Physical Medicine and Rehabilitation - International

Open Access

Austin Publishing Group

Research Article

Study of Red Ginseng Preparation HRG80 for Relieving Muscle Pain/Soreness and Supporting the Neuromuscular Performance of Elite Weightlifters in Intense Resistance Exercise: An Open-Label, Randomized, Crossover Trial

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Received: October 08, 2022; **Accepted:** November 08, 2022; **Published:** November 15, 2022

Abstract

This study aimed to assess the efficacy of new *Panax ginseng* C.A.Mey preparation of increased bioavailability in fatigue assessed as relief of muscle soreness and improving the neuromuscular performance of healthy subjects following a bout of intense resistance exercise. The effects of the hydroponically cultivated red ginseng root powder HRG80™ (RG) γ-Cyclodextrin -based chewable tablets and cyclodextrin-free RG capsules were compared in an open-label, randomized, crossover trial on 20 elite weightlifters. The RG treatments for 10 days have a statistically significant effect on the relief of the muscle's soreness compared to the control. No statistically significant difference was observed in the effects of two capsules *vs*. one tablet suggesting that γ-Cyclodextrin based chewable tablets of red ginseng preparation HRG80 are almost 4-fold active of cyclodextrin-free HRG80 capsules.

Furthermore, the effect of tablets vs. control was significant on the 5th day of the treatment, while the effect of capsules vs. control was observed three days later - on the 8th day. However, in push-ups on the uneven bars (PUB) test of neuromuscular performance, the capsule intake results in increased physical performance compared to tablets or control with maximal effect on the 7th day of treatment. The results of this study provide evidence for the efficacy of γ-cyclodextrin-based chewable tablets containing 100 mg of red ginseng HRG80™ for relief of muscle soreness and supporting the neuromuscular performance of healthy subjects in intense resistance exercise.

Keywords: Red Ginseng; Fatigue; Muscle Pain; Athletes; γ-Cyclodextrin

Introduction

Panax ginseng C.A.Mey. is likely one of the most widely used botanicals in the world [1,2]. This adaptogenic plant [2-8] is approved in Europe and other countries as an herbal medicinal product to enhance cognitive functions and physical capacities in weakness, exhaustion, tiredness, loss of concentration, and during convalescence [9-10].

The number of recent publications indicates on beneficial effects of Korean red ginseng in healthy subjects [11-13], increasing their psychomotor and physical performance [11] and cognitive functions [14-15] in stress. Thus, hydroponically cultivated red ginseng root powder HRG80™ (RG) effectively prevents and mitigates the stress-induced deterioration of cognitive functions in healthy subjects [14] and elderly patients with mild cognitive disorders [15]. In this study, we aimed to assess the efficacy of RG in relieving muscle soreness and improving the neuromuscular performance of elite weightlifters.

Major active constituents of RG, ginsenosides Rg5 and Rk1comprising about 1.9% and 1.0% of RG [16], exhibit pleiotropic pharmacological activity [16-19]; however, their content in the blood circulation system is low due to poor solubility in water [20-22]. A recent study suggests that Gamma-Cyclodextrin (GCD) can increase the clinical efficacy of RG due to the enhanced solubility of the main active ingredients, ginsenosides Rg5 and Rk1[23]. In this study, we compared the effectiveness of RG capsules with chewable tablets containing the γ-cyclodextrin incorporated RG.

The primary aim of this study was to compare the effects of the GCD-based complex of RG chewable tablets with cyclodextrin-free RG capsules on measures of perception and physical performance following an acute bout of intense resistance exercise.

Materials and Methods

Participants Eligibility

A study of the efficacy of RG preparation in healthy athletes was conducted in National Team Training Center (Abovyan City, Armenia), with the approval of the Kardiomed Family Medical Centre Ethics Committee (approval date: Jul 22, 2022). It is an extension of a comparative study of dissolution and pharmacokinetics

Citation: Hovhannisyan AS, Mosinyan DN, Hayrumyan SA and Panossian AG. Study of Red Ginseng Preparation HRG80 for Relieving Muscle Pain/Soreness and Supporting the Neuromuscular Performance of Elite Weightlifters in Intense Resistance Exercise: An Open-Label, Randomized, Crossover Trial. Phys Med Rehabil Int. 2022; 9(3): 1207.

of ginsenosides released from cyclodextrin-based chewable tablets in healthy human subjects (ClinicalTrials.gov ID: NCT04932265. The study was performed per the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). All participants provided written informed consent (Supplement 2, page 1) to participate in the study before being screened.

Study-Population Selection

Twenty 18.6 ± 4.7 years old professional weightlifting athletes (Supplemental Table S1 in Supplement 1) were assessed for eligibility to participate in the study from July to September 2022. Fourteen males and six females were enrolled in the study and included in the Intention-To-Treat (ITT) analysis Supplemental Tables S2 -S4 in Supplement 1. The athletes were part of the Armenian National Weightlifting team competing at the Word and European championships 2020-2021.

Inclusion Criteria

The athletes were experiencing stress, fatigue, and muscle soreness after two hours intensive physical exercise but were

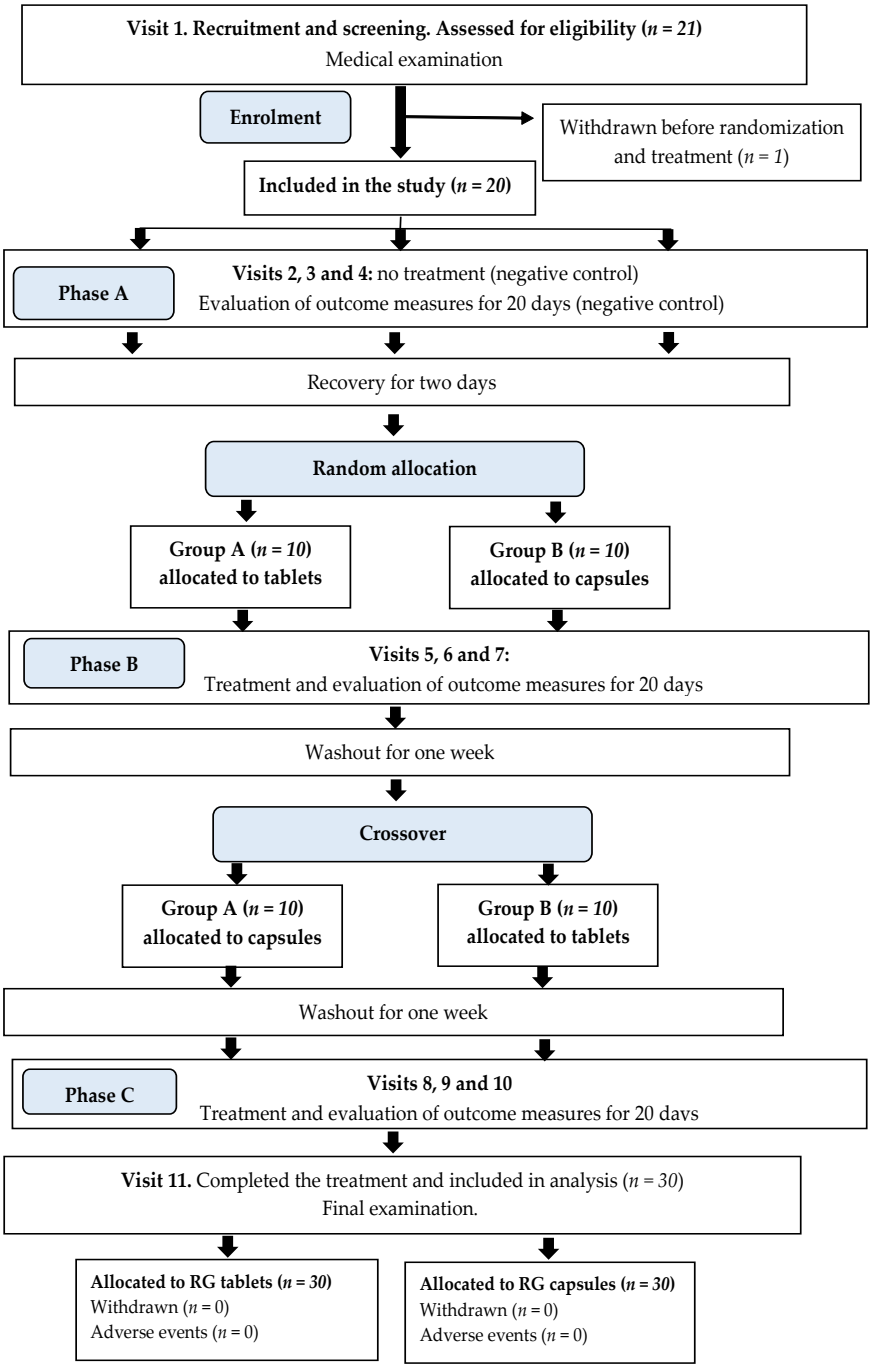

Figure 1: Schematic diagram of the trial. For details on the disposition of patients, see Supplement 1.

otherwise healthy. The inclusion criteria were as follows: 16-35 years old healthy athletes (males and females of any race and ethnicity) who admitted the presence of daily strength training and the absence of competition during the study period, can understand and provide signed informed consent (Supplement 2, page 1), and were able to participate in a 6-week study.

Exclusion Criteria

The exclusion criteria were as follows: taking over-the-counter medications or dietary supplements that may have potential effects on pain, the presence of muscle trauma or injury, and any other condition that precluded participation according to the investigator's judgment.

Investigational Products

Commercially available Dietary Supplements of Red Ginseng Energy Chewable Tablets (Lot 2241-0201, Exp. date Jan 2023) containing 100 mg of red ginseng preparation HRG80 and 400 mg GCD and Red Ginseng Energy Capsules (Lot 201049, Exp. date Jan 2023), containing 200 mg of red ginseng preparation HRG80 were provided by Europharma U.S.A. (Green Bay, WI, USA). Their chemical characterization was described in detail in our recent publications [14,15,23].

Doses and Treatment Regimens

Participants received either two Red Ginseng Energy Capsules containing 200 mg of red ginseng preparation HRG80 (daily dose 400 mg HRG80), or one Red Ginseng Energy Chewable Tablet containing 100 mg of red ginseng preparation HRG80 (daily dose 100 mg HRG80) once a day in the morning after breakfast for 10 consecutive days.

Evaluation of Compliance

Participants were questioned about their overall compliance with the study protocol during the study, and the study personnel counted the remaining capsules. Compliance was monitored by the doctor of the study, who checked the participants' records that were attached to the case report form (CRF, Supplement 2). The study monitor checked overall compliance with the study protocol upon their visits, and the remaining capsules were counted at the end of the study.

Study Design and Procedure

It was an open-label, randomized crossover trial where the same subject took both preparations and was used as a control (no treatment), (Figure 1). On day one, all participants started phase A of the study for ten days, which provided outcomes used as the negative control for treatments. After three days of recovery without physical exercises, all participants were randomly separated into two treatment groups (10:10) allocated to interventions A and B to enter Phase B of the study for ten days. After one week of washout, the athletes entered Phase C of the study, where the subjects were crossover switched from intervention A to B and vice versa – from B to A.

Every morning during the study, after waking up, all participants filled in the Pain/muscle soreness questionnaire form (Montgomery and Hopkins questionnaire [24,25], MHQ) for ten consecutive days of Phases A, B, and C, (Figure 2).

The doctor recorded the results of Psychomotor and Physical Performance tests (Figures 3,4) conducted on days 1, 3, 7, and 10that 10 am after the first morning training session.

Efficacy Outcome Measures

A perceptual measure of fatigue: One of the three efficacy measures used in this study was muscle soreness, frequently utilized to monitor fatigue in athletes after training. It was assessed by an advanced and validated modification [25] of MHQ [24], including the questions related to muscles of upper and lower sites [25]. A scale from 1 to 5 was used to quantify the soreness level of 9 different muscles/muscle sites from both sides of the body: left and right quadriceps, groin, chest, shoulder, calf, hamstrings, gluteus, lower back, upper back. A measure of Lower Body muscle soreness (LB) was calculated from the sum of the left and right quadriceps, groin, calves, hamstrings, and gluteus soreness. A measure of the Upper Body (UB) soreness was calculated from the average of the left and right chest, shoulder, lower back, and upper back muscle soreness. Finally, whole-body soreness was calculated from the total muscle soreness ratings from all muscles/muscle regions. The athletes were

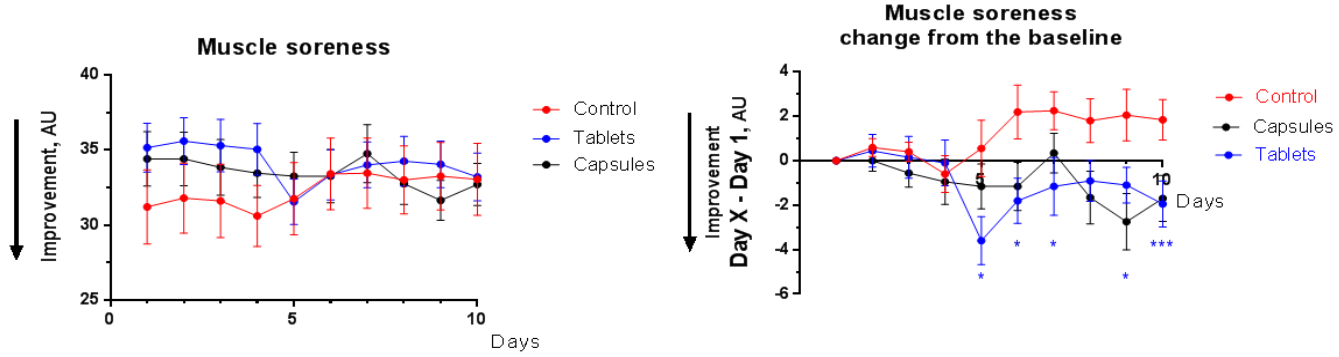

Figure 2: (a) – Muscle soreness MHQ score (mean ± SD) of athletes over the time of treatment with tablets (decreased, p <0.05), capsules (decreased, p >0.05), and negative control (increased p<0.05) from Day 1 to Day 10 (within-group repeated measures ANOVA, Supplementary table S2). (b) - Relieve the muscle soreness; the changes from the baseline (day 1) of muscle soreness MHQ score (mean ± SD) of athletes over the time of treatment with tablets and capsules vs. negative control from Day 1 to Day 10.Comparison of alleviations of the muscle's soreness from the baseline over time of treatment with RG tablets or RG capsules vs. negative control shows a significant interaction effect (p < 0.0001), which was insignificant between tablets vs. capsules (two-way ANOVA). The efficacy of RG preparations vs. negative control (assessed by two-way between–within ANOVAs) was revealed by an interaction effect (p=0.028), indicating a different response over time between RG tables and control, while the interaction effect of capsules ns negative control was insignificant (p=0.1173).The significance of difference is expressed by symbols *p < 0.05, **p < 0.01, ***p < 0.001, ns: not significant.

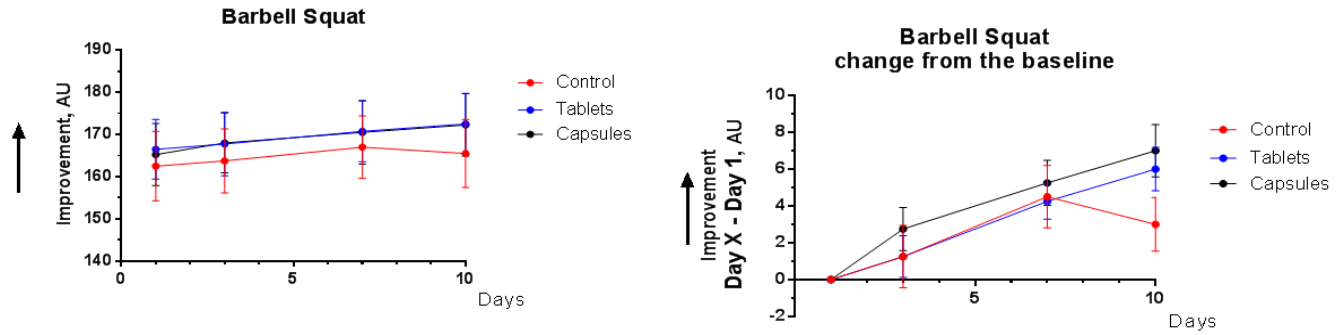

Figure 3: (a) – Effect of RG tablets or capsules on a maximal weight of the rod in barbell squat (BS) test. The maximal number of PB scores (mean ± SD) of athletes over the time of treatment with tablets, capsules, and negative control from Day 1 to Day 10 (within-group repeated measures ANOVA, Supplementary table S2). (b) - The changes from the baseline (day 1) of athletes' PU score (mean ± SD) over the time of treatment with tablets and capsules vs. negative control from Day 1 to Day 10. Comparison of alleviations of PU scores from the baseline over treatment time with RG tablets or RG capsules vs. negative control was insignificant (p >0.05, two-way ANOVA).

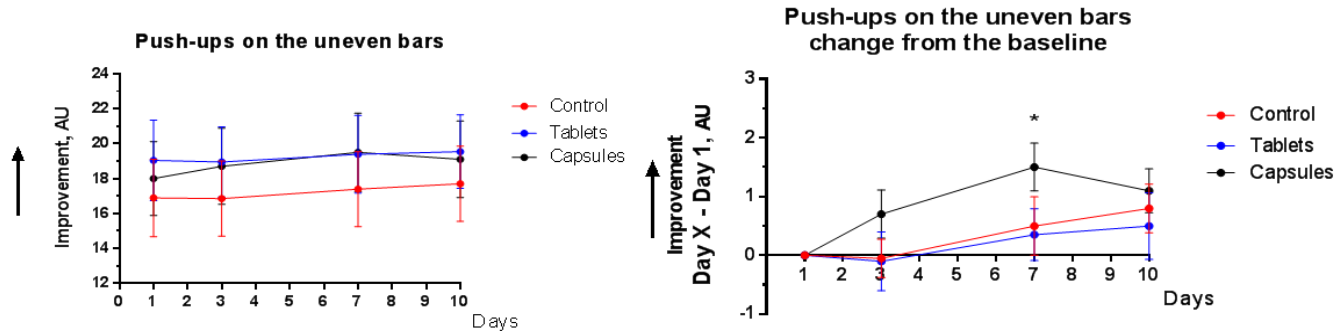

Figure 4: (a) – Effect of RG tablets or capsules on the maximal number of push-ups on the uneven bars (PUB) Test (mean ± SD) of athletes over the time of treatment with tablets, capsules, and negative control from Day 1 to Day 10. (b) - The changes from the baseline (day 1) of PUB score (mean ± SD) of athletes over the time of treatment with tablets and capsules vs. negative control from Day 1 to Day 10. The efficacy of RG capsules *vs*. tablets and negative control (assessed by two-way between–within ANOVAs) was revealed by an interaction effect (p = 0.006 and p=0.0005 correspondingly), indicating a different response over time between RG capsules and control with the maximal difference on day 7 (p< 0.05), while the interaction effect of tablets vs negative control was insignificant (p=0.0725). The significance of the difference is expressed by symbols *p <0.05.

monitored for muscle soreness during a 10-day in-season period (phases A, B, and C) to get a control curve of changes in muscle soreness score from the "baseline" (day 1).

Psychomotor and Physical Performance: Tests to Measure Strength Ability

Barbell Squat (shoulder position): This test assesses the legs' absolute (maximum) strength (gluteal muscles; quadriceps femoris; posterior thigh muscles; adductors).The test requires a standard 20 kg bar, two locks, a frame for the barbell, and enough plates to perform maximum effort with the ability to vary weights in the 5 kg range. When carrying out squats with a barbell with top weight, a prerequisite is using a frame with safety beams or having two assistants who insure the subject and provide assistance if necessary. The subject sits down under the power rack barbell, takes it on his shoulders in a low or high position, and takes a step back. The athlete must squat to a 90° angle and fully extend the legs. Assistants are located on both sides of the bar and are ready to assist the subject at any time.

The first warm-up approach was accomplished with light or medium weights relative to the strength capabilities of the subject, followed by a rest of 1 minute. A warm-up weight is set, presumably allowing the athletes to perform the exercise from three to five repetitions. After execution and rest for 2 minutes, the weight was increased by 5 kg or 10-20% for lower limb exercises. After implementation and rest for 2-4 minutes, the weight was increased by another 5 kg or 10-20% for lower limb exercises. The test continues until the maximum possible weight is selected. The maximum weight of the rod was considered as the final result.

Push-Ups on the Uneven Bars

The athlete stands facing the ends of the bars, jumps up, assumes a support position, bends his arms at an angle of 90°, and then straightens his arms again. The maximum number of push-ups is taken into account as the final result. The athlete repeated as many push-ups as possible.

Efficacy Endpoints

The primary endpoints for assessment of the efficacy of RG preparations were:

A difference in changes in muscle pain/soreness scores from the baseline (day 1)over the time to the last day (day 10) of treatment compared to the negative control (no treatment),

A difference in changes in psychomotor/physical performance tests scores from the baseline over the time to the last day of treatment

compared to the negative control (no treatment); time frame: 1, 3, 7, and 10 days.

The secondary endpoints for assessment of the efficacy of Red Ginseng Energy Chewable Tablets were differences in changes in muscle pain/soreness and physical performance test scores from the baseline over the time to the last day of treatment compared to Red Ginseng Energy Capsules.

Statistical Analysis

All the data were recorded in standardized case report forms and tabulated in an Excel dataset (Supplemental Tables S1, S2, and S3), which was used in statistical analysis by Prism software (version 3.03 for Windows; Graph Pad, San Diego, CA, USA).

Statistical analysis was conducted using "observed" data for time-to-event outcomes of the intent-to-treat population, defined as all randomly assigned participants who received at least one dose of the study product.

The mean outcomes were evaluated at baseline (Supplemental Table 4), days 1 of phases B and C vs. phase A by the Student's parametric independent-measures t-test (variables with normal distribution according to the D'Agostino & Pearson omnibus normality test).

Within-group repeated measures analysis of variables was conducted with one-way ANOVA (data with normal distribution) test.

Evaluation of the efficacy of study preparation was achieved by comparison of mean changes from the baseline (differences before and after treatment of particular participant) between treatments using two-way between–within ANOVA (Supplemental Table 2) in which an interaction effect indicates a different response over time between the treatments and negative control or between two treatments (capsules vs tablets) and would therefore indicator a treatment effect, as well as by multiple comparison t-test (one unpaired test per row). The level of statistical significance was set at 5% in all methods.

Results

Between-group comparisons showed no significant difference at the baseline day one on all three phases A (visit 2), B (visit 5), and C (visit 8) of the trial, (Figure 1 and Supplement Table S4).

Muscle soreness significantly increased ($p< 0.05$, within group, repeated measures ANOVA, Supplement Table S2) from baseline (day 1) over time from days 6th to 10th of phase A of the study used as a negative control (Figure 2a). When the same 20 athletes took one Red Ginseng Energy Chewable Tablet daily (daily dose 100 mg RG) for 10 consecutive days - a significant decrease in muscle soreness score was observed ($p< 0.05$, within group, repeated measures ANOVA, Supplement Table S2), (Figure 2a). The pain ameliorating effect of Red Ginseng Energy capsules (daily dose 400 mg RG) was insignificant (Figure 2a).

A significant increase in muscle soreness score, measured as a change from baseline (day 1) over time, was observed on days 6, 7, 8, 9, and 10 of phase A (negative control), while the pain relief effect of Red Ginseng Energy Chewable Tablet daily (daily dose 100 mg HRG80) was significant on days 5, 6, 7, 8, 9 and 10, compared to control (assessed by two-way between–within ANOVAs and multiple comparison test, (Figure 2b), and Supplementary table S2). When the same athletes took two Red Ginseng Energy Capsules daily (daily dose 400 mg HRG80) for 10 consecutive days - a significant decrease in muscle soreness score, measured as a change from baseline (day 1) over time from baseline (day 1) was found for days 8, 9 and 10, (Figure 2b). No statistically significant difference was observed in the effects of two capsules vs. one tablet (Figure 2b) using two-way between–within ANOVAs; however, the impact of tablets vs. control was significant on the 5th day of the treatment, while the effect of capsules vs. control was observed three days later - on 8th day.

All athletes performed Barbell Squats (BS) and Push-ups on the uneven bars (PUB) as measures of neuromuscular performance to monitor fatigue, Figures 3 and 4. The capsule uptake results in an increase in physical performance in the PUB test compared to tablets or control (assessed by two-way between–within ANOVAs and multiple comparison tests) with maximal effect on the 7th day of treatment.

Discussion

In an effort to improve the bioavailability of ginsenosides and, accordingly, the efficacy of Reg Ginseng preparations, we compared the γ-cyclodextrin based complexes containing red ginseng preparation HRG80 with the γ-cyclodextrin free dosage form. The efficacy outcomes measures were relieving fatigue, assessed as muscle pain/soreness, and neuromuscular performance in elite weightlifters during regular, intense resistance exercise for 10 days.

Both RG preparations were effective in subjective assessment of fatigue and objective measure of physical performance. Furthermore, in this study, we demonstrated that one "Red Ginseng Energy" chewable tablet containing 100 mg of red ginseng preparation HRG80 is (daily dose 100 mg HRG80) is as effective as two "Red Ginseng Energy" capsules containing 200 mg of red ginseng preparation HRG80 (daily dose 400 mg HRG80).

The results of this study provide evidence of the efficacy of Red Ginseng Energy" chewable tablet for relief of muscle soreness and supporting the neuromuscular performance of healthy subjects in intense resistance exercise.

Conclusion

- Daily intake of Red Ginseng preparations ameliorates the progression of fatigue, measured as muscle soreness, in athletes after repeated heavy physical loads for 10 consecutive days.
- γ-Cyclodextrinbased dosage form of red ginseng preparation HRG80 are almost 4 fold active of cyclodextrin free HRG80 preparation: one" Red Ginseng Energy" chewable tablet containing 100 mg of red ginseng preparation HRG80 is (daily dose 100 mg HRG80) is as effective (or more effective) as two "Red Ginseng Energy" capsules containing 200 mg of red ginseng preparation HRG80 (daily dose 400 mg HRG80).

Supplementary Materials

The following are available online at www.mdpi.com/xxx/s1; supplementary data 1.

Author Contributions

AH contributed to the study execution and good clinical practice, data management, analysis, and study reporting; MDN contributed to the study subjects' recruitment, implementation of treatment, and data collection; HSA contributed to the overall study management of the study; AP contributed to the study conception, evaluation, design, data analysis, interpretation of the results, drafting and preparation of the manuscript. All authors read and approved the final manuscript.

Funding

This work was partly funded by Europharma USA (Green Bay, WI, USA). The research sponsor was Mr. Terrence Lemerond, Europharma USA Inc., USA.

Acknowledgments

The authors acknowledge the support of Europharma USA (Green Bay, WI, USA) for supplying and characterizing the investigational dietary supplements. The authors thank Nate Paske for technical assistance and Dr. Karen Stepanyan for monitoring the study. The authors are grateful to all participants of the study and Armenian Weighlifting National Team coach Kirakosyan Ervand for supervising Push-ups on the bars and Barbell Squat tests. The authors are thankful to all participants of the study. The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

HAS, MDN, and HSA declare no conflicts of interest. AP has an independent-contractor agreement with Europharma USA and is head of the research and development company Phytomed AB. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Institutional Review Board Statement

Supplement 3.

Informed Consent Statement

Supplement 2.

Data Availability Statement

Data are included in the article and supplementary materials.

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