was the only studied physical stimulation for sarcopenia under the searching criteria. Whole body vibration is emerging as alternative physical intervention attracting researchers' attention most recently [60] (https://clinicaltrials.gov/ct2/show/NCT04028206).

Based on the findings from the ongoing and/or completed clinical trials for sarcopenia training exercise is demonstrated to be the most effective intervention on sarcopenia alleviation. Of a total of 34 studies

Table 1
List of studies and main findings indicating correlation and age-dependent increment in proinflammatory cytokines in elderly.

Markers	Study	Main findings
TNF-α	[48]	Elevated plasma TNF-α in elderly (81 years) vs young adults (19–31 years)
	[49]	Elevated plasma TNF-α in elderly (>80 years) (2.5 pg/mL) vs young adults (18–30 years) (1.4 pg/mL)
	[50]	Elevated plasma TNF-α in elderly (60–75 years) (>9 pg/mL) vs young adults (18–30 years) (±7 pg/mL)
	[51]	Significant correlation between age and TNF-α
	[52]	TNF-alpha was related to lower appendicular skeletal muscle mass and body cell mass, suggesting that TNF-alpha contributes to sarcopenia in ageing.
	[53]	Higher plasma concentrations of IL-6 and TNF-alpha are associated with lower muscle mass and lower muscle strength in well-functioning older men and women.
IL-6	[54]	Elevated plasma IL-6 in elderly male (55–75 years) vs young male (26–54 years)
	[55]	Compared three groups of elderly (>90 years, 80–89 years, 70–79), found elevation in log IL-6 concentration and median IL-6 level with increment in age
	[56]	Compared three groups of elderly, > 80 years and 71–72 years of age and found elevation in log IL-6 concentration from 0.73 ± 0.66 pg/mL to 0.96 ± 0.65 pg/mL
	[57]	Elevated plasma IL-6 concentration in elderly >75 years (>1.4 pg/ml) vs. young adults (20–39 years) (0.6 pg/ml)
	[53]	Higher plasma concentrations of IL-6 and TNF-alpha are associated with lower muscle mass and lower muscle strength in well-functioning older men and women.
	[58]	Higher levels of IL-6 and CRP increase the risk of muscle strength loss
hS-CRP	[57]	Plasma [CRP] in elderly >75 years (>2.6 mg/l) vs. young adults (20–39 years) (1.0 mg/l)
	[59]	Plasma [CRP] in elderly >80 years (>2.4 mg/l) vs. elderly 65–69 years (2.2 mg/l)
	[50]	Serum [CRP] in elderly ♀ (>50 years) (>1.1 mg/l) vs. younger ♀ (30–59 years) (±0.95 g/l)
	[58]	Higher levels of IL-6 and CRP increase the risk of muscle strength loss

IL-6, interleukin 6; CRP, C-reactive protein; TNF-α, tumour necrosis factor α.

listed, only those involving physical activity interventions showed a significant improvement in muscle strength and performance regardless of whether it is aerobic, anaerobic, or resistance type of exercise. On the other hand, nutraceuticals and pharmaceutical interventions were not as effective nor did they show promising synergistic effect when administered concurrently with exercise regime.

Physical exercise and sarcopenia

Physical exercise regardless of it being aerobic or anaerobic, high or low resistance has been well accepted to be an important regime to prevent and treat not only chronic and degenerative diseases but also age-associated diseases such as cardiovascular diseases, cancer, neurodegenerative diseases, psychiatric disorders, chronic pulmonary diseases, diabetes, morbid obesity, and sarcopenia [61,62]. Muscle, being the main player in both locomotion an endocrine secretion, it is not surprising to see changes in secretory profile of muscles such as elevation in cytokines (IL-6, IL-8, IL-10, IL-15, CC-chemokine ligand 2 (CCL2), IL-1 receptor antagonist, VEGF), angiopoietin-like 4 (ANGPTL4), brain-derived neurotrophic factor, connective tissue growth factor, cysteine-rich angiogenic protein 61, fractalkine and nicotinamide phosphoribosyl transferase upon exercise or physical training [63–65].

As mentioned, inflammation, nutritional deprivation, and mitochondrial dysfunction are well-known factors contributing to sarcopenia progression. The production of exercise-induced cytokines in muscle tips the inflammatory microenvironment of the aged body towards anti-inflammatory. In the immune system, there are cells which are proinflammatory, such as type I macrophage and T-helper cells [66,67], and anti-inflammatory cells such as type II macrophages and regulatory T (Treg) cells [66,67]. In the aged body, where a proinflammatory microenvironment is present, proinflammatory cells are mainly activated, resulting in the production of TNF-α. In the case of exercised muscle, the role of inflammatory cytokines such as IL-6 and chemotactic proteins such as monocyte chemotactic protein 1, fractalkine/CX3CL1 function to recruit immune cells, and facilitate their migration and infiltration into the muscle [68], however, concurrently, the production of IL-10 and the IL-1 receptor antagonist switches the proinflammatory reaction to an anti-inflammatory reaction [69] which is reflected by the decrease in systemic concentrations of several inflammatory cytokines which are associated with low-grade systemic inflammatory state such as obesity and insulin resistance, cardiovascular diseases, atherosclerosis, and neurodegenerative disorders [70,71] (Fig. 4).

Other than the anti-inflammatory effects of exercise, physical training also significantly has improvements in the cardiovascular aspects, such as increased cardiac output and enhanced blood volume. One of the most important angiogenic factor produced by skeletal muscle upon physical training is vascular endothelial growth factor (VEGF) [72]. Yet, there is no evidence suggesting an altered VEGF level after training, indicating that VEGF increment and its effects are mainly localized to the muscles [73] (Fig. 4). In addition to the localized release of VEGF, extracellular matrix associated proteins, cysteine-rich angiogenic protein 61/CNN1 and connective tissue growth factor/CNN2 [74], together with IL-8 are elevated after exercise, and these molecules have been proposed to play important roles in skeletal angiogenesis by activating endothelial cell proliferation, capillary tube organization, and extracellular matrix remodelling. Finally, the production of ANGPTL4 in exercised muscle further enhances the angiogenesis in skeletal muscle, and it also increases vascular permeability and lipid metabolism muscle. These secretory angiogenic factors in all produce an enhanced angiogenic effect in muscle, allowing more blood being supplied to the muscle and more efficient nutrient delivery to the muscle tissue, an important function in preventing and delaying the progress of sarcopenia [75] (Fig. 4).

Finally, it is a well-known fact bone and muscle have a very close working relationship as such secretory factors from muscles are known to regulate bone development or remodelling and vice versa. In vitro study demonstrated that conditioned medium of osteocyte cells could stimulate myogenic differentiation of C2C12 myoblasts. [76] (Fig. 4). Moreover, exercised induced mechanical loading has been shown to induce production of IGF-1, VEGF, and hepatocyte growth factor in osteocytes cell line, which may play roles in regulating muscle growth [77,78]. Importantly, physical training also induces the production of osteocalcin (OCN), an osteoblast-derived hormone which was shown to promote adaptation to exercise in mice [134]. Finally, it was also found that older adults with regular exercise expressed an increased activity of mitochondrial oxidative enzymes and expression of mitochondrial biogenesis genes such as PGC-1, NRF-1, and TFAM, suggesting that physical training is able to enhance and even restore mitochondria function and homeostasis via direct or indirect stimulation of mitochondria biogenesis (Fig. 4) [79].

Limitation of physical exercise in sarcopenia treatment

Despite its effectiveness as a sarcopenia therapeutic regime, exercise intervention is only available to patients or elderly who are reasonably mobile, in other words, exercise intervention is not expected to benefit bedridden patients despite the fact that these are the patients who needed such intervention the most (Table 3). Furthermore, as physical abilities vary from patients to patients, it is essential to customize exercise regime for individual patient to maximize its beneficial effect, making physical training for a huge population of patients unrealistic and difficult. As such other sarcopenia interventions such as whole-body electricity myostimulation and vibration have been proposed as potential emerging therapeutic interventions which are able to cater to the

Table 2
List of sarcopenia clinical trials using nutraceuticals, protein supplements and exercise as therapeutic interventions individually or concurrently.

Year	Sample size/ gender	Age (mean or average)	Treatment method	Cotreatment	Treatment	Control groups	Longest follow-up time point	Assessment	Reference
2013	170/ Women	Aged ≥65	Drug	Vitamin D and protein supplementation	MK-0773 50 mg twice daily	Placebo	6-month	DXA, muscle strength power, physical performance measures.	[80]
2015	380/All	Aged ≥65	Nutritional supplement		Vitamin D and leucine-enriched whey protein nutritional supplement twice daily	Isocaloric control product twice daily	13-week	Handgrip strength, SPPB score, chair-stand test, gait speed, balance score, appendicular muscle mass (by DXA)	[81]
2016	330/All	Aged ≥65	Nutritional supplement	Contained other vitamins, minerals, and nutrients in varying amounts	Experimental ONS (E ONS, 20 g protein; 499 IU vitamin D 3; 1.5 g CaHMB) taken twice daily	Control ONS (C ONS, 14 g protein; 147 IU vitamin D 3)	24-week	Isokinetic peak torque leg strength, grip strength, gait speed (m·s −1), Left and right leg muscle mass (by DXA), Muscle quality (MQ) was leg strength expressed relative to the tested LMM	[82]
2017	100/ Men	Aged ≥70	Physiological intervention and Nutritional supplement		WB-EMS and protein supplementation (WB-EMS&P) Isolated protein supplementation	Non-intervention control	16-week	Sarcopenia Z-Score, body fat rate (%), skeletal muscle mass index, handgrip strength	[83]
2017	46/ Women	Aged 67.3	Exercise		EG underwent elastic RET Each exercise session involved a general warm-up of 10 min, followed by resistance training exercises (35–40 min), and finally a cool-down routine	No RET intervention	12-week	Body composition (by DXA), muscle quality defined as a ratio of muscular strength to muscle mass, physical capacity assessed using functional mobility tests	[84]
2018	110/All	Mean age 73.8	Exercise	Education including home-based exercise	IC group consisted of different modalities of exercise LEE group performed machine-based low extremities exercise		3-month	Fat-free mass, muscle strength, physical performance	[85]
2014	76/ Women	Mean age 75	Physiological intervention		WB-EMS group (WB-EMS, n = 38) that performed 18 min of WB-EMS (bipolar, 85 Hz) 3 sessions in 14 days (1.5 sessions/week)	Semi-active control group	54-week	Body composition (by DXA), maximum strength	[86]
2017	35/ Women	Aged ≥60	Exercise		Study group underwent progressive elastic band resistance training for 12 weeks (3 times per week)	A 40-min lesson about the exercise concept	12-week	DXA	[87]
2015	60/Men	Aged ≥65	Exercise and Nutritional supplement	Guided training programme on fitness devices (pull down, leg press, bench press, back press, etc.) involving all larger muscle groups	Collagen peptide supplementation (15 g/d)	silica	3-month	Change in FFM Fat-free mass, Body composition (by DXA), Muscular strength (by measuring isokinetic quadriceps strength)	[88]
2017	46/All	Aged 61–77 years	Nutritional supplement		Phytochemical compound Protandim® (LifeVantage) at the commercially available dose (one pill/day) Conjugated linoleic acid (CLA; 4 g/day)	Control (CON) group consumed placebo pills (high oleic sunflower oil; 4 g/day)	6-week	Body composition (by DXA)	[89]
2015	60/All	Aged 60–85 years	Nutritional supplement		n-3 PUFA consume 2 pills in the morning with breakfast and 2 pills in the evening with dinner	Placebo control (4 identical looking pills/ d that	6-month	Thigh muscle volume, handgrip strength, one-repetition maximum (1-RM)	[90]

(*continued on next page*)

Table 2 (*continued*)

Year	Sample size/ gender	Age (mean or average)	Treatment method	Cotreatment	Treatment	Control groups	Longest follow-up time point	Assessment	Reference
						contained corn oil)		lower- and upper-body strength, average power during isokinetic leg exercises	
2016	30/ Women	Aged 61–86 years	Exercise	Practice sessions for the maximum voluntary isometric contraction (MVIC) and knee extension and leg press 1RM test	Two training groups performed bilateral squat and knee extension exercise training 2 days/week for 12 weeks The MH-Tr group exercised at two exercise intensities ranging from 5.6 to 8.4 on the OMNI perceived exertion scale for resistance exercise (OMNI-RES) for active muscle scale (0-extremely easy to 10-extremely hard) which has been noted to correspond to exercise intensity levels ranging from approximately 70%–90% of 1RM for women The BFR-Tr group used one gold band for squatting, and one black (Special Heavy) band for knee extension. The gold band was approximately twice the resistance level as the black band, thus the two exercises for the BFR-Tr group were one-half (low-intensity level) the intensity as that for the MH-Tr group	no training (Ctrl, n = 10) groups	12-week	MRI-measured muscle cross-sectional area (CSA) at mid-thigh, maximum voluntary isometric contraction (MVIC) of knee extension, central systolic blood pressure (c-SBP), central-augmentation index (c-AIx), cardio-ankle vascular index testing (CAVI), ankle-brachial pressure index (ABI).	[91]
2018	99/Men	Aged ≥65	Drug		Receive 10 g of a transdermal gel (100 mg of testosterone)	Placebo	6-month	mMscle strength and physical function (assessed by loaded stair-climbing power)	[92]
2017	91/All	Aged ≥60	Drug		3 × 500 mg metformin (every 4 weeks)	Placebo group	16-week	Handgrip strength, gait speed, myostatin serum level, and health-related quality of life (HR-QoL)	[93]
2015	64/All	Aged 50–71 years	Nutritional supplement		Creatine before (CR-B: n = 15; creatine (0.1 g/kg) immediately before resistance training and placebo (0.1 g/kg cornstarch maltodextrin) immediately after resistance training), creatine after (CR-A: n = 12; placebo immediately before resistance training and creatine immediately after resistance training)	Placebo (PLA: n = 12; placebo immediately before and immediately after resistance training)	32-week	Body composition (by DXA), muscle strength (1-repetition maximum leg press and chest press)	[94]
2015	79/All	Mean age 73.8	Nutritional supplement	Patients received calcium 1 g and vitamin D 800 IE; specifically, cholecalciferol (Calcichew-D3®; Takeda Pharmaceutical Company Limited, Osaka, Japan)	The nutritional supplementation group (protein + energy = N group) received a 200 ml package twice daily, each containing 20 g of protein and 300 kcal (Fresubin®, Fresenius Kabi, Bad Homburg, Germany). This supplement was given for the first six months following hip fracture and was combined with risedronate (Optinate® Septimum; Sanofi AB, Warner Chilcott, Weiterstadt, Germany), 35 mg once weekly for 12 months	Controls (group C, n = 25) received calcium 1 g and vitamin D3 800 IU daily	12-month	Body composition (by DXA), handgrip strength (HGS) and health-related quality of life	[95]

(*continued on next page*)

Table 2 (*continued*)

Year	Sample size/ gender	Age (mean or average)	Treatment method	Cotreatment	Treatment	Control groups	Longest follow-up time point	Assessment	Reference
					The second group (B) received risedronate alone, 35 mg once weekly for 12 months				
2017	50/All	Mean age 70.6	Nutritional supplement	Participated in lower-limb resistance exercise training twice weekly	Long-chain n-3 PUFA (n = 23; 3 g fish oil/d)	Placebo (n = 27; 3 g safflower oil/ d)	18-week	Muscle size, strength, and quality (strength per unit muscle area), functional abilities, and circulating metabolic and inflammatory markers	[96]
2016	15/Men	Aged 62-66	Drug	Progressive resistance exercise training program of bilateral knee extension that was designed to hypertrophy and strengthen the m. quadriceps femoris	COX inhibitor (acetaminophen, 4 g/day; n = 7; 64 ± 1 years)	Placebo (n = 8; 64 ± 2 years)	12-week	Muscle samples were examined for Type I and II fibre cross-sectional area, capillarization, and metabolic enzyme activities (glycogen phosphorylase, citrate synthase, β-hydroxyacyl-CoA-dehydrogenase)	[97]
2018	54/All	Mean age 82.4	Exercise and Nutritional supplement		Elastic band resistance training (N. = 16) nutritional supplementation (N. = 21)	Control group (N. = 17)	6-month	Skeletal muscle mass (by DXA), , isokinetic knee extension and flexion force and handgrip strength	[98]
2016	20/Men	Aged 55–75 years	Exercise		Ingest 30 g protein from a soy-dairy PB (n = 9) or WPI beverage (n = 10) at 1 h post-RE		1 day	Blood and muscle amino acid concentrations and basal and postexercise muscle protein turnover	[99]
2014	100/All	Aged ≥60	Nutritional supplement		210 g of ricotta cheese (IG/ HD + RCH)	Control group was instructed to consume only their habitual diet (CG/HD)	12-week	Appendicular skeletal muscle mass (by DXA), handgrip strength by a handheld dynamometer, and physical performance using the short physical performance battery (SPPB) and the stair-climb power test (SCPT)	[100]
2013	54/All	Aged ≥65	Nutritional supplement		Phase I consisted of two non-exercise groups: (a) placebo and (b) 3 g CaHMB consumed twice daily. Phase II consisted of two resistance exercise groups: (a) placebo and resistance exercise and (b) 3 g CaHMB consumed twice daily and resistance exercise (RE)		24-week	Strength and functionality were assessed in both phases with isokinetic leg extension and flexion at 60°·s(-1) and 180°·s(-1) (LE60, LF60, LE180, LF180), hand grip strength (HG) and get-up-and-go (GUG). DXA was used to measure arm, leg, and total body lean mass (LM) as well as total fat mass (FM). Muscle Quality was measured for arm (MQ(HG) = HG/arm LM) and Leg (MQ60 = LE60/leg LM) (MQ180 = LE180/leg LM).	[101]
2017	57/ Women	Aged 50–70 years	Exercise and Nutritional supplement	Consumed 0.33 g/kg body mass of a milk-based protein matrix (PRO)	Engaged in a PRT intervention (PRO + PRT)	Consumed 0.33 g/kg body mass of a milk-based protein matrix (PRO)	12-week	DXA, maximal voluntary isometric contraction, maximal 900 m effort	[102]
2013	46/ Women	Mean age 75	Physiological intervention		WB-EMS group (n = 23) which performed 18 min of intermittent, bipolar WB-	"Active" control group (n = 23)	12-month	Whole-body and regional body composition was assessed (by DXA) to	[103]

(*continued on next page*)

Table 2 (*continued*)

Year	Sample size/ gender	Age (mean or average)	Treatment method	Cotreatment	Treatment	Control groups	Longest follow-up time point	Assessment	Reference
					EMS (85 Hz) three sessions in 14 days			determine appendicular muscle mass, upper leg muscle mass, abdominal fat mass, and upper leg fat mass. Maximum strength of the leg extensors was determined isometrically by force plates.	
2015	52/All	Mean age 78	Exercise		16 weeks of progressive high velocity resistance training performed at low external resistance (40% of the 1-repetition maximum [1-RM] [LO]) high external resistance (70% of 1RM [HI])		16-week	Neuromuscular activation was assessed using surface electromyography and muscle cross-sectional area (CSA) was measured using computed tomography.	[104]
2013	80/All	Aged 70-85	Nutritional supplement	Completed a progressive high-intensity RT intervention	Receive WPC (40 g/day)	Isocaloric control	6-month	Change in whole-body lean Muscle cross-sectional area, muscle strength increased, Stair-climbing performance	[105]
2016	91/ Women	Mean age 83.6	Exercise		Intervention groups (RT, resistance training; RTS, resistance training plus nutritional supplementation; CT, cognitive training)		6-month	Circulating levels of myostatin, activin A, follistatin, IGF-1 and GDF-15, as well as MQ and functional parameters	[106]
2015	19/All	Aged 61-71	Drug		Continuous T (WK, n = 5; 100 mg T enanthate, im injection) monthly cycled T (MO, n = 7; alternating months of T and placebo)	Placebo (n = 7)	5-month	Muscle biopsies slow and fast fibres included fibre diameter, peak force (P0), rate of tension development, maximal shortening velocity, peak power, and Ca(2+) sensitivity.	[107]
2009	81/All	Aged 65-85	Exercise	A 10-week unilateral ST program using the untrained leg as an internal control preceded 12 weeks of whole-body ST	Phase 1 ST Warm-up set: 5 repetitions at 50% of 1RM 30 s rest Set 2: 15 repetitions at 5RM* 90 s rest Set 3: 10 repetitions at 5RM* 150 s rest Set 4: 15 repetitions at 5RM* 180 s rest Set 5: 20 repetitions at 5RM* Phase 2 ST Warm-up set: 5 repetitions at 50% of 1RM 30 s rest Set 2: 5 repetitions at 5RM	Nonexercise control group	22-week	Body composition Mid-Thigh Subcutaneous Fat, Intermuscular Fat, and Muscle Volume of the Knee Extensors Muscle strength Muscle power Muscle Power	[108]

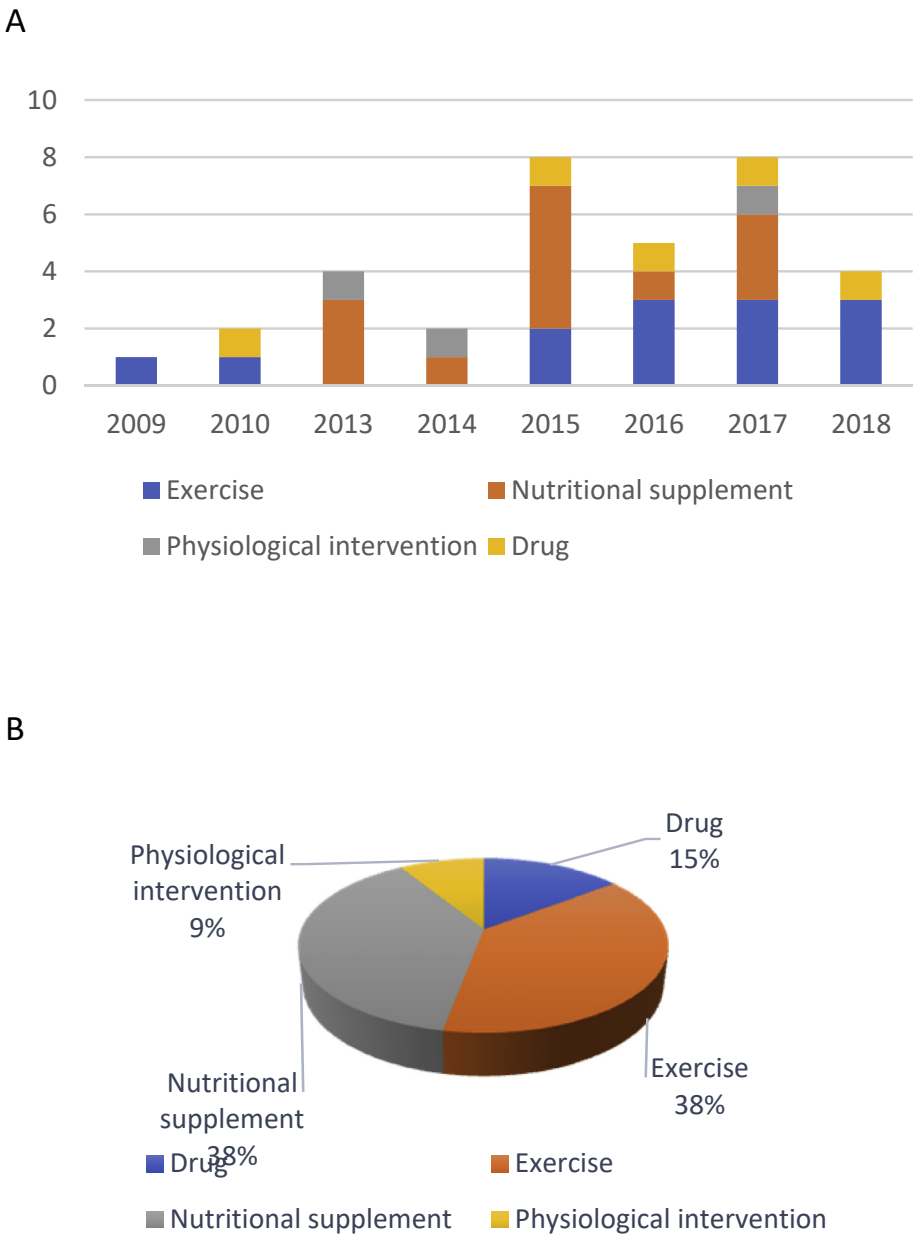

Figure 3. A) Comparison of a number of clinical trials on sarcopenia interventions in accordance with a year of development. Each colour-coded part of the bar depicts the corresponding interventions by year. (B) Percentage of treatments developed relative to the total number of studies.

needs of larger group of patients. However, more trials with larger patient population will be needed to effectively determine their efficacy.

New therapeutic approaches – the pros and cons of stem cell transplantation and potential alternatives in sarcopenia

Despite potential novel interventions are being developed in a timely manner, the number of effective options available against sarcopenia till date is still restricted solely to exercise as pharmaceutical intervention options for sarcopenia is limited and ineffective as it is a multifactorial age-associated condition (Fig. 1) (Table 3). Hence, novel therapeutic interventions that are able to concurrently promote mitochondria biogenesis or restore mitochondrial functions, reduce age-associated inflammation response in muscle tissue, and promote muscle tissue regeneration and thereby restoring muscle strength must be developed to elicit an effective treatment or synergistic effect when used alone or concurrently with exercise.

Regenerative medicine and stem cell therapy are attractive therapeutic intervention strategies for age-associated conditions such as neurodegenerative diseases and cardiovascular diseases, and so on owing to their ability to regenerate and repair damaged parts of the body. Stem cells are defined as cells with infinite replication capabilities and the ability to differentiate into mature somatic cells such as neurons and muscle [109]. Therefore, in view of the aetiology of sarcopenia, stem cell transplant could be a potential therapeutic strategy. However, that brings out numerous therapeutic associated questions such as the type of stem cells to be use, the safety and efficiency of stem cells, and most importantly in the pharmaceutical manufacturing process, how are the stem cells defined and what are the quality control in placed to ensure product consistency and stability?

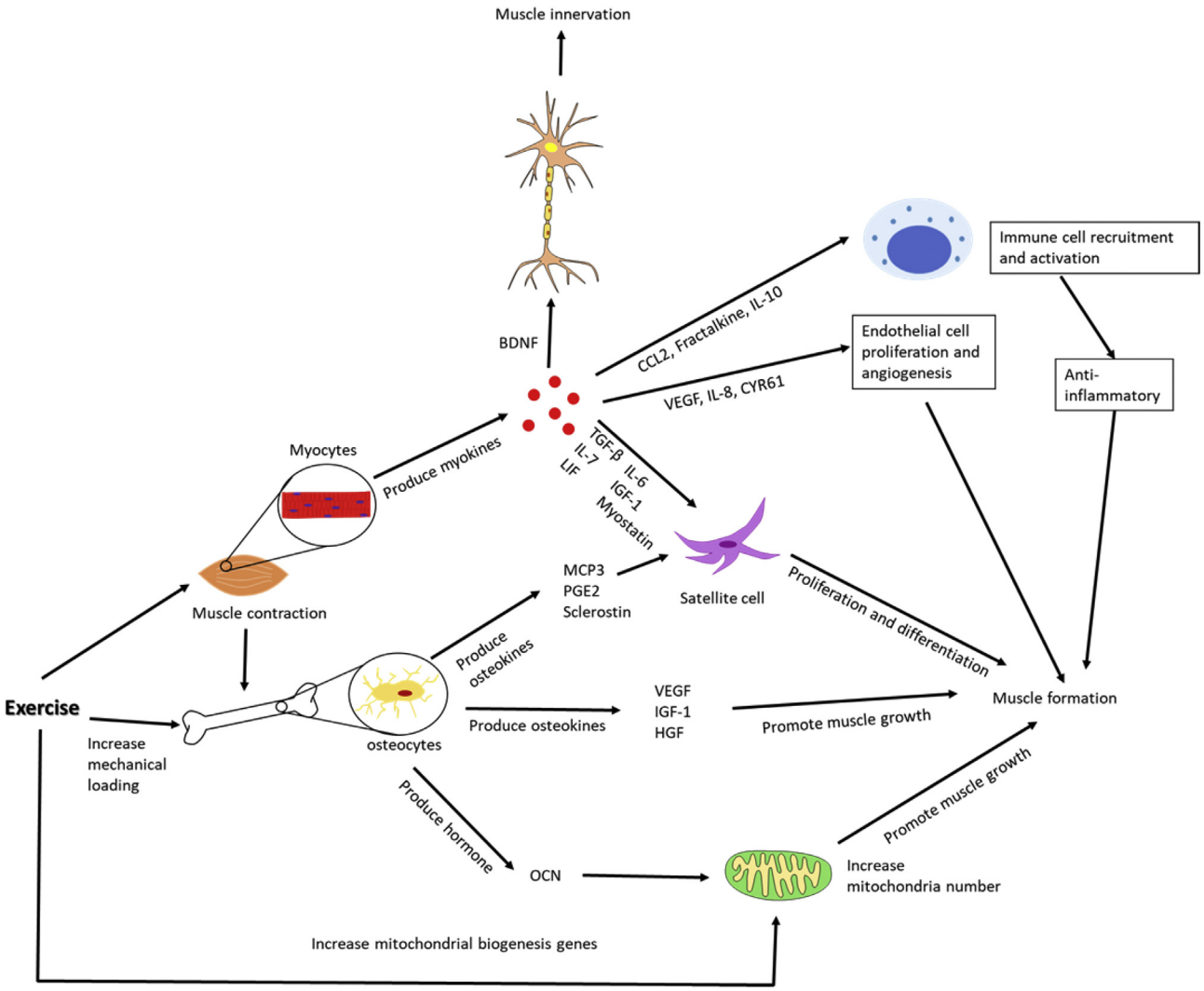

Figure 4. A schematic illustration of alleviating sarcopenia via exercise. Exercise stimulates muscular contraction which in turn stimulate myocytes to produce myokines that can enhance muscle innervation, stimulate angiogenesis in muscle, and stimulate satellite cell proliferation and differentiation. Exercise also stimulates the bones directly via mechanical loading or indirectly via muscular contraction. Stimulation of the bones by exercise activates osteocytes to produce osteokines that can promote satellite cells proliferation and differentiation, promote muscle growth and induce mitochondria biogenesis. The overall effects of myokines and osteokines switch the microenvironment towards an anti-inflammatory spectrum that supports angiogenesis, neurogenesis, and myogenesis.

Table 3
Pros and cons of sarcopenia therapeutic strategies.

Current strategies	Treatment	Pros	Cons	Reference
Nutritional supplementation	Protein supplements	Improve the muscle mass	Not improve the muscle strength and physical performance	[110]
	Essential amino acid (EAA) supplementation	Improve the muscle mass	Not improve the muscle strength and physical performance in elder women	[111]
	β-hydroxy β-methylbutyric acid (HMB) supplementation	Not consistent in several studies regarding muscle mass, strength and physical performance.		[101], [112],[113]
	Fatty acid supplementation	Improved both muscle volume and physical performance	Need further investigation on the dosage and frequency use	[90],[114]
Exercise	Resistance training	Increased muscle mass and strength, skeletal muscle protein synthesis and muscle fibre size and improvement in physical performance	Motivation to exercise in older adults is low Highly dependent on patients' mobility	[7]
	Aerobic exercise	Increase mitochondrial volume and activity		[7]
Medications	ACE inhibitors	Some evidence for increased exercise capacity	Renal function needs monitoring	[7]
	Myostatin inhibitors	Enhance muscle lean mass	No conclusive idea on muscular strength and physical performance improvement.	[115]
	Testosterone	May increase muscle strength and physical performance and decrease fat mass and hospitalization in older adults.	Side effect, such as CVDs, fluid retention, gynaecomastia, worsening of sleep apnoea, polycythaemia, and acceleration of benign or malignant prostatic disease can be observed	[116]
	Growth hormone	Increased lean tissue mass and decreased fat mass	Side effects may be induced fluid retention, orthostatic hypotension, cancer induction.	[116,117]

Embryonic stem cells and induced pluripotent stem cells

Up till now, there are three main types of stem cells, namely embryonic stem cells (ESCs), inducedpluripotent stem cells (iPSCs) and adult stem cells. ESCs and iPSCs are defined as pluripotent stem cells with the potential to give rise to tissues from three primary germ layers. However, unlike ESCs which are mainly derived from the inner cell mass of the blastocyst, which is a stage of preimplantation embryo that usually occurs 5–6 days after fertilization, iPSCs are man-made pluripotent stem cells that are produced by introducing pluripotency genes, such as Sox2, Klf4, Oct3/4 and c-myc, which are collectively known as Yamanaka factors, into somatic cells and reprogramming them back to a pluripotent state [109,118,119]. However, since the beginning of the use of ESCs/iPSCs in research, not only are many ethical restrictions are being formed in place that limit the application of ESCs/iPSCs in therapeutic interventions for human, the safety concern over the formation of teratoma by ESCs/iPSCs in transplanted patient is also a major concern that limits the medical application of ESCs/iPSCs.

Somatic or adult stem cells

Somatic or adult stem cells on the other hand, are undifferentiated and found among differentiated cells in the whole body after development. Their main function is to enable healing, growth and replacement of cells that are lost everyday [120]. The more well-known examples of adult stem cells include mesenchymal stem/stromal cells (MSCs), neural stem cells, haematopoietic stem cells, and satellite cells [109,120–122]. As sarcopenia is a muscular degenerative disease in which loss of Pax7 satellite cells was known to attribute to sarcopenia progression, it is therefore sensible to derive and expand Pax7 satellite cells followed by transplantation of sufficiently expanded satellite cells into sarcopenic muscle [122,123]. However, such transplantation strategy did not take into account of the proinflammatory environment in aged muscle, which is detrimental for the transplanted satellite cells. Furthermore, the population of Pax7 satellite cells present in the muscle is too little, making isolation and expansion in vitro a huge challenge [122,123]. More importantly, in the aspect of pharmaceutical manufacturing, the European Medicines Agency have set Good Manufacturing Practice guidelines for Advanced Therapy and Medicinal Products, which stated the importance of having proper quality control measures to stability in medicinal products, in this case Pax7 satellite cells. However, it has been reported by multiple research groups that satellite cell culture is extremely unstable under in vitro culture condition with Pax7 expression and Pax7 positive cells dropping with every cell passage [124]. Hence, to effectively apply satellite cells in sarcopenia treatment, it is paramount to resolve the issue on how to effectively derive and expand satellite cells without losing their pax7 positivity.

Mesenchymal stem/stromal cells

MSCs on the other hand are attractive stem cells to be used in therapeutics development owing to their high abundance and presence in many tissues such as fat, bone marrow, dental pulp, and umbilical cord [120,125,126]. Moreover, MSCs are easily expandable in vitro and hence MSCs are used in many clinical trials targeting a huge range of diseases and conditions from neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, autoimmune disease such as multiple sclerosis to injury conditions such as spinal cord injury and stroke [127–131]. Interestingly, many MSC transplantation/therapeutic effects were found to be mainly owing to their immune modulating effects that include the production of anti-inflammatory cytokines such as IL-10 and IL-13 [127,128,130]. In addition, MSCs have also been reported to secrete basic fibroblast growth factor, VEGF, monocyte chemotactic protein 1 which are also known to have a neuro-supportive effect [132,133]. This creates an anti-inflammatory microenvironment which is beneficial for endogenous stem cells in the damaged tissue to carry out essential repair and thereby restoring tissue function. Given the proinflammatory microenvironment and innervation condition in aged muscle which attributes to sarcopenia progression, transplantation of MSCs might be able to tip the proinflammatory microenvironment in aged muscle to an anti-inflammatory microenvironment which is beneficial for the endogenous satellite cells to carry out muscle regeneration while at the same time stimulating muscular innervation by the peripheral nervous system. It was also suggested that MSC could mediate mitochondria transplantation into aged cells which could have a therapeutic benefit by restoring mitochondrial function in both the muscle cells and neuronal cells in aged muscle. However, the efficiency and effects of mitochondria transplant by MSCs remain to be debated. Most importantly, as protocol for MSCs manufacturing is more established it is easier from the manufacturing point of view to set up in-process quality control parameters to minimize batch to batch variation in MSCs, potentially making them the more suitable candidate for cellular transplantation in sarcopenia.

Yet, cellular transplantation, such as organ transplantation, involves the administration of cells which could come from a foreign source, in other words, to allow the transplantation to work, patients might need to undergo vigorous regime of steroids to improve the survival of cellular transplant in their body, that can be detrimental to the body. Hence, to overcome the restrictive hurdles yield by stem cell transplantation and by support of the fact that the therapeutic effects mediated by transplanted stem cells could be elicited by secretory factors produced by the stem cells, it is therefore sensible to administer secretory factors instead of cells into target tissue to enable tissue repair and regeneration. Through the approach of administering secretome of stem cells, manufacturing hurdles involving quality controls that minimize batch to batch variation can be easily put in place owing to higher product stability. Furthermore, the manufacturing cost can be lowered as harvesting of stem cell secretome can be carried out via continuous culture medium harvesting manner, similar to a fed-batch fermentation rather than a batch manufacturing that involves resuscitation of a new batch of stem cells.

Conclusion

In conclusion, sarcopenia is an age-associated loss of muscle mass that involves numerous attributing factors. Stem cell therapy could potentially be a novel therapeutic intervention for sarcopenia alleviation owing to its regenerative capabilities and its ability to produce anti-inflammatory cytokines that in turn change the microenvironment into one that promotes reinnervation and regeneration. However, stem cell transplantation is limited by several factors, ranging from ethics, rejection and production limitations and hence, using the secretome of stem cells, which is the main anti-inflammatory component produced by stem cells could be a better option over the direct use of stem cells. More importantly, until now, numerous studies for sarcopenia has looked into the effects of exercise, nutraceutical and protein supplements in sarcopenia alleviation but none has looked at the effects of exercise along with the concurrent use of stem cell secretome, which could be a novel anti-sarcopenia approach that could potentially provide an even better outcome than the other classical approach.

Conflicts of interest statement

The authors have no conflicts of interest to disclose in relation to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2020.04.002.

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