REVIEW ARTICLE

Efficacy of Herbal Supplementation on Muscle Health Among Adults: A Scoping Review of Randomized Controlled Trials

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ABSTRACT

The review specifically assesses the impact of herbal supplements on muscle mass, strength, and performance in adults. Given their potential anti-inflammatory and antioxidant properties, herbal supplements such as *Curcuma longa* and *Panax ginseng* are hypothesized to counteract muscle degradation and enhance muscle function, which are key factors in managing sarcopenia among the elderly. Of 3,332 records found after a comprehensive database search, 13 trials were analyzed. Importantly, high-dose *Viscum album coloratum* and formulated *Curcuma longa* increased muscle mass and TUG, and handgrip strength and endurance, respectively, supporting their inclusion in preventive strategies against sarcopenia. *Schisandra chinensis, Glycine max*, and *Arctium lappa* also proved beneficial in improving handgrip strength and performance. Most trials reported minimal adverse events. This review underscores the benefits of herbal supplements in enhancing muscle health and calls for further studies on the long-term effects of *Asparagus racemosus, Cistanche tubulosa,* and *Anacardium occidentale* to better understand their mechanisms.
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INTRODUCTION

Muscle loss is a critical factor to consider in overall health, particularly when addressing the needs of the elderly. Despite consistent energy consumption and exercise routines, a 5.0% to 25.0% decrease in basal metabolic rate can be observed as people age, which increases body weight and body fat (1). Furthermore, the average muscle loss rate in older people is 1.5% per year after the fifth decade, accelerating to 3.0% annually after the eighth decade (2). The increased rate further supports the notion that body composition is an ever-changing variable in progressive muscle and fat mass redistribution.

Low muscle mass, along with low strength or performance, is also found to be a prerequisite for sarcopenia, a condition of gradual muscle degeneration commonly affecting older people as defined by the Working Groups for Sarcopenia (3). Petermann-Rocha and colleagues have reported the global prevalence of sarcopenia to range from 10.0% to 27.0% in older adults aged 60 years and older (4). In Malaysia, the prevalence of sarcopenia was found to be slightly higher, ranging from 12.5% to 33.6% (5,6). Given the detrimental effects of reduced mobility, increased risk of falls and reduced quality of life, it is crucial to explore and implement effective management strategies through nutritional and physical interventions.

Among the various dietary improvement methods concerning muscle loss, dietary protein remains the prominent source of amino acids instrumental in building muscle. Supplementation, defined by the United States Food and Drug Administration through the Dietary Supplement Health and Education Act 1994 as 'Products that are consumed and are meant to supplement or add to a diet,' is an excellent addition in enhancing nutritional intake (7). Supplements were perceived to be consumed for three main goals: to cure chronic or acute illnesses, prevent them, and promote health (8). However, individuals with digestive issues or dietary restrictions due to certain conditions (chronic

kidney disease) or personal preferences (vegetarian, vegan) may have limited protein intake and might choose herbal supplementation over conventional medicine to maintain nitrogen balance.

For widespread and judicious therapeutic use of a drug, active molecules are usually extracted and tested rigorously in pre-clinical and clinical research prior to commercialization. According to recent market research, the Malaysian global herbal industry has an anticipated growth rate of 7.6%, with potential gross domestic product (GDP) contributions from RM19 billion to RM28 billion by 2027, proving significant economic prospects (9). Considering the anticipated growth and possible economic impact, there is an increased interest in the role of herbal supplements in protecting against oxidative damage. Although various studies have shown promising results of herbs such as ginseng, Indian bay leaf, and safflower in enhancing muscle mass, strength and recovery, the evidence is scattered and fragmented throughout various disciplines, including biomedical and sports nutrition (10–12). Thus, this scoping review aims to synthesize available RCTs that evaluate the effectiveness of herbal supplements in enhancing muscle mass, strength, and performance among older adults.

This review was also conducted as a preliminary assessment of the current scientific research evidence regarding the effect of herbal supplements on muscle recovery and growth and their potential role in improving sarcopenia in adults. The following research questions guided this review: 1) What are the characteristics of herbal supplementation trials conducted on humans? 2) How effective were the supplements in improving muscle mass, strength, and performance? 3) Were any adverse events reported during or immediately after the trial?

METHODS

Eligibility criteria

This review included peer-reviewed trials focusing on the effects of herbal or plant-based supplementation (such as green tea, curcumin, ginseng, and *Ginkgo biloba*) on muscle-related parameters including muscle strength, muscle mass, and muscle performance. The chosen studies included trials published from 2012 to 2022 in English, only involving RCTs on the adult and older adult populations, with or without clinical conditions. We excluded studies if they were either in vitro or in vivo, or focused on protein, vitamin, and mineral supplementation as this review is intended to focus on natural plant products and their bioactive counterparts in humans. Conference abstracts, trial protocols, unpublished articles and were also excluded.

Search strategy

A comprehensive search was conducted in September 2022 on three different databases: Google Scholar, Scopus, and Science Direct, including articles published within ten years from the search date. A search string was formulated from the research questions. Terms were added to increase conciseness and improve article relevance through the Boolean connectors "OR", "AND," and "NOT," which finally resulted in the search string: [(Herbal supplementation "OR" herbal medicine "OR" plant-based supplementation)] "AND" [(sarcopenia) "OR" (muscle loss)] "AND" [(older adults) "OR" (elderly)] "AND" [(randomized controlled trial) "OR" (intervention study)] "NOT" [(systematic review) "OR" (narrative review) "OR" (overview)]. As we did not intend to include studies on exercise interventions alone, phrases pertaining to exercise interventions were not included.

Information sources

The most recent search was executed on 26 September 2022, and the search results were imported into the Mendeley Desktop application using the Mendeley Web Importer online extension. We identified duplicates through the 'Check for Duplicates' feature and removed or merged them. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines, two reviewers began the initial screening by independently searching through the titles and abstracts of all 3,200 publications, excluding sources not meeting the inclusion criteria. To improve consistency, the reviewers discussed and revised the findings through discussions to shortlist viable articles. Subsequently, one author assessed full-text articles by performing manual hand-search to further identify studies relevant to the review and simultaneously confirmed the peer-review status of selected articles. Any uncertainties or discrepancies were resolved through discussion and consensus with a third reviewer. Potentially relevant trials were selected, and full-text articles were obtained. Due to the nature of this scoping review, no ethical approval or informed consent was needed.

Data charting process and data items

One author created a data-charting form to decide which variables to extract from the various sources of evidence. In an iterative procedure, the authors charted the data, discussed the findings, and revised the data-charting form. Relevant information included the study origin (author, year of publication, and country of origin), specific study design (RCT, use of placebo, blinding method, grouping, sample size, sample population, and study duration), intervention (herbal/ botanical supplementation, exercise intervention (if any)), and outcomes related to muscle parameters along with any reported adverse effects.

RESULTS

Trials selection

We identified a total of 3,332 records through electronic

database searches. Of these, 132 duplicates were removed. We screened 3,200 publications, and only 62 full-text records were assessed for eligibility. Forty-nine records were excluded due to review article format (n=24), animal study (n=7), in-vivo/ in-vitro study (n=3), cross-sectional study (n=4), cognitive study (n=2), non-herbal/ non-botanical supplementation study (n=9). Thus, we included 13 studies and analyzed them in the qualitative synthesis. Fig. 1 shows the PRISMA-ScR flow diagram, while the studies included in this review have been summarized as shown in Table I.

Table I: Summary of the final articles included in the review

Study (Author, Year, Country)	Population, Study duration, Sample size (n=completed/ enrolled)	Type of herb	Intervention	Muscle parameters	Outcomes
Varma, 2020, India	Healthy OAs, 12 weeks, n=30/30	Cureit™ Bioactive component: Curcuminoid	500 mg of Cureit™ or placebo (food-grade starch), OD	1. HGS 2. Weightlifting strength 3. Distance covered before feeling tired	1.The Cureit™ group showed significant HGS increase over time (p<0.001) at 1.43%. 2.No significant between-group difference in weightlifting strength, increased by 6.08% in the Cureit™ group, whereas the weightlifting strength was decreased (4.54%) in the placebo group. 3.No significant between-group difference in endurance. Cureit™ had a positive impact on the distance covered before feeling tired over time as indicated by an increase of 5.51% over time (p=0.09).
Cho, 2016, South Korea	Healthy adults with normal BMI, 12 weeks, n=46/65	Eriobotrya japonica (Loquat) Leaf Extract or LLE Bioactive component: Ursolic acid	500 mg (1 capsule: 250 mg LLE, BD) or placebo, 30 minutes after breakfast and dinner (Ursolic acid: 50.94 mg)	1. Peak TQ at 60°/s knee extension, HGS 2. Muscle mass (DXA)	1. No significant between-group difference in HGS. Right HGS significantly increased in both groups at 12 weeks (p<0.001, p<0.05) However, no significant differences were reported in HGS between the two groups over time. 2. No significant between-group difference in MM at 12 weeks. 3. No significant between-group difference in SPPB at 12 weeks. However, 4MGS and chair-rising time significantly improved in both groups at 12 weeks (p=0.017 and p=0.033; p< 0.001 and p<0.001).
Raj, 2020, India	Healthy adults from an urban tertiary care teaching hospital, 12 weeks, n=83/90	NR-INF-02, an extract from *Curcuma longa.* Bioactive component: Turmerosaccharide	Turmacin 0.5 g or 1g or placebo in the morning after food, OD. The participants were subjected to 10-minute strenuous exercise. (Turmerosaccharide: 12.6% w/w)	1. KS	1. There was a significant between-group difference in isokinetic contractions of the quadriceps at angular velocities of 120 and 180. The adjusted mean of peak force in Turmacin 0.5 g group was significantly higher when compared to that of the placebo group (p<0.05).
Salehi, 2021, Iran	Healthy female adults with moderate PAL, 8 weeks, n=65/80	*Curcuma longa L.* (turmeric) extract Bioactive component: Curcumin	500 mg encapsulated curcumin or placebo (encapsulated corn starch), OD.	1. Body composition (BIA)	1. No significant between-group differences between mean values of weight, BMI, BF, and MM.
Liu, 2013, China	Equol-producing post-menopausal women with prehypertension, 24 weeks, n=253/270	*Glycine max* (Whole soy) Bioactive component: Daidzein.	40 g soy flour or 40 g low-fat milk powder + 63 mg daidzein, or placebo (40 g low-fat milk powder), OD. (Daidzein: 63 mg)	1. Body composition (BIA)	1. No significant between-group difference in the 6-month change or percent changes in body weight, BMI, waist and hip circumferences, WHR, BF%, FM, and FFM.

CONTINUE

Table I: Summary of the final articles included in the review. (CONT.)

Study (Author, Year, Country)	Population, Study duration, Sample size (n=completed/ enrolled)	Type of herb	Intervention	Muscle parameters	Outcomes
Lim, 2017, South Korea	Healthy OAs with normal BMI, 12 weeks, n=54/79	*Viscum album coloratum* (Korean mistletoe) extract Bioactive component: Chlorogenic acid	Low-dose (1 g), high-dose (2 g) or placebo. The participants were subjected to resistance exercise programs 3 times a week. Subjects were advised to take 4 tablets, BD.	1. Body composition (BIA) 2. KS and HGS 3. SPPB	1. MM increased significantly in the high-dose group compared to the baseline value ($p<0.05$.). No significant between-group changes were found in body weight, MM, and FM after being adjusted by age, gender, protein, and energy intake. FM decreased in the high-dose group only ($p=0.065$), resulting in a significant change in SMI ($p=0.041$), FFM index ($p=0.030$), BF% ($p=0.044$), and FM to lean mass ratio ($p=0.030$). 2. KS showed a significant increase in the KME supplemented groups compared to placebo, as indicated by peak TQ ($p=0.026$) and set total work ($p=0.057$) for flexor 120°/sec after baseline adjustment. The improvement in KS was the highest in the low-dose group among the three groups. 3. No significant between-group difference in SPPB.
Inada, 2021, Japan	Pre-symptomatic / mild locomotive syndrome OAs, 12 weeks, n=26/28	*Cistanche tubulosa* (CT) extract Bioactive component: Acteoside	One stick with 1800 mg CT extract, 72 mg fine silicon dioxide, and 1,782 mg dextrin or placebo. Taken with swallowing aid jelly, OD. (Acteoside: 97.38 mg)	1. Muscle mass (BIA) 2. HGS 3. SPPB	1. No significant between-group differences in the MM of the body trunk, arms, and legs, or BW. 2. HGS, 5MWS, 2ST, and SUT scores revealed no significant difference in the outcomes. 3. The improvement in the 2ST test score in the CT extract group was significantly larger than that in the placebo group in subjects aged >60 years ($p<0.05$). A more evident positive effect of CT extract on the two-step test score was observed in subjects aged >65 years.
O'leary, 2021, United Kingdom	Healthy post-menopausal women, 6 weeks, n=20/20	*Asparagus racemosus W.* Shatavari	2 capsules, OD. Shatavari (500 mg powder: 13,250 mg fresh weight Shatavari root) or placebo.	1. HGS and KS	1. HGS but not KS was increased in Shatavari group ($p<0.05$).
Cho, 2021, South Korea	Healthy adults with low MM (<110% of the standard skeletal MM), 12 weeks, n=46/54	*Schisandra chinensis B.* (SC) extract Bioactive component: Schizandrin	1g SCe/d (or two 250-mg capsules) or placebo (corn starch) 30 min after breakfast and after dinner. All participants were required to walk for 30–60 min/d for >3 d/week during the trial period. (Schizandrin: 3.16 mg)	1. KS 2. HGS 3. Body composition (DXA)	1. SC group had significant increase in right KS by 10.2 Nm and left KS by 6.7 Nm compared toplacebo (both $p<0.05$). 2. Per-protocol analysis of HGS was significantly higher (increased by 5 kg) in SC group than that in the placebo ($p<0.05$). 3. No treatment-related effects of SC on MM were found.
Kaewbutra, 2016, Thailand	Middle-aged and OAs, 12 weeks, n=45/45	*Anacardium occidentale L.* (cashew apple) juice. Bioactive component: Quercetin	120 and 240 mg cashew apple juice or placebo (fruit juice extract), OD. (Quercetin 120mg: 6.46 mg/ 500 ml)	1.SPPB	1. The treatment group has a significant increase in the 30-second CST and 6MWT ($p<0.01$).
Ha, 2018, South Korea	Female OAs, 12 weeks, n=40	(*Arctium lappa*) Burdock extract Bioactive component: Arctigenin	Aqua exercise program. Burdock extract Supplement: 100 ml of extract, TDS (after breakfast, lunch, and supper) for a total intake of 300 ml per day.	1. Senior Fitness test	1. Both HGS and CST of the AEG and AEBG at post-test significantly increased compared to pre-test ($p<0.05$). The 6MWT of the CG at post-test significantly increased compared to pre-test ($p<0.01$). There was a significant difference in the rate of muscle endurance (walking ability test, 6MWT) change among groups ($p<0.001$), (BG, AEG, and AEBG>CG).

CONTINUE

Table I: Summary of the final articles included in the review. (CONT.)

Study (Author, Year, Country)	Population, Study duration, Sample size (n=completed/ enrolled)	Type of herb	Intervention	Muscle parameters	Outcomes
Kinoshita, 2020, Japan	Female OAs, 16 weeks, n=64/76	Licorice flavonoid oil (LFO) derived from *Glycyrrhiza glabra L.* Bioactive component: Glabridin	300 mg LFO or placebo, OD. Strength training program to increase subjects' daily step count by 1000. (Glabridin: 3% w/w: 9 mg)	1. 10MWS 2. Balance test 3. KS 4. HGS 5. Body composition (BIA)	1. No significant improvements in the 10MWS in LFO group. 2. One-leg standing time was significantly prolonged with LFO intake (p=0.03). However, the percentage of individuals who achieved a 120s stance in the one-leg standing test increased from 35.0 to 53.3% in the LFO group and from 47.2 to 56.3% in the placebo group. A significant increase in those achieving 120s was not found with LFO supplementation. 3. KS increased significantly in both groups. However, this increase was more pronounced in the placebo group. 4. No significant between-group difference in HGS. 5. No significant between-group difference in MM and visceral fat levels.
Lin, 2016, Taiwan	Healthy middle-aged and OAs, 12 weeks, n=23/24	*Panax ginseng* and *Salvia miltiorrhiza* extracts. Bioactive component: 1. Ginsenoside Rb1 2.Salvianolia acid B	1 dose (3 capsules) of Chinese herb supplement (250 mg of *Panax ginseng* and 250 mg *Salvia miltiorrhiza* extracts) or placebo per day. All subjects underwent 12 weeks of unilateral eccentric-only exercise training on knee extensor (Ginsenoside Rb1: 2.24 mg/g, Salvianolia acid B: 28.2 mg/g)	1. Body composition 2. [Muscle quality: (the ratio of isometric strength (kg) and quadriceps muscle mass (kg)] 3. KS	1. Relative increases in MM were significantly greater in the placebo group than in the supplement group. 2.Maximal leg strength and muscle quality increased in both groups (p<0.05)

Abbreviations: OA: Older adults, HGS, Handgrip strength, BMI: Body Mass Index, TQ: Torque, DXA: Dual X-ray Absorptiometry, SPPB: Short Physical Performance Battery, OD: Once daily, BD: Twice daily, TDS: Three times daily, MM: Muscle mass, 4MGS: 4-metre gait speed: ROM: Range of Motion, PAL: Physical activity level, BIA: Bioelectrical impedance analysis, BF: Body fat, LBM: Lean body mass, WHR: Waist-hip ratio, FM: Fat mass, FFM: Fat-free mass, MUAP; Motor unit action potentials, TUG: Time-up and go, 6MWT: 6-min walking test, SMI: Skeletal muscle index, KS: Knee strength, BW: Body weight, 5MWS: 5-metre walking speed, 2ST: Two-step test, SUT: Stand-up test, CST: Chair-stand test, 10MWS: 10-metre walking speed.

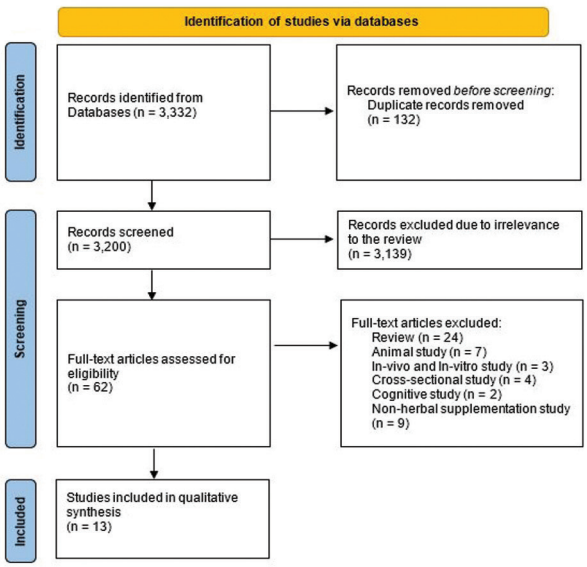

Figure 1: PRISMA-ScR flow diagram

Trials characteristics

The trial distribution is throughout eight countries, 87.5% (n=7) of which originated in Asia and 12.5% from Europe, with South Korea being the highest in frequency (n=4) (13–16), India with two trials (17,18), Japan with two trials (19,20), and one trial in Iran (21), China (22), Taiwan (23), Thailand (24), and United Kingdom (25), respectively. The heavy concentrations of trials in the Asian region suggest a strong interest towards herbal supplementation, possibly due to strong historical and cultural influences (26). As such, most herbs commonly related to traditional Chinese medicine (TCM) and Ayurveda, for example, appear more frequently in this review. Additionally, the results are more applicable to the Asian population due to the differences in genetic, dietary, and lifestyle factors, offering less generalizability towards the non-Asian counterpart.

A range of 23 up until 253 participants have completed the trials, indicating a moderate variation in the scale of the study, of which 61.5% (n=8) trials included both genders (13–15,17–19,23,24) while the other 38.5% included only females (16,20–22,25). Studies were conducted on females exclusively to observe the anticipated estrogen-like effects of the herbs. The herbs were believed to be beneficial for estrogen-deficient post-menopausal women in ameliorating protein synthesis through the binding of estradiol receptors (25). Additionally, due to limited studies, the researchers were interested in investigating gender-specific effect

of the herbs as different genders metabolize substances and respond to treatments differently.

Eight trials randomized the participants into two-arm (13,15,17,19–21,23,25), 30.8% (n=4) into the triple-arm (14,18,22,24), and 7.7% (n=1) (16) into the multiple-arm design (16). All except one (16) of the placebo-controlled trials applied double-blinding, with the largest trial conducted on 253 participants (22) and the smallest trial with 20 participants (25). Most studies (n=9, 69.2%) were conducted for 12 weeks (13–21,23,24), with the shortest and the most extended length of intervention being six weeks (25) and up to 24 weeks (22), respectively. All trials were sourced from peer-reviewed journals.

The types of herbal supplementation tested differed throughout trials with the most frequent being turmeric (*Curcuma longa*) and its derivatives at 23.1% (n=3) (17,18,21), followed by loquat (*Eriobotrya japonica*) (13), Korean mistletoe (*Viscum album*) (14), desert hyacinth (*Cistanche tubulosa*, CT), Shatavari (*Asparagus racemosus*) (25), five-flavor berry (*Schisandra chinensis*) (15), cashew apple (*Anacardium occidentale*) (24), burdock (*Arctium lappa*) (16), licorice (*Glycyrrhiza glabra*) (20), Asian ginseng (*Panax ginseng*) and red sage (*Salvia miltiorrhiza*) (23), and soy (*Glycine max*) (22) with one trial each, respectively. Furthermore, the most common dosage form of herbal supplements administered to the participants was in the form of capsules (n=9) (13–15,17,18,20,21,23,25), followed by powder (22), stick jelly (19), juice (24), and liquid extract (16) in one trial each, respectively.

Given the diversity of the muscle measures prescribed to the participants, the outcomes were categorized into three major groups: muscle mass, muscle strength, and muscle performance. Muscle mass was measured in eight (61.5%) trials (13–15,19–23), with the most common technique being Bioelectrical Impedance Analysis (BIA) (n=5), followed by Dual X-ray Absorptiometry (DXA). Ten trials (76.9%) included muscle strength as their primary or secondary outcome, with the most common measure being handgrip strength (HGS). Muscle strength was observed through upper body strength (HGS, weightlifting strength) and lower body strength (torque/peak torque/change in peak torque at different angular velocities to measure isometric knee extensor and flexor strength (KS)). Muscle performance, on the other hand, comprises of short physical performance battery (SPPB), time-up and go (TUG), 6-min walk test (6MWT), five or 10-min walk speed (5MWS, 10MWS), electromyography induced by the maximal volitional knee extension, stand-up test, tandem stand test, one leg standing time with eyes open, and distance covered before feeling tired.

Evidently, only one (14) (12.5%) out of eight trials reported significant differences in body composition, particularly muscle mass. Of seven trials, four (57.1%) presented significant increase in HGS (15–17,25). Meanwhile, of five trials reporting on KS, three (60.0%) reported significant improvement (14,20,23). Of the 16 cumulated tests in seven trials (13,14,16,17,19,20,24) assessing muscle performance, 10 (62.5%) resulted in significant improvements throughout various measures, herbs, and study populations.

In summary, most trials were conducted in Asia and characterized by a two-arm, double-blinded, randomized design. The interventions were typically administered in the form of capsules and lasted for twelve weeks. BIA and HGS were the most common techniques to assess muscle mass and strength, respectively, while performance was measured using multitudes of tests.

Dosage Strategies

Consensus has yet to be reached on the optimal dosage required to achieve significant improvements in muscle mass, strength, and performance, as it is unfeasible to do so without standardized trials or cohort studies observing the long-term effects of the potential herbs. The variability in dosage is further explained by the diverse nature of herbal plants and their bioactive components, which may exhibit different effects depending on the preparation method.

In the reviewed trials, supplement dosage varied widely, with the most common amount of supplements administered by researchers being 500 mg/day (13,17,18,21,25) followed by 1,000 mg/day (14,15,18,24) and 1,800 mg/day (19). Dosages ranged from as low as 63 mg/day (22) to as high as 2,000 mg/day (14). Previous studies deemed the different amounts efficacious, prompting the researchers to maintain or increase the dosage for more relevant or distinct improvement. However, only a minority of trials (n=8) reported the concentrations of bioactive components used in their studies, with the highest concentration at 126.0 mg/g of turmerosaccharide (15), followed by ursolic acid 101.9 mg/g (10), acteoside 54.1 mg/g (16), schizandrin 31.6 mg/g (12), glabridin 30.0 mg/g (17), salvianolia acid 28.2 mg/g and ginsenoside Rb1 2.2 mg/g combination (20), quercetin 12.9 mg/g (21), and daidzein 1.6 mg/g (19) daily. The values were reported as mg/g for standardized comparison as the actual daily dosages throughout the trials are included in Table I. Standardized reporting of bioactive components is critical to facilitate comparative analysis.

Despite preliminary in vivo and in vitro studies conducted prior to the studies to ensure utmost safety for human consumption, the lack of dose-response relationship trials remains a significant gap. This gap limits recommendations for effective treatment dosages applicable to the broader population, indicating the need for more rigorous, long-term studies to enhance the reliability and generalizability of conclusions.

Reported Adverse Events

Out of 13 trials, only four (n=4, 30.8%) reported adverse effects following herbal supplementation (13,18,21,22).

In the study of soy and its isoflavones daidzein, a total of 182 adverse events were reported. Gastrointestinal (GI) discomfort (n=166), sore throat (n=21), weight increase (n=18), rash (n=13), and breast swelling (n=7, two in the soy flour group, three in the daidzein group, and two in the placebo group) were the most prevalent complaints (22). Two women in the daidzein group who had experienced menopause during the previous three-year period reported two to three days of vaginal bleeding episodes post-intervention, though without recurrence. This suggests a potential endocrine interaction that merits further action. Raj et al. reported grade 1 dyspepsia in four participants (n=4/90) from their Turmacin supplementation trial, with three cases in the placebo group and one in the Turmacin 1g group (18). Similarly, a study administering 500 mg/day of turmeric extract excluded four participants due to GI complications, indicating a possible dose-dependent GI sensitivity to turmeric (21). One participant in the control group of a study on LLE supplementation complained of a rash and dropped out of the study (13).

The low incidence of adverse events across these studies suggests that most of the herbal supplementations were generally safe to consume with minimal side effects. However, precautionary actions and monitoring should be of concern for researchers, especially for individuals predisposed to allergies and possible endocrine and gastrointestinal complications. Rigorous safety reporting and monitoring should be of importance for future studies to better understand the safety profiles of various herbal supplements.

Limitations

Our scoping review, while comprehensive, has several notable limitations that require careful consideration when interpreting the findings. One significant limitation is selection bias, as relevant literary works may not be identified due to the exclusion of terms such as 'herbal supplementation' in the title or abstract. However, by including the terms 'herbal medicine' and 'plant-based supplementation' combined with the inclusion of a 10-year publication span, this review should uncover sufficient studies to portray the current trend of herbal supplementation RCTs in improving muscle parameters in the past few years.

The second limitation is publication bias, where our findings and suggestions made based on the results may have been influenced by the search terms used and the selection of the database. This bias could potentially skew the representation of herbal supplementation RCTs in muscle health improvement studies. Additionally, our review did not account for participant compliance towards the nutritional interventions, which is crucial for accurately assessing their effectiveness in real-world settings. Thus, future reviews should prioritize monitoring of supplementary compliance so that improved deductions can be made for the general population.

This review does not include changes in biological markers level for deeper insights into the internal mechanical effects of the interventions. As per ESCEO guidelines, four mandatory biochemical markers evaluating musculoskeletal status in any new Phase II or Phase III trial (myostatin-follistatin couple, brain-derived neurotrophic factor (BDNF), N-terminal type 3 procollagen (PIIINP), and the Sarcopenia Index [using the formula (serum creatinine (mg/dL)/serum cystatin C (mg/L)) 100]) are recommended for assessing musculoskeletal status. Incorporating these markers in future trials could enhance the understanding and comparability of results across studies. Thus, priority should be given to the listed markers as suggested by the consensus based on current available evidence.

While this review provides insights into the current trends in herbal supplementation for muscle health, the limitations highlight the need for caution in interpreting our findings. Future research should address these gaps by conducting more inclusive search strategies, minimizing publication bias, ensuring participant compliance, and incorporating biochemical markers. These steps are instrumental to provide more robust conclusions and better inform clinical practice.

DISCUSSION

This scoping review identified 13 articles related to the effects of herbal supplementations in improving sarcopenia indices over time across adults of all ages from 2012 through 2022. Growth in the interest in nutritional intervention in ameliorating muscle loss beyond protein-based supplementation is increasing by the decade, which prompts us to investigate the topic deeper. Thus, this scoping review may enhance the current understanding of herbal supplementation and its effects on human muscle growth and regeneration. Following the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCO)-WHO five-year agreement, this review is in line with the Decade of Healthy Ageing 2020-2030 goals to promote action through knowledge on musculoskeletal disorders in improving the lives of the world's older population.

Viscum album coloratum

Viscum album coloratum, known as the Korean mistletoe (KM), is a subspecies of the European mistletoe, a semi-parasitic woody perennial typically found on deciduous trees (27). The herb is prevalent in several countries, including Korea, Japan, and China. Recognized for its medicinal properties, KM contains various beneficial

components including lectins, polysaccharides, and flavonoids such as chlorogenic acid. Additionally, homoflavoyadorinin-B, a bioactive flavonoid uniquely present in KM, plays a role in averting and managing diseases and conditions linked to excessive reactive oxygen species accumulation in the human body (40).

In vivo testing on mice fed with chow containing KM extract exhibited greater overall body weights, heavier quadriceps muscles, enhanced grip strength and increased endurance in the group receiving a high dose of KME, compared to control chow-fed mice (28). Reflecting these benefits, a trial by Lim et al. demonstrated that a high-dose (2,000 mg/day) of KM extract coupled with resistance exercises significantly improved muscle mass and TUG time in healthy older adults compared to baseline ($p<0.05$) (14). The finding was supported by molecular analyses such as reverse-transcriptase polymerase chain reaction, multiplex analysis, and immunocytofluorescence staining, suggesting that a high-dose KM ameliorates myogenesis, possibly through the insulin-like growth factor (IGF-1) hormone signaling pathway. KM was found to have strong antioxidant activity as it inhibited lipid peroxidation more effectively than a comparable dosage of vitamin C. This was evidenced by a significantly higher relative antioxidant activity against linoleic acid peroxidation of 86% compared to vitamin C at 48% (40). Interestingly, significant between-group improvement was observed in KS, with the results being more prominent in the low-dose group (1,000 mg/day), even after being adjusted for age, gender, protein, and energy intake ($p<0.05$) (14). This findings demonstrated that a lower dose of KM extract might be more efficacious for certain outcomes, highlighting the possible dosage impact on muscle health.

Panax ginseng and Salvia miltiorrhiza

Panax ginseng, known as Asian or Korean ginseng, is a rooted perennial herb native to East Asian mountains and primarily cultivated in Korea. The word Panax means 'all healing,' coming from the traditional belief that ginseng can cure all ailments (29). Ginsenoside Rc, a major component of ginseng, proved effective in suppressing hydrogen peroxide-induced cytotoxicity in C2C12 myoblast and sustaining mitochondrial mass and biogenesis, inhibiting muscle breakdown, and scavenging intracellular reactive oxygen species in C2C12 myotubes (30). These findings suggest strong antioxidant capability and muscle-preserving effects of ginseng.

Salvia miltiorrhiza, also known as red sage or Danshen in TCM, has its name derived from the characteristic red color of the root which matches the heart called Chi (Red) Shen, hence the name Danshen. The herb has been tested in over thirty clinical trials for cardiovascular health, with overall effectiveness on markedly and moderately improved conditions ranging from 63.4% to 99.2% (31). The primary compounds in Danshen, Tanshinone IIA and salvianolic acid B, have been demonstrated to inhibit the production of the vasoconstrictor endothelin-1 in vivo, improving blood pressure, vascular basal tone and subsequently cardiac output (32). Both herbs were usually used in combination in TCM to address multiple pathological targets synergistically.

Underwhelmingly, a 1:1 combination of *Panax ginseng* and Danshen supplementation with weekly eccentric exercise training reported significant improvement in muscle quality in both the intervention and placebo groups, as measured using the ratio of isometric strength and quadriceps muscle mass obtained from DXA (23). The improvement is postulated to be attributable solely to the exercise training through the activation of SIRT1 and PGC-1α. Notably, this pathway is activated in conditions of energy depletion (exercise and caloric restrictions), where low levels of intracellular ATP trigger AMPK activity. This activation leads to the transcription factor PGC-1α being activated, promoting the transcription of genes related to energy metabolism, enhancing recovery and ATP synthesis (33,34). However, the potential inhibitory effects of antioxidant supplementation on oxidative stress may blunt the redox signaling pathway involved in muscle adaptation, which may further dampen muscle regeneration. The finding aligns with a growing body of evidence indicating that antioxidant supplementation may attenuate the adaptive responses induced by resistance exercise training (35–37). Thus, future studies combining nutritional and physical interventions should apply the triple-arm grouping system, which involves nutritional, physical, and the combination of both in trials as opposed to either group versus placebo, to substantiate and establish efficacious intervention.

Curcuma longa

Curcuma longa, or turmeric of the ginger family, is among the oldest cultivated spices in Asia (38). The rhizomes are used fresh or boiled in water and then dried before being ground into a deep orange-yellow powder. This powder is widely used as a coloring and flavoring agent in many Asian cuisines, particularly curries. It is also valued for its dyeing properties, imparted by the primary dietary polyphenol, curcumin. Various pre-clinical studies have elucidated curcumin's therapeutic efficacy, including enhancing anti-bacterial, anti-viral, anti-fungal, and anti-metastatic effects (39,40). A suggested mechanism includes suppressing nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signaling pathways, inducing protein phosphorylation and delaying cell cycle progression (17,18,21).

Despite demonstrated effectiveness in numerous experimental models, poor physicochemical properties such as poor aqueous solubility in physiological pH and chemical instability along with sub-optimal

pharmacokinetics (poor oral absorption, rapid elimination) limit the potential of curcumin as a promising drug candidate (41,42). Thus, new studies emerged to overcome the limitations by using nanoparticle or micronized formulation, increasing surface area and subsequently enhancing bioavailability with maximal concentrations up to 27-fold higher than non-formulated curcumin (43,44). Additionally, a solid lipid particle-based formulation was proposed in order to reduce the degradation rate, slowing systemic excretion (45).

In these trials, Varma and colleagues supplemented Cureit™, a patented formulation, found a significant 1.3% increase in strength (HGS) and performance (distance covered before feeling tired) compared to placebo ($p<0.001$) (17). Another patented formulation registered as Turmacin® with >10 % w/w of turmerosaccharides, reported significant increase in peak force of muscles around the knee in Turmacin 0.5g group compared to placebo ($p<0.05$). Turmerosaccharides, water-soluble compounds present in turmeric root, have been shown to possess anti-inflammatory and antioxidant properties independent of curcumin (46). The enhanced bioavailability may boost the anti-inflammatory and anti-oxidant effects on skeletal muscle cells. Salehi et al., administering 500mg/day of turmeric extract found a significant increase in VO2 max compared to placebo ($p<0.001$), with no improvement in muscle mass. The lack of muscle mass increase in the aforementioned study may be attributed to the rapid metabolism of unformulated curcumin, resulting in inadequate effects on muscle protein synthesis. The results were in tandem with several non-human studies emphasizing the antifatigue effects of curcumin (47–49).

Arctium lappa

Arctium lappa, known as greater burdock, is a rooted herb native to Europe and Asia and widely eaten in Japan, Korea, and Taiwan. Dried burdock roots, fruits, seeds, and leaves are commonly utilized in TCM, which is believed to 'detoxify' blood, improving blood circulation to the skin's surface and treating eczema, wounds, rashes, and hair loss (50). Burdock root also exhibited the second highest antioxidant properties after comfrey root among five other herbs (51). Burdock's major active ingredients, arctigenin and its glycoside arctiin are thought to protect against inflammation by suppressing nitric oxide production through the inhibition of inducible nitric oxide synthase (iNOS) at both the expression and activity levels (52). A 12-week trial reported significant improvements in HGS and Senior Fitness Test with burdock extract supplementation, but only when combined with an aqua exercise program ($p<0.05$) (16). The increased physical endurance likely contributed to this outcome, as evidenced by a systematic review reporting a significant increase in HGS in adults participating in aqua exercises alongside other skeletal muscle benefits (53). The researchers highly suggested aqua exercise especially for older adults, due to its low-impact nature, reducing loads on body parts and the risk of exercise-related injuries (54). However, it is essential to note that combining both interventions yielded more substantial HGS improvements than either intervention alone, suggesting a synergistic effect in enhancing muscle strength. Additionally, a trial involving adults with knee osteoarthritis who consumed three cups of burdock tea daily for six weeks demonstrated a significant reduction in pain intensity and mean TUG score, proving its effectiveness independent of exercise (all $p<0.001$) (55). Therefore, pairing burdock extract supplementation with aqua exercise is advisable for improving muscle strength and performance.

Asparagus racemosus

Asparagus racemosus, or Shatavari, is a species of asparagus native from Africa throughout South Asia to northern Australia, with its root being synonymous with Ayurveda medicine. Shatavari, which translates to 'who possesses a hundred husbands' or 'acceptable to many,' reflect its reputation as both a general tonic and a tonic for female reproductive health (56). Pre-clinical studies established the anti-bacterial, anti-ulcer, anti-proliferative, and antioxidant effects of Shatavari (56,57). A trial among post-partum mothers using oral Shatavari formulation, Shavari Bar®, reported a significant increase in total milk volume ($p<0.05$) (58). The enhanced breast milk production is due to its galactagogue properties, which boost milk supply during breastfeeding by raising prolactin levels (58). The beneficial effects are attributable to the presence of various bioactive compounds, including fructo-oligosaccharides, polysaccharides, asparosides, shatavarins, sapogenins, racemosols, isoflavones, glycosides, mucilage, and fatty acids. Among these, saponin stands out as a primary active component in the roots of Shatavari (59). However, limited human clinical trial complicates the substantiation of these claims, hindering critical evaluation of its physiological metabolism (60).

In a six-week trial by O'Leary et al., Shatavari supplementation improved HGS ($p<0.05$) but not KS in healthy post-menopausal women (25). The phytoestrogens in Shatavari might mitigate muscle degeneration caused by menopause-induced estrogen depletion (61,62). The study found that Shatavari increased myosin light chain phosphorylation in the vastus lateralis muscle, which may enhance striated skeletal muscle contraction by encouraging the myosin head's movement towards the thin filament, thus increasing the likelihood of myosin contact with actin (63). Overall, while this study is promising, more extensive RCTs on muscle mass, strength, and performance are necessary to fully confirm Shatavari's health benefits on muscle health and understand its mechanisms of action.

Schisandra sinensis

Schisandra sinensis (SC), also known as the five-flavor berry due to its distinct sweet, bitter, pungent, salty, and sour taste, is a deciduous plant native to China, Russia, and Korea (64). It is widely utilized in medicine, cosmetics, and health products and is also suitable as a functional food in tea, beverages, and jams. SC is rich in beneficial nutrients, including lignans, phenolic acids, flavonoids, triterpenoids, organic acids, vitamins, and polysaccharides. Lignans, primarily responsible for the health benefits of SC, are most abundant in its fruits but are also present in the leaves, shoots, and seeds (65). Pre-clinical studies have shown therapeutic effects on angiotensin-II-induced hypertension and obesity-induced muscle atrophy, each with different investigated bioactive compounds (66,67). SC was also thought to have anti-microbial, anti-cancer, anti-obesity, and anti-depressant effects (65,68).

A trial on physically active adults over 50 showed that a 1,000 mg/day dose of SC extract given for 12 weeks significantly improved HGS and KS (15). Specifically, SC extract increased right and left KS by 10.2 Nm and 6.7 Nm, while HGS significantly increased by five kg compared to the placebo ($p<0.05$). Another trial published a year prior found significant enhancing effects of SC on quadriceps muscle strength, attributable to the ATPase activity in gastrocnemius and soleus muscles ($p<0.001$) (69). These findings align with a 2015 study by Kim et al., suggesting *Fructus schisandrae* (FS, SC fruit extract) prevented dexamethasone-induced muscle weakness in mice. FS was shown to downregulate atrogin-1 and muscle RING-finger protein-1 (involved in the breakdown of muscle proteins), myostatin (a potent inhibitor of muscle regeneration), and sirtuin 1 (a muscle regeneration inhibitor). Conversely, FS upregulated PI3K, Akt1, adenosine A1 receptor and TRPV4 involved in muscle growth and protein synthesis activation (70). The findings demonstrated the beneficial ameliorating effects of SC on muscle strength, especially through the anti-inflammatory and antioxidant actions.

Glycyrrhiza glabra

Glycyrrhiza glabra, more commonly known as licorice, is derived from the ancient Greek terms '*glykos*,' sweet, and 'rhiza,' meaning root. The name reflects its sweet, aromatic flavoring attributable to glycyrrhizin, which is 50 times sweeter than sucrose (71). Licorice proved beneficial in the pre-clinical treatment of various cancers, respiratory tract infections, cardiovascular diseases, liver diseases, and dental caries (72). Although research on licorice on muscle mass improvements was lacking, past studies from decades ago up until recently proved the capability of licorice in altering body composition by visceral fat and fat mass reduction in overweight and obese adults (73,74). A 16-week trial in Japan using licorice flavonoid oil (LFO) supplementation found a significant between group, pre-post intervention KS and balance (one leg standing test with one eye open) (both $p<0.05$) but not HGS (20). Interestingly, the increase in the isometric KS was more pronounced in the placebo group compared to the intervention group. The results were justified by the imbalance in strength at baseline between the two groups, which was assumed to be resolved by physical exercise (20). This finding indicates that adults aged 40 years and older who regularly engage in strength training have better body balance control, which should help prevent falls and reduce the need for geriatric care. Notably, licorice and its component glycyrrhizin salts exhibit moderate toxicity and should be used cautiously during pregnancy (75). Side effects, potentially caused by the compound glycyrrhizinic acid, include hypertension and hypokalemia-induced secondary conditions, especially with prolonged high consumption. However, licorice is safe to use in appropriate doses at a no-observed-adverse-effect level (NOAEL) of glycyrrhizinic acid at 2 mg/kg/day (76).

Eriobotrya japonica

Eriobotrya japonica, or loquat, native to the hill regions of south-central China, is grown commercially for its yellow-orange fruit. Loquat extracts have been utilized to treat coughs, chronic bronchitis, inflammation, diabetes, and cancer in TCM and have been cultivated for more than 2,000 years in China (77). The phytonutrient composition of loquat extracts differs significantly between various plant parts. Loquat leaves and flowers are rich in phenolics and triterpenes, while the seed is an excellent source of proteins, starch, tannins, and minerals (77). The fruit contains sugars, organic acids, carotenoids, flavonoids, phenolic acids, and pectin (78).

Numerous studies using varying experimental models found beneficial effects on each part of the plant, including fruit, leaf, and seed (79–81). Pre-clinical studies reported the antifatigue potential of loquat leaf extract (LLE) in vitro and in vivo (82). Additionally, LLE improved muscle contraction-induced activation of p70S6K phosphorylation in rat skeletal muscles, preventing atrophy (83). Ursolic acid, the bioactive component of LLE mediates cell growth and proliferation through the Akt (13,14) and IGF-1 (84) signaling pathways by suppressing mRNA expression linked to muscle atrophy. Surprisingly, a trial by Cho and colleagues on LLE observed significant improvement in the 4MGS ($p<0.05$) and chair-rising time ($p<0.001$) but not SPPB in both the intervention and placebo group (13). Given the efficacious effects of ursolic acid in previous non-human studies, a prevalent effect was expected in the trial despite insignificant improvement in other muscle parameters. According to the researchers, one possible reason might be the insufficient dosage of the bioactive components (50.94 mg of UA, 500 mg/day LLE) administered throughout the 12-week intervention. Therefore, LLE might merit a dose-response curve synthesis.

Cistanche tubulosa

Cistanche tubulosa (CT), sometimes known as the 'desert hyacinth,' is one of the 22 species of *Cistanche*, a type of plant that lacks chlorophyll and derives its nutrients and water from the roots of host plants it parasitizes (85). Recently, a taxonomic decision considered CT synonymous with *Cistanche tinctoria* (Forssk.) *Beck* due to its classification as a polyphyletic group (86). However, the current review continues to refer to CT as is for consistency.

CT is predominantly found in warm desert areas, six of which are located in China and thus, are commonly used in TCM. CT is recognized for its benefits in tonifying kidney yang, enhancing sperm and blood production, and acting as a laxative and intestinal moisturizer (85). Out of 120 compounds isolated from *Cistanche*, which include phenethyl glycosides, cycloenne ether terpenes and their glycosides, studies have shown that phenylethanoid glycosides (PhG) make up more than 80% of these compounds (85). The active ingredients of CT included echinacoside and acteoside (87). Pre-clinical studies have demonstrated CT's advantageous antioxidant (85), neuroprotective (88), hypocholesterolemic (89), and steroidogenesis effects (90), some of which were thought to be regulated through gut microbiota homeostasis (88,91). However, studies regarding muscle health including mass, strength, endurance, and performance were lacking (92).

In terms of muscle health, an in vivo study found that CT extract improved hindlimb function by suppressing the shift from slow to fast myofiber type in cast-immobilized mice (93). Although two of the muscle performance parameters in the study by Inada showed no significant improvement (5MWS and stand-up test), the researchers did observe significant between-group differences in the two-step test in older adults over 60 and over 65 (19). The possible beneficial effects of acteoside in enhancing axonal innervation from neurons to skeletal muscle might be hindered by the low bioavailability of acteoside (94). Thus, future research on CT should consider the pharmacokinetics of active compounds to ensure optimal bioavailability.

Anacardium occidentale

Anacardium occidentale (AO), also known as cashew, is native to the Caribbean and Northeast Brazil and thrives in humid, tropical countries. The term '*Anacardium*' originates from Greek and translates to 'inverted heart,' referring to the shape of its fruit (95). The fruit consists of two main parts: the nut, the true botanical fruit, and the apple, the false fruit, which constitutes 90% of the fruit's weight. Both parts are edible and valued for their nutritional and medicinal purposes (96). The cashew apple is typically yellow or red with sweet and astringent flesh. Its ascorbic acid levels are almost five times higher than oranges, notably higher in yellow cashew apples, while the red variety has more amino acids and tannins than the former (96,97). In vivo studies suggest a significant ameliorating effect of AO leaf extract on muscle strength, though further research on muscle mass and performance remains unexplored (98).

Kaewbutra et al.'s study on physical fitness using AO apple juice found significant improvements compared to placebo in the 30-second chair-stand test and 6MWT (both $p<0.01$) but not in TST (24). The study also reported a significant increase in plasma glutathione peroxidase (GPx) ($p<0.001$), though no significant changes were observed in superoxide dismutase and catalase levels following supplementation. The enhanced GPx activity may attenuate oxidative stress, thus reducing muscular inflammation (24). Quercetin, a flavonoid of the cashew apple, might contribute to increase in muscle performance due to its antioxidant activity (99). However, other RCTs studying quercetin's effects on muscle performance in both exercising and non-exercising individuals produced inconsistent results (100–102). These results warrant further studies across a more varied population background and age to gain better insight on quercetin's mechanisms.'

Glycine max

Glycine max, commonly known as soy, is a legume native to East Asia. Due to its rich antioxidant and polyphenolic content, high protein quality, and rapid digestibility, soy is considered a promising plant-based protein (103). It rivals animal-based proteins in its ability to support muscle protein synthesis and enhance exercise performance. Daidzein and genistein are the most abundant forms of phytoestrogen in soy, including fermented soy products such as Japanese miso and natto, Korean doenjang, and Indonesian tempeh (104).

Equol, formed by the gastrointestinal bacteria metabolism of daidzein, has greater biological activity than its precursor. It is more stable and more readily absorbed by the human body due to its ability to bind to estrogen receptors (105). However, only 33% to 50% of humans possess the necessary microbes to metabolize daidzein, allowing them to potentially gain the most benefit from soy consumption. Daidzein and its metabolite equol have been shown to increase muscle mass in vivo and in vitro (106–109). However, a six-month RCT of whole soy and daidzein on body composition in equol-producing postmenopausal women with prehypertension found no significant effect on anthropometrical and body composition data, including muscle mass (22). Interestingly, a previous RCT among older adults found that muscle strength gains during resistance training are reduced with soy protein compared to dairy or typical protein intake (110). According to a systematic review by Zare et al., soy proteins of ≥1.6 g/kg/day may increase muscle mass during resistance training similar to whey protein; however, some studies suggest that milk and whey proteins might be more effective for faster muscle mass gains (103). Thus, reiterating one of the reasons for

determining herbal effect on muscle mass, individuals with dietary restrictions can enjoy similar advantages of soy in maintaining and improving muscle health.

CONCLUSION

In summary, the reviewed herbal supplements were shown to have a more prominent effect on strength and performance rather than muscle mass. High-dose *Viscum album coloratum* and formulated *Curcuma longa* increased muscle mass and TUG, and handgrip strength and endurance in adults, respectively, which supports their inclusion in preventive strategies against sarcopenia. Other herbs such as *Schisandra chinensis, Glycine max,* and *Arctium lappa* also proved beneficial in improving handgrip strength and performance, especially when paired with specific exercises. Notably, *Asparagus racemosus, Cistanche tubulosa,* and *Anacardium occidentale* demonstrated capability in improving strength and performance despite severely lacking pre-clinical and clinical studies on muscle health. Future studies should consider the pharmacokinetics of active biocomponents, focusing on increasing bioavailability through formulation, for example, to ensure robust and meaningful results. A good study design should elucidate dose-response relationships to establish efficacy, safety, and toxicity of herbal supplementation. Finally, it is important for future studies to investigate long-term effects of herbal supplement intake to confirm its role in improving muscle growth and motor function.

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