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REVIEW

EXERCISE PHYSIOLOGY AND BIOMECHANICS

The effect of *Panax ginseng* supplementation on markers of resistance exercise-induced muscle damage: a systematic review

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ABSTRACT

INTRODUCTION: According to the PRISMA guidelines, this systematic review of randomized controlled trials examined whether *Panax ginseng* supplementation reduces resistance to exercise-induced muscle damage (EIMD).
EVIDENCE ACQUISITION: Web of Science, SPORTDiscus and Medline databases were searched from the 16th of December 2021 to the 18th of February 2022. Inclusion criteria were studies in humans consuming *Panax ginseng* that employed resistance training as the damaging muscle protocol and measured markers implicated in the etiology of EIMD (muscle damage, muscle function and muscle soreness). The PEDro risk of bias assessment tool was used to appraise the studies critically.
RESULTS: Conflicting evidence was evident in markers of muscle damage, muscle function and muscle soreness. The quality assessment suggested that all studies had some level of bias.
CONCLUSIONS: From 180, six studies were included in the systematic review. The main findings suggest that *Panax ginseng* does not attenuate markers of EIMD following resistance training. However, research is still preliminary. Adequately powered sample sizes and well-controlled studies are warranted to clarify *Panax ginseng*'s efficacy.

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KEY WORDS: Exercise; Panax; Resistance training; Myalgia.

Introduction

Strenuous or unaccustomed exercise that requires eccentric contractions places substantial stress on the muscle, resulting in muscle damage.[1] Subsequently, athletes often experience discomfort or soreness post physical activity, known as exercise-induced muscle damage (EIMD). The associated pain can persist from the cessation of the exercise and continue in the days to follow.[1, 2] Delayed onset muscle soreness (DOMS), impaired muscular function, limited range of motion, and elevated intramuscular proteins are symptoms that accompany the onset of EIMD.[2, 3]

The etiology of EIMD is not fully understood but is proposed to be linked to the high mechanical forces exerted during eccentric actions, to which the muscle fibers are exposed due to the lengthening of the muscle.[4] Other

scientific literature has offered similar findings, with muscle damage occurring due to morphological alterations in the sarcomeres Z-disk.[5] The mechanical deformation of muscle fibers is required to bring about the adaptive remodeling effect.[6] This has been identified as the primary phase of EIMD.[7] In the second phase of muscle damage, an inflammatory response is triggered to repair the injured myofibrils.[7, 8] Biochemical markers that are used to assess muscle damage and are identified along with the inflammatory process include, but are not limited to, serum cortisol, lactate concentration and creatine kinase.[9, 10]

The damaging exercise's intensity, volume, and duration influence the magnitude and duration of EIMD symptoms.[7] The individual's vulnerability to the harmful stimulus also influences EIMD symptoms, with age, sex, and physiological training status playing a role.[7, 8] The issues associated with primary phase of EIMD concern the quality of training, adaptations, the increasing risk of overtraining and injuries.[11] For example, it has been found that muscular strength can drop by up to 40-50% post-exercise due to EIMD.[12]

Many athletes utilize resistance training as part of their training program.[13] This can involve eccentric, concentric, multi-articular and isoinertial contractions with various loads.[11] Resistance exercise, particularly for individuals who are new or deconditioned to it, can stimulate symptoms of EIMD.[14, 15] However, evidence suggests that EIMD may not be avoidable, regardless of training background, following muscle-damaging resistance training protocols.[14] Athletes often need to endure a quick turnaround; therefore, there is a need to ameliorate the persistence of EIMD symptoms for the desired acceleration of recovery.[16]

Over many decades, eclectic research on strategies for accelerating the recovery process has been conducted, with the first study occurring in 1902.[17] Such methods include active exercise, pharmacological approaches, cryotherapy, manual therapies, electrical therapies and nutritional interventions.[16] The effectiveness of each strategy varies depending on the specific approach employed, the affected muscle and the athletes' physical characteristics.[18] Appraising such literature enables researchers to better understand the ability of different strategies to alleviate EIMD signs and symptoms**.**

Recently, research have examined the effects of nutritional supplements on EIMD symptoms.[19] These remedies range from fruits, fruit-derived supplements, vitamin supplements, amino acid and protein supplements to other nutritional strategies such as caffeine.[19] Certain nascent areas require additional research to determine the potency as a nutritional intervention, including ginseng supplementation.

Ginseng is a member of the Araliaceae plant family, also identified under the species-genus Panax.[20] The roots are known as the lord of herbs because they entail the spirit, body and mind, also recognized as the three main human essences.[21] Traditionally, ginseng was used in Chinese medicine over five millennia ago to treat several diseases.[22] The nutraceutical herb has suggested benefits ranging from cardiovascular protection to improved memory, highlighting its proposed adaptogenic properties.[23, 24]

There are several species of ginseng, with the most commercially obtainable types being *Panax ginseng* (Asian) and *panax quinquefolius* (American).[23] The phytochemical makeup of these forms varies, including 30 different types of triterpenes saponins, also known as ginsenosides.[24] *Panax ginseng* is more commonly available, making it an intriguing research subject.[22] While it is still not fully understood, it has been purported that ginsenosides are the integral component of ginseng which triggers the immunomodulatory effects.[25] Studies report that prolonged ingestion of ginseng may have a vital role in moderating markers of EIMD compared to a placebo.[26]

A narrative review by Harty *et al.*[19] was conducted on nutritional strategies to reduce EIMD symptomatology, including ginseng. The research suggests that although it discovered anti-inflammation, reduced direct markers of muscle damage, DOMS, fatigue, and increased muscle function to be potential benefits, it is preliminary and needs further investigation.[19] Furthermore, a systematic review and meta-analysis explored root plant supplementation strategies to reduce markers of EIMD, including ginseng.[27] The study found that the root plants positively influenced the amelioration of EIMD symptoms, although ginseng appeared less effective than the other root plants.[27]

However, a pertinent gap in research for ginseng was identified as the effect on muscular force remained unclear.[27] The nature of exercise utilized as the muscle damaging protocol varied, with the majority being endurance interventions. Additionally, the type of ginseng used in the collective studies was mixed, although they entail different phytochemical properties.[19, 27] The evidence on ginseng's effectiveness is equivocal and continues to be disputed.[28]

Therefore, this study aimed to perform a systematic review to examine if *Panax ginseng* supplementation mitigates markers of EIMD following resistance exercise and is thereby an effective ergogenic recovery aid. Considering the purported effects identified in other research leads

to the hypothesis that individuals who use *Panax ginseng* to aid EIMD recovery will see a beneficial impact.

Evidence acquisition

According to the PRISMA 2020 statement guidelines, this systematic review was conducted.[29]

Eligibility criteria

The PICOS strategy[30] was employed with the following inclusion criteria being used to assess the eligibility of retrieved articles: 1) "P" (population), studies with human participants with no restrictions to sex or age; 2) "I" (intervention), participants in the intervention group that received any kind of ginseng supplementation; 3) "C" (comparator), comparison between individuals who undertook ginseng to those who did not receive it (placebo, or a product that contains no ginseng); 4) "O" (outcome), the timing, frequency, dose, and duration of ginseng supplementation was included in the study methodology as well as markers of post-exercise muscle damage, muscle function or muscle soreness being recorded; 5) "S" (study design), randomized controlled trials performed in humans (no exclusion criteria were applied for study design, or blinding).

Studies were excluded from analysis when: 1) the exercise intervention had an endurance aspect; 2) the supplement was an extract or component of ginseng; 3) multiple supplements were administered supplements; and 4) thesis, dissertations, conference papers or other were also excluded.

Information sources and search strategy

Eligible studies were searched for on Web of Science, SPORTDiscus and Medline from the 16th of December 2021 to the 18th of February (Figure 1). Full texts not available in English were excluded, although no language restrictions were applied in the search. The terms and algorithms used to conduct the search are shown in Supplementary Digital Material 1, Supplementary Figure 1. The search results were downloaded and filtered in the Mendeley Reference Manager v2.64.0 (Mendeley Ltd. UK) systematic review software. The PICOS design framework was used to screen the titles and abstracts of retrieved articles by an independent author (Supplementary Digital Material 2: Supplementary Table I). A manual search helped

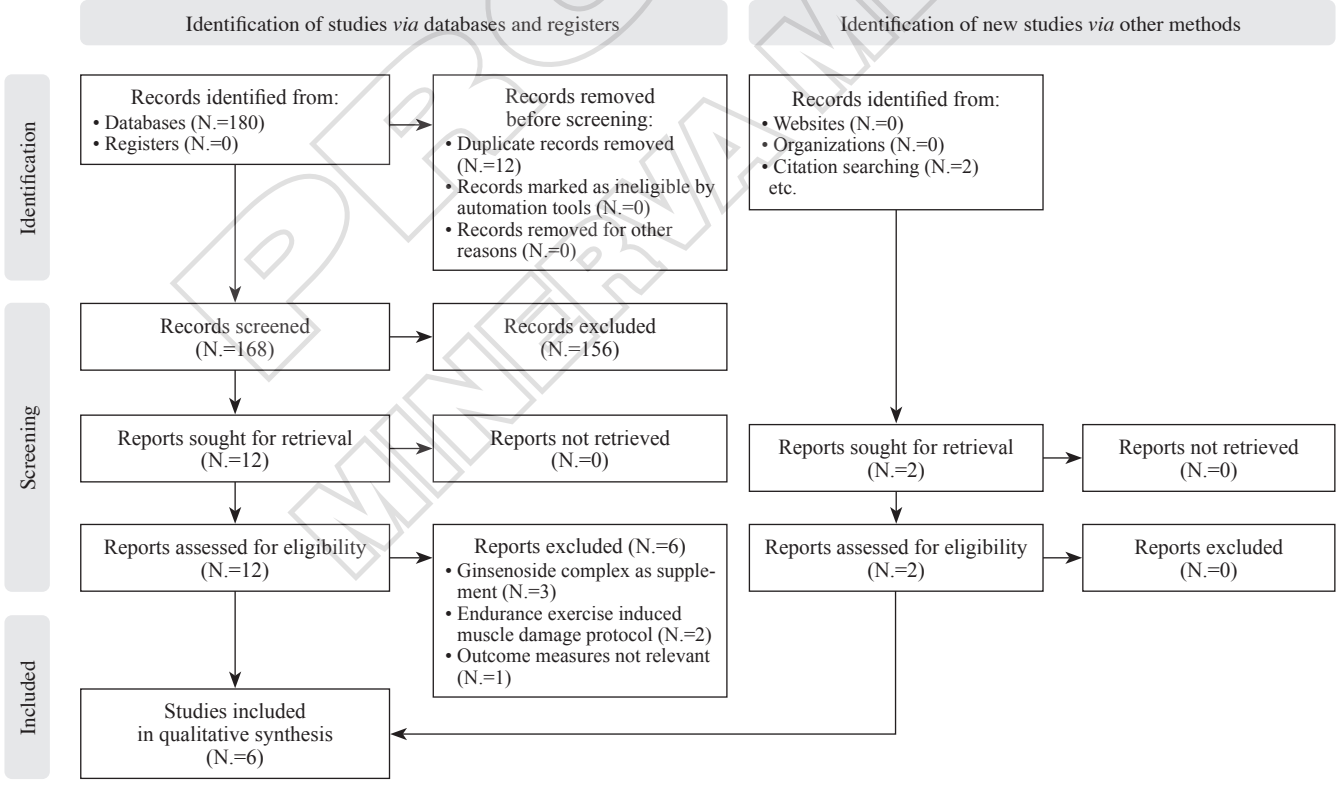

Figure 1.—Flow diagram showing the search strategy of this systematic review.

identify other suitable articles in eligible full-text articles to be incorporated in the systematic review. A consensus was formed on the final studies included by all authors.

Data collection process and data items

Following completion of the search, results were compared between researchers (J.S. and T.C.) to ensure that the same number of articles was found. Then, a Microsoft Excel Spreadsheet adapted from an example provided by the Introduction to Systematic Reviews Course at York University (UK) was used to extract and tabulate data.[31] Data collection included: 1) authors and year of publication; 2) study design (*e.g.*, double-blind, parallel, or cross over); 3) participants characteristics (*e.g.*, age); 4) supplementation protocol (timing, frequency, dose, and duration); 5) exercise protocol (type, duration, repetitions, and sets); (f) sample size, and 6) relevant outcome measures. The outcomes included in the spreadsheet include muscle function, muscle soreness, and (indirect) markers of muscle damage (*e.g.*, creatine kinase, lactate, and cortisol). The time points extracted started from post-supplementation until the cessation of measurement per individual study.

For each outcome measure, the data was extracted as mean±standard deviation (SD).

Study risk of bias assessment

The authors J.S. and T.C. assessed the study quality using the PEDro risk of bias assessment tool.[32] This tool specified 11 individual classifications to determine the risk of bias within each selected study. Considering the inclusion of cross-over studies, one additional category was included to assess the bias arising from the carry-over period.[33] The risk of bias for each study was assessed for the following domains: 1) eligible criteria specified; 2) random allocation; 3) concealed allocation; 4) groups similar at baseline; 5) blinding of participants; 6) blinding of therapists; 7) blinding of the assessor; 8) <15% drop out; 9) intention to treat analysis; 10) between-group difference reported; 11) point measures and variability reported; 12) having a sufficient carry-over period. When it was unclear whether a study had successfully met the criteria, a score of 0 was allocated. The typical score thresholds were converted to percentages to account for the additional category, with qualitative ratings defined as "poor" (<40%), "fair" (40-60%), "good" (60-80%) and "excellent" (80-100%).[32]

Synthesis methods

Data is described narratively and are presented in the results section (specifically, in Table I, II).[9, 15, 22, 24, 34, 35] There was insufficient studies and data available to conduct a meta-analysis.

Evidence acquisition

Study selection

Results from the search strategy are presented in Figure 1. The Web of Science, Medline and SPORTDiscus data-

TABLE I.—*Study characteristics, focusing on study design and participants' characteristics.*[9, 15, 22, 24, 34, 35]

Author	Design	Sample Size (n)	Physical characteristics	Training background
Azizi & Moradi[34]	Randomized Control Trial	CG: 10 SG: 10 N.=20	PG Age 31.2±3.9 years; height 180.4±6.9cm; BW 80.7±9.1kg; BMI 24.8±3.3kg/m^2 SG: Age 30.6±7.4 years; height 177.6±7.0cm; BW 81.1±9.4kg; BMI 25.7±2.3kg/m^2	Male bodybuilders with at least two years of regular participation in body building exercises (3x week)
Kang *et al.*[35]	Randomised control trial	CG: 4 SG: 4 N.=8	Age 21.3±0.7 years; BW 68.6±1.4kg	Healthy male college students
Caldwell *et al.*[22]	Cross over randomised design	CG: 19 SG: 19 N.=19	Male: Age 41±10 years; height 1.77±0.05 m; weight 88.5±5 kg Female: Age 39±8 years; height 1.64±0.05 m; weight 76.0±11.6 kg	Healthy, active participants
Zarabi *et al.*[9]	Cross over randomised design	CG: 10 SG: 10 N.=10	Age 23.4±0.69 years; height 163±1.76 m; weight 57.61±6.9 kg; BMI 21.76±2.81 kg/m^2	Young female non-athlete students
Cristina-Souza *et al.*[15]	Cross over randomised design	CG: 10 SG: 10 N.=10	Age 15.4±1.5 years; height 178±0.05m; weight 60.4±9.1kg; Body fat 5.2±1.6%	Ten young men athletes (runners, sprinters, and jumpers)
Flanagan *et al.*[24]	Cross over randomised design	CG: 19 SG: 19 N.=19	Male: Age 41±10 years; height 1.77±0.05 m; weight 88.5±5 kg Female: Age 39±8 years; height 1.64±0.05 m; weight 76.0±11.6 kg	Healthy, active participants

CG: control group; SG: supplement group; N.: number of participants; BMI: Body Mass Index; BW: body weight.

TABLE II.—*Study characteristics, focusing on supplement and placebo administration, EIMD and outcomes.*[9, 15, 22, 24, 34, 35]

Author	Administration method	EIMD Protocol	Outcome measures compared to placebo		
			Biomarker	Muscle Performance	DOMS
Azizi & Moradi[34]	SG: 500 mg/day of ginseng (2 x 25 0mg doses) CG: 500 mg/day of starch (2 x 250 mg doses) Duration: 6-week period	Resistance training 3 sets, 8 reps Intensity of 70-80% of 1RM 1-2 minutes rest between set	T ¯* C « T/C ratio «	Bench press « Leg press	NR
Kang *et al.*[35]	SG: 20 g of Korean ginseng root extract (GIN) with 500ml water. CG: 500 mL water (CON) Duration: 7 days	Resistance training 3 sets, 7 reps of previously determined 7RM	LC « Plasma GH « C « T « IGF-1 « Insulin «	NR	NR
Caldwell *et al.*[22]	SG high dose: 960 mg/day of ginseng (5 x 160mg doses) SG low dose: 160 mg/day of ginseng (1 x 160mg/day, 4 x maltodextrin supplement) CG: maltodextrin supplement Duration: 14 days+7 days wash out period	Resistance training 5 sets, 12 reps Intensity of 70% of 1RM 2 min rest in between sets	NR	Ballistic jump « Quick board «	0-100mm VAS ¯* RPE ¯*
Zarabi *et al.*[9]	SG: 100 mg/day of ginseng (1 x 100mg doses) CG: 100mg/day of maltodextrin (1 x 100mg doses) Duration: 4 weeks	Resistance training 3 sets, 8-10 reps Intensity of 80% of 1RM 1-2 min rest in between sets	GH « C « LC «	NR	NR
Cristina-Souza *et al.*[15]	SG: 100mg.kg^{-1} of BM/day of ginseng (3 doses)+200ml of water CG: 100mg.kg^{-1} of BM/day of starch (3 doses)+200ml of water Duration: 8 days+7 days wash out period	Resistance training 4 sets, reps Intensity 70% of 1 RM (until concentric failure) 2 min rest between sets	LDH « CK «	MIVC *	0-100mm VAS RPE -*
Flanagan *et al.*[24]	SG high dose: 960 mg/day of ginseng (5 x 160mg doses) SG low dose: 160 mg/day of ginseng (1 x 160mg/day, 4 x maltodextrin supplement) CG: maltodextrin supplement Duration: 14 days+7 days wash out period	Resistance training 5 sets, 12 reps Intensity of 70% of 1RM 2 min rest in between sets	CK * Superoxide dismutase * Total antioxidant power * C «	NR	0-100 mm VAS

EIMD: exercise-induced muscle damage; DOMS: delayed onset muscle soreness; NR: non-reported; CG: control group; SG: supplement group; RM: rep maximum; C: cortisol; NR: not reported; LC: lactate concentration; GH: growth hormone; VAS: Visual Analogue Scale; RPE: rating of perceived exertion; LDH: lactate dehydrogenase; CK: creatine kinase; MIVC: muscle isometric voluntary contraction.
*Statistically significant outcome for supplement group compared to the placebo group.

base search found 180 studies. After removing duplicates, there was a total of 168 studies remaining. The screening resulted in the exclusion of 156 studies, mainly because the subjects were animals. Two more studies were identified via citations from other studies during the screening. A full-text screening excluded 50% of the studies as they did not meet the intervention criteria regarding the type of exercise to induce muscle damage. Upon the completion of screening, there was a total of six studies remaining.

Study characteristics

The study characteristics of the included studies are summarized in Table I, II.[9, 15, 22, 24, 34, 35]

There were 86 participants from the six studies, with 72 participants in the experiment and placebo groups, respectively, due to the cross-over study designs. The participant's ages ranged from 13 to 51 years old. Three studies had only male participants,[15, 34, 35] and two had both male

and female participants,[22, 24] while one solely had female participants.[9] The sporting background of each study varied: four studies had healthy, active participants, while Zarabi *et al.*[9] recruited young non-athlete students, and Azizi and Moradi[34] focused on bodybuilders with at least two years of regular participation.

The studies in this review all utilized a randomized design approach. Azizi and Moradi[34] and Kang[35] adopted a parallel design, while the remaining four opted for a cross-over design approach.[9, 15, 22, 24] Two studies that utilized a cross-over design differentiated two arms by having a high-dose and low-dose group.[22, 24] One study[24] separated the results for female and male participants.

Different ginseng dosages were used in the included studies; two studies used a high (960 mg) and low dose (160 mg).[22, 24] Within the other studies, the quantity ranged from 100 mg to 20 g of ginseng extract per day.[9, 15, 36, 37] The placebo's used in studies included: starch, maltodextrin, or a non-specifically stated item containing 0g of ginseng. The drug administration period ranged from seven days to six weeks. The cross-over trials typically had a wash-out period of seven days,[15, 22, 24] although Zarabi *et al.*[9] did not specify this.

Each study employed resistance training as the EIMD protocol, with the selected exercises being performed at a previously measured one or seven repetition maximum approach. The sets, repetitions and exercises varied between studies, presented more clearly in Table II.[9, 15, 22, 24, 34, 35]

All studies had a different approach to the outcome measures when testing the efficacy of the ginseng supplement. The biomarkers analyzed in three or more studies were cortisol and lactate. Azizi and Moradi[34] found non-significant effects on cortisol levels (P=0.059). Kang *et al.*[37] found no difference from baseline or between supplement and control group with cortisol or lactate concentration. Zarabi *et al.*[9] had similar results, with no significant differences found between groups for cortisol (P=0.61) or lactate concentration (P=0.90), respectively. Bar cortisol for the supplement group, there was a significant increase in these biomarkers for both groups, with measurements compared from pre- to immediately post-exercise. Cristina-Souza *et al.*[15] measured the biomarkers immediately post exercise, with 24-, 48- and 72-hour measurements as follows ups. However, only immediately following exercise elicited a higher than pre-exercise lactate dehydrogenase measurement, which was evident for both participation groups.[15] No-significant findings were reported on this biomarker (P=0.431).[15] Similarly, Flanagan *et al.*[24] found ginseng had no effect on cortisol levels between groups when measured at 24-hours. Nonetheless, a significant (P<0.05) suppression effect was detected between dosage type and sexes immediately, 30- and 60-minutes post-exercise intervention. The interaction evidenced men to have lower cortisol levels post exercise and women having higher resting cortisol concentrations by the control group.

Growth hormone and creatine kinase were used as markers for muscle damage in two separate studies. Zarabi and colleagues[9] found no significant effect (P=0.71) in between-group comparison for growth hormone, although there was a significant effect to baseline for both groups. The other study[35] replicated the non-significant between group finding, although a non-significant spike was visible 15-minutes post intervention. Creatine kinase recorded a significant difference between groups in the study comparing low and high dosages, and sexes.[24] The high dose group response to exercise stress was significantly lower at 24-hours compared to the other low dosage and control testing groups.[24] Additionally, the recovery values showed men to have higher outputs than women.[24] On the other hand, no significant outcome was established in another study (P=0.318),[15] where increases for both testing groups were present post-, 24- and 48-hours post-exercise for creatine kinase.

Other measurements included testosterone, insulin, IGF-1, and markers of oxidative stress. Azizi and Moradi[34] found a significant effect (P=0.026) on the supplement group (-13%) compared to the control group (+19.5%) in the change of testosterone levels, following the exercise intervention. However, the testosterone to cortisol ratio was also deemed non-significant (P=0.463).[34] The rest of the biomarkers (Table II)[9, 15, 22, 24, 34, 35]assessed by Kang and colleagues[35] found no baseline difference and no between group difference after 2-hours. All markers in this study were also assessed immediately post-exercise, at 15-, 30- and 60-minutes post-exercise, with some minor fluctuations, although none were of significance or with lasting effects.[35] Flanagan *et al.*[24] found a significant (P<0.05) between dosage group difference for three markers of oxidative stress; total glutathione, superoxide dismutase and total antioxidant power, at time points ranging from immediately post-exercise up to 60-minutes post-exercise. No differences between sexes were reported.

Three studies measured muscle performance.[15, 22, 34] In one study,[34] both leg press and bench press were performed. No difference was found between groups in the bench press performance, although an improvement in leg press performance was post supplementation, yet neither was deemed significant.[34] On the other hand, Caldwell and his colleagues[22] explored peak power aspects to assess muscle performance, utilizing ballistic jumps and quick board to

evaluate ginseng's purported effects. Responders (N.=13) and non-responders (N.=6) were identified, with responders eliciting a significant higher peak power (P=0.003) for the high dose treatment compared to low and placebo.[22] However, 24-hours post-exercise, no significant treatment effect was evident, regardless of treatment group and respondent capabilities.[22] Muscle Isometric Voluntary Contraction (MIVC) was used as another measuring tool to assess muscle performance.[15] Following a reduction for both groups immediately post-exercise (P=0.006), *Panax ginseng* influenced the ability of the MIVC to return to baseline 24-hours post-exercise, although non-significant (P=0.115). While the reduced MIVC occurred up until 48-hours post-exercise for the placebo group (P=0.031).[15] Notably, the ginseng group produced significantly higher MIVC outputs at 24-hours (P=0.022) and 48-hours (0.030) than the control group, with no difference between groups at 72-hours (P=0.085).[15] Furthermore, the muscle excitation, examined using EMG (%$MIVC_{RMS}$), was found to have significantly increased following ginseng supplementation (P=0.044).[15]

Three selected studies also examined DOMS by examining the rate of perceived exertion (RPE) and 0-100 mm Visual Analogue Scale (VAS).[15, 22, 24] The Cristina-Souza *et al.*[15] study assessed participant RPE during four exercise intervention sets, rather than post-exercise. The RPE score was significantly lower for the ginseng group in the 2nd, 3rd and 4th set compared to the placebo group (P=0.022).[15] In comparison, there was no significant main effect of the supplement for DOMS, which was measured using the 0-100m VAS system.[15] Caldwell *et al.*[22] further established a main effect for treatment (P<0.018) with high dosage (P=0.004), reporting a significant reduction in RPE when compared to other treatments. VAS outcomes showed no significant results, while assessing the change in muscle soreness (+24HR-RPE), found a significant treatment effect for high (-9.48) and low (-11.28) doses, respectively.[22] Another study found ginseng had no influence on muscle soreness, regardless of timing, dosage and sex, when evaluating mood state, sleep quality or muscle soreness scale ratings.[24]

All physical characteristics and selected outcome measures discussed within this section appeared comparable in the supplement and placebo conditions.

Risk of bias assessment

Using the PEDro Scale, the risk of bias assessment can be viewed in Table III.[9, 15, 22, 24, 34, 35] All studies successfully specified the eligibility criteria, randomly allocated participants, intended to treat analysis and did not experience participant dropout. It was unclear whether the allocation was concealed in most studies due to a lack of specification or study design. Additionally, it was difficult to determine whether groups were similar at baseline due to a lack of baseline measurements, apart from participant characteristics.[9, 22, 24] Although the blinding of participants and therapists was generally deemed successful, the assessor's blinding was another challenging factor in scoring accurately. Only one study was deemed not to have completed a sufficient wash-out period.[9]

No study was identified as having a high risk of bias, as no study was rated below "good." Four studies[9, 24, 34, 35] raised some concerns, albeit being in the "good" category, while the other two[15, 22] indicated a low risk of bias, falling in the "excellent" qualitative rating. The risk of bias assessment should be interpreted cautiously, as only two assessors completed this.

Discussion

This systematic review examined if *Panax ginseng* supplementation mitigates markers of EIMD following resistance exercise and is thereby an effective ergogenic recovery aid. Some studies[15, 24] provided promising evidence in the ability of ginseng to accelerate recovery, while others[9, 22, 34, 35] showed limited promise. The mixture of results from the six studies makes it difficult to conclude *Panax*

TABLE III.—*PEDro SCALE assessing the risk of bias.*

Study	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	Total (%)
Kang *et al.*[35]	1	1	0	1	1	0	0	1	1	1	1	N/A	72.7
Caldwell *et al.*[22]	1	1	0	1	0	0	0	1	1	1	1	N/A	63.6
Zarabi *et al.*[9]	1	1	1	0	1	1	1	1	1	1	0	1	83.3
Cristina-Souza *et al.*[15]	1	1	0	0	1	1	0	1	1	1	1	0	66.7
Flanagan *et al.*[24]	1	1	0	1	1	1	0	1	1	1	1	1	83.3
Kang *et al.*[35]	1	1	0	0	1	1	0	1	1	1	1	1	75

[1] Eligibility criteria specified, [2] Random Allocation, [3] Concealed Allocation, [4] Groups similar at baseline, [5] Blinding of participants, [6] Blinding of therapists, [7] Blinding of assessor, [8] <15% dropouts, [9] Intention to treat analysis, [10] Between-group difference reported, [11] Point measures and variability reported, [12] Have a sufficient carry-over period.

ginseng's ability to attenuate recovery adaptations when assessing muscle soreness, muscle function and muscle damage markers which makes us suggest more research in this field. It needs to be acknowledged that the research within this field is still in its infancy, thus, drawing an overarching conclusion on ginseng's practical value as a recovery aid following resistance training is premature.

Serum cortisol levels respond to the stress induced by muscle damage, typically resulting in increased circulating cortisol levels.[38] However, none of the included studies provided substantial evidence that would suggest ginseng to be of benefit following resistance training, when assessing this biomarker.[9, 24, 34] A significant effect was detected for time periods up to 60-minutes post-exercise across dosage groups, indicating that ginseng was able to suppress the acute stress response.[24] Following 24-hours post-exercise intervention ginseng showed no signs of influence.[24] Gender differences were also identified in the acute response, with women having higher resting levels, but lower levels post-exercise, in the control and low dosage group.[24] Notably, an alternative study[9] found post-exercise, cortisol levels rose significantly for the placebo group, but not for the ginseng group.

Lactate has previously been used as an indicator of fatigue, with one meta-analysis discovering ginseng to have had a positive influence.[39] This contradicts the finding of this review, however, exercise was not a part of the intervention to assess ginseng.[9, 15, 24, 39] Cristina-Souza and colleagues[15] tested at four separate times post-interventions, ranging from immediately post-exercise to 72-hours post. Although non-significant findings were reported, a higher value than pre-exercise was recorded immediately post-exercise, for both testing groups, which was not evident in other studies.[9, 15, 24] However, this study specifically assessed lactate dehydrogenase compared to lactate, which could be one of the reasons, apart from exercise prescription and intervention design, that could have led to this finding.[15] Nonetheless, it reinforces the value of assessing lactate as an indicator of fatigue.[39]

Like lactate, creatine kinase is needed for muscle repair and regeneration.[7] Previous analysis have revealed ginseng's lack of influence on this enzyme,[15] while contradictory findings were established by Flanagan and colleagues.[24] This result may be due to the different dosages of ginseng administered.[24] Not only did men show higher outputs than women, possibly due to muscle mass differences, but the high dose group also elicited significantly lower values, which were detected at 24-hours post-exercise. Furthermore, the conflicting findings may be attributed to creatine kinase's high sensitivity and inter-subject variability when measuring muscle damage.[10]

Growth hormone is used as a biomarker to assess muscle damage due to its protein synthesis role. Therefore, research have suggested that decreasing level of growth hormone may contribute to lower training adaptations.[40] Both studies assessing growth hormone found non-significant effects between group comparisons. Zarabi *et al.*[9] found a significant rise in this biomarker compared to baseline, evident in both groups, while Kang's research[35] revealed a spike in growth hormone levels at 15-minutes post-exercise.

The meta-analysis of Doma *et al.*[27] investigated root plant supplementations, including ginseng, and found that ginger and garlic attenuated a significant effect when compared to ginseng when analyzing markers of muscle damage. The results of this review indicated similar findings, as ginseng did not attenuate markers of muscle damage, except creatine kinase, which was evident in only a single study. Other biomarkers not discussed in depth showed little to no difference between the placebo and ginseng groups, except for the significant reduction of testosterone levels[34] and markers of oxidative stress.[24, 35] Flanagan *et al.*[24] suggest that ginseng, specifically a high dosage of 960mg, primarily affects the stress response. However, this conclusion may be premature as these effects were only evident in an acute period up to 60-minutes post-intervention.

Muscle function is a crucial indicator of EIMD, as it typically decreases post-muscle-damaging exercise.[8] This study attempted to address the effect of ginseng on muscular force, with three of the included studies evaluating muscle function as a marker of EIMD, which has practical relevance to athletes.[27] Cristina-Souza *et al.*[15] reported significantly greater MIVC levels for the supplementation condition than for the placebo condition at 24- and 48-hours post-exercise intervention. Furthermore, muscle excitation significantly increased in the ginseng group compared to the placebo.

Azizi and Moradi[27] employed two compound lifts as their exercise intervention, with no significant benefit of ginseng evident, even though an improvement for leg press was apparent in the ginseng group. Caldwell *et al.*[22] curiously distinguished, in a second round of analysis, between responders and non-responders to the supplement, evidencing a significant (P=0.003) peak power difference for the high dose treatment group over the other two groups. This showed that muscle force generation capacity recovered quicker for the ginseng condition than the placebo condition. However, this was the only significant power assessment finding, as 24-hours post-exercise groups returned to normal.

Despite the previous efforts, it is still elusive how the combinations of multiple components work together to produce the clinical effects of ginseng; however, there have been reports on pain-relieving effects.[41] In a review, two mice studies were identified where ginseng could regulate pain and demonstrated anti-inflammatory effects.[41] Interestingly, in individual studies, subjective muscle soreness was significantly influenced by ginseng supplementation.[15, 22, 24]

Cristina-Souza *et al.*[15] findings regarding RPE was significant between sets two to four. Other findings in this study regarding DOMS found nothing of significance.[15] This finding was mirrored by other studies.[22, 24] However, when changing the interpretation method, Caldwell *et al.*[22] found significant effects for both high and low dose groups when assessing the reported change in muscle soreness. The peak response of DOMS may not have been examined, apart from in one study.[15] Further studies did not collect data at 48- and 72-hours, with some only measuring immediately post-exercise.[9, 34, 36] This is distinguished in a meta-analysis assessing root plant supplements found muscle soreness significantly reduced at 24- and 48-hours post-exercise.[27]

Overall, the analysis indicated that the risk of bias for the studies included was low; however, there were some issues. Firstly, all studies had a relatively low sample size, ranging from 8 to 20 participants. None of the included studies reported a priori power analysis, suggesting all studies were not powered enough to detect or bring about an actual effect.[37] Secondly, due to the lack of clarity in most studies, it was difficult to determine the extent of concealed allocation and assessor blinding. Another potential source of bias is the period and carry-over effect in the cross-over study design. Most studies fail to address the carry-over effect, not considering the possible residual effect of the intervention.[38] Only one study in this review justified the 7-day wash-out period; however, this was extrapolated based on the results of a study in rats.[22] Other studies evaluating ginseng in various contexts utilized wash-out periods of two weeks or longer, thus leading to debate regarding whether seven days is a long enough wash-out period.[42] Lastly, one study did not use a placebo in the experiment, which may have introduced bias.[9] Nevertheless, all studies did employ a randomized design, whether parallel or cross over, and employed appropriate interventions and did not experience participant dropout.

The selection of participants amongst the included studies in the review was varied. Sixty-five percent of the participants in the included studies were male. Evidence suggests an attenuated response in women following muscle damage compared to men, particularly the inflammatory responses.[36] Nevertheless, no analysis could be undertaken to evaluate sex as an influencing factor. There was a heterogeneous selection of age ranges, but the findings may not apply to individuals above 50 years of age. As a result of the limited studies, the influence of age could not be investigated. Although the included studies had a range of trained and untrained participants, it is unknown whether these results apply to elite athletes.

The duration of supplementation differed across studies, with no apparent pattern identified to distinguish the optimal period of the intervention. The length of supplementation in each study ranged between seven days to six weeks. This highlights the need for an agreement regarding the duration of supplementation to bring about the desired effects. Additionally, as alluded to previously, more studies should explore EIMD symptoms at 24-, 48- and 72-hours post-exercise intervention.[36] However, measurements post this time frame may provide substantial evidence to alter the findings in this analysis.[14]

The optimal dose depends on its bioavailability and the quantity administered.[41] This is the first review where the ginseng administered in the included studies came from the same plant family. The dosage ranges from 100mg-960mg/day, with one study having an outlier of 20g. A range of dosages can help clarify which doses are effective, if any at all, to bring about purported effects, which is evident within some of the included studies reporting successful outcomes.

This is the first systematic review to shed light on *Panax ginseng*'s impact on recovery from resistance training-induced muscle damage, so only limited comparisons could be made with other studies. However, as the mechanistic and metabolic pathway of *Panax ginseng* is not fully understood, it is hard to pinpoint a justification for these findings.

Limitations of the study

Several limitations within this review have been identified. Firstly, the small number of studies presented in this review limits the conclusions that can be drawn regarding the effectiveness of ginseng. Alongside this, the studies selected had a small-scale selection of participants in which may account for the limited promising outcomes. Benefits observed in individual, well-control studies that operated under strict and specific conditions that demonstrate real effects may be disguised by the heterogeneity between studies.[43] Such possibilities should be taken into consideration when interpreting the findings.

Limitations regarding the individual studies include the repeated bout effect, familiarization and the lack of dietary control. The repeated bout effect can arise from employing

a cross over design, limiting the study's findings.[44] This may partly explain some of the individual study findings as the participants have been exposed to the same stimulus and can therefore lessen the magnitude and damage induced. Additionally, a limitation was familiarization with exercise. One study conducted testing to identify the participants one or seven repetition(s) maximum, that may have exposed participant muscles to the stimulus, thus making it more difficult to elicit the same effect when undertaking the assigned resistance training during the experiment.[35] Finally, a potential limitation was the lack of dietary control in the studies, which was only discussed in one study.[15] Recording the intake of the participants ensures similar metabolic conditions before experimental trials and that the outcomes are not due to chance.[45]

Future research

As a result of the present study, several suggestions for further research can be provided. Firstly, future studies should consider reporting a range of biomarkers to demonstrate mechanisms of EIMD markers, inflammation and oxidative stress.[14] Further, with the limited research on ginseng's influence on muscle strength, future research should employ measures of muscle function for meta-analysis to be undertaken. Possible measures may include muscle isometric/isokinetic voluntary control of elbow or knee, one-repetition maximum, and jump assessments. Alluding to the proposed difference in gender responses to EIMD, future studies may also thoroughly address the potential effects on the female population.[36]

Additionally, future research should aim to compare the effects of ginseng supplementation on EIMD in elite athletes to determine if the findings from this review are applicable. Other considerations for future research include using a placebo with the control group, examining the participants' diet throughout the study, and ensuring transparency in the methodological approach. Future studies may also seek to assess other ginseng types or the independent components to examine the efficacy compared to *Panax ginseng*. Further research is also required to determine ginseng's wash-out period to diminish residual effects. Finally, as evidenced by the studies included in this review, future studies should present all data to enable a meta-analysis[46] to be performed.[43]

Conclusions

The complex mechanisms of *Panax ginseng* and EIMD remain elusive. The current review suggests that *Panax ginseng* is unlikely to attenuate recovery following EIMD from resistance training. Nevertheless, some promising evidence by Flanagan *et al.*[24] and Cristina-Souza *et al.*[15] should be highlighted. This conclusion is based on limited studies with a heterogeneous cohort, ginseng dosage and timing, and a small number of participants. These limitations restrict the generalizations of this review to other more diverse groups. Future research is required to adequately power studies and clarify whether ginseng supplementation can aid recovery adaptations.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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