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Failure of *Rhodiola rosea* to alter skeletal muscle phosphate kinetics in trained men

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Abstract

Rhodiola rosea is an herbal supplement purported to improve resistance to stressors and to enhance physical performance, potentially by improving adenosine triphosphate (ATP) turnover. Phosphocreatine (PCr) kinetics serves as a reflection of ATP turnover. The purpose of this investigation was to examine the effect of *R rosea* ingestion on human skeletal muscle PCr recovery after exhaustive exercise. Twelve resistance-trained men, aged 19 to 39 years, completed incremental forearm wrist flexion exercise to volitional fatigue, once after ingesting 1500 mg *R rosea* per day for 4 days, and once after ingesting an equivalent placebo dose. During exercise and recovery from exercise, muscle phosphates were examined using phosphorus 31 nuclear magnetic resonance spectroscopy. [PCr] during recovery was fit with a monoexponential function, and the resulting rate constants (k) were compared between groups. Rating of perceived exertion per stage and time to exhaustion were also compared between groups. For *R rosea*, $k = 0.3744 \pm 0.1532$, whereas for placebo, $k = 0.3956 \pm 0.2238$. Although rating of perceived exertion significantly increased within groups as workload increased, it did not differ between conditions, nor did time to exhaustion (*R rosea*, 10.71 ± 0.54 minutes; placebo, 10.48 ± 0.68 minutes). Estimates of [PCr] at time 0, 5, 10, 15, and 20 minutes of recovery were nearly identical between groups. In summary, there were no significant differences between groups for any of the parameters measured. Based on these results, we conclude that *R rosea* ingestion does not improve ATP turnover during or immediately after exercise.

1. Introduction

Rhodiola rosea (Crassulaceae family) is an herb that grows in the mountainous and arctic regions of North America, Europe, and Asia [1]. Also known as Arctic root, rose root, and golden root, *R rosea* has been used in folk medicine, primarily to combat fatigue, in Eastern Europe, Scandinavia, and Asia for centuries [2]. *Rhodiola rosea* is unique among its genus in its possession of 3 glycosides, collectively known as rosavins. The presence of these rosavins is presumed to give *R rosea* its adaptogenic characteristics [1]. The first published investigations of an ergogenic effect of *R rosea* began to surface in the West in the late 1980s after the disintegration of the Soviet Union [1] and were overwhelmingly supportive of the notion that *R rosea* could enhance performance. More contemporary studies that investigated the ability effectiveness of *R rosea* to enhance exercise performance have produced somewhat mixed results. Several studies have indicated that it may yield such positive effects as improved cognitive function [3], reduced mental fatigue [2,4], improved free radical mitigation [5,6], and enhanced endurance performance [3,7,8].

Of particular relevance to the current investigation was the study produced by Abidov et al [7] wherein they observed an ergogenic effect of *R rosea* and proposed a mechanism by which it may occur. They found that rats treated with *R rosea* extract (50 mg/kg per day) significantly prolonged (by 24.6%) their swim time to exhaustion (TTE) compared with control rats. In their search for a potential mechanism, they measured adenosine triphosphate (ATP) content in isolated rat muscle mitochondria by bioluminescence assay before and after 6 consecutive days of

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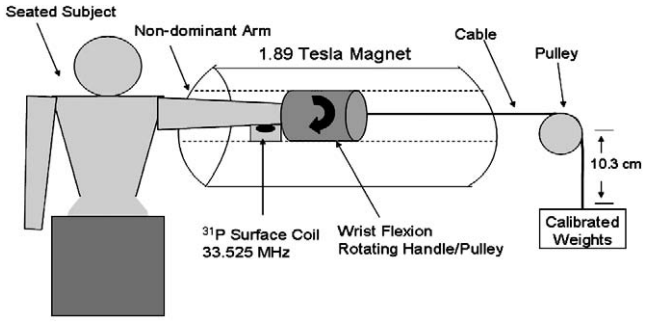

Fig. 1. Schematic of exercise apparatus.

exhaustive swimming. They reported that ATP content was significantly higher in treated rats than in controls both immediately after swimming on the sixth day (ATP was 4.85 ± 0.30 μmol/g in the treated rats vs 3.86 ± 0.40 μmol/g in the controls) and after an additional 24-hour rest period (5.22 ± 0.40 vs 4.69 ± 0.50 μmol/g.) They concluded that *R rosea* extract activated the synthesis or resynthesis of ATP in mitochondria and stimulated restorative energy processes after exercise. They did not discuss specific mechanisms by which such stimulation may have occurred, such as through its apparent antioxidation properties. However, their introduction of increased ATP turnover as a potential general mechanism was logical and compelling. Other studies have proposed mechanisms as varied as increased β-endorphin activity (8), reduced inflammation (7), and CNS stimulation (3) for an observed ability of *R rosea* to improve performance.

The purpose of the current study was to examine the effect of *R rosea* ingestion on human skeletal muscle ATP turnover as reflected by muscle phosphate kinetics after exhaustive exercise using phosphorus 31 nuclear magnetic resonance spectroscopy (^{31}P MRS). Secondary purposes were to compare TTE and rating of perceived exertion (RPE) during exercise between subjects after ingestion of *R rosea* vs after ingestion of placebo.

2. Methods

2.1. Subjects

Twelve male subjects, aged 19 to 39 years, participated in this study after completing an informed consent form approved by our institutional review board. All subjects had participated in resistance training for at least 6 months. Resistance-trained men were used because (*a*) larger forearm circumferences generally improve MRS signal and (*b*) they were accustomed to forearm wrist flexion exercise. None of the subjects had taken other herbal supplements or any form of supplemental creatine within 30 days of their trials. All subjects underwent a preliminary familiarization session before their trials to ensure correct arm placement in the magnet, exercise technique, and stable forearm and body postures during exercise.

2.2. Exercise protocol

After 5 minutes of rest signal collection, with their nondominant arm extended inside the bore of a 1.89-T superconducting magnet, subjects remained in place and performed seated incremental wrist flexion exercise to volitional fatigue. The subjects were not permitted to alter body position and/or type of contraction motion during increasing exercise intensities because that would have altered muscle recruitment profiles. The exercise apparatus (Fig. 1) was a cable-pulley system that consisted of a wooden handle at the end of a stretch-resistant nylon cable that extended into the magnet. The cable ran through a pulley system and was loaded with small, calibrated free weights attached to a carabiner. A wooden cage around the handle ensured it remained stationary except for moving in the prescribed range and angle of motion. This helped to minimize arm movement, as did the fact that the subjects' forearms were strapped in place to the mounting of the phosphorus peripheral coil within the magnet throughout exercise and recovery. Wooden stops on the cage restricted motion to 10.3 cm per repetition by the cage/handle apparatus. Subjects' ability to consistently hit the stops also served as a method by which to determine muscle exhaustion. Repetition timing to a predetermined concentric contraction, eccentric contraction, and relaxation cycle of 2, 1.5, and 0.5 seconds was aided by a custom computer program (LabVIEW, National Instruments, Austin, TX) that provided visual and auditory cues at the start of each contraction phase. Subjects began exercise with a load of 1.0 kg. Every 2 minutes, the load was increased by 1.0 kg. When a subject could no longer keep pace with the cues and/or could no longer hit the cage/handle stops, the exercise test was terminated. After test termination, subjects remained in their seated exercise posture, keeping their forearm within the magnet and motionless for 20 minutes of recovery.

2.3. ^{31}P nuclear magnetic resonance spectroscopy

For ^{31}P MRS, a 3.4-cm-diameter, 2-turn surface coil made of 14-gauge copper wire and mounted under a 3-mm acrylic sheet in a shielded probe was used. This probe sat in the bore of the 1.89-T magnet and the subject's forearm rested on the probe's acrylic sheet. A rubber washer was glued to the acrylic sheet immediately above the copper coil to provide tactile and visual (skin indentation) feedback to the subject and researchers regarding correct arm placement in the magnet and on the probe. ^{31}P spectra were acquired every second using radio frequency pulses of 40 microseconds at 32.525 MHz, with each free induction decay summed and averaged over 30-second intervals. Free induction decays were smoothed, Fourier transformed, phased, and fit with a 5-peak Lorentzian function using commercial spectral analysis software (OriginPro, Origin Lab, Northampton, MA) to resolve the area under the curve for each of free P_i, phosphocreatine (PCr), and each of the 3 ATP peaks. Resting muscle concentrations for ATP was

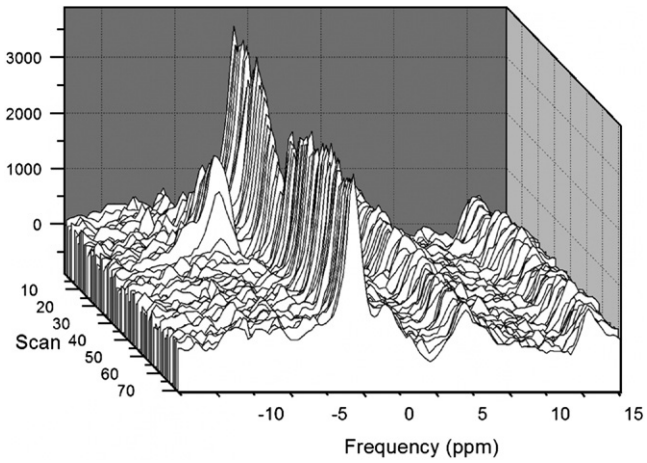

Fig. 2. Sample ^{31}P spectrum for 35-minute trial.

assumed to equal 5.5 mmol/kg wet weight. This amount was used to convert relative areas under the curve to metabolite concentrations. Muscle pH was determined by using the chemical shift change in the distance between P_i and PCr in a modified Henderson-Hasselbach equation [9].

2.4. Treatment

Subjects ingested 1500 mg *R rosea* in 3 divided doses or equivalent placebo per day for 3 days before the exercise test and 1000 mg the day of the test. The treatment (herb vs placebo) was administered in a randomized, double-blind fashion. Treatment trials were separated by at least 7 days and no more than 14 days. *R rosea*, standardized to 3% rosavins, was purchased commercially in powder form (Bali Herbal, Singapore) and transferred into 250-mg capsules. The quality/purity of the *R rosea* was verified by independent laboratory testing (Analytical Laboratories, Anaheim, CA). Placebo capsules containing wheat flour were indistinguishable from the treatment capsules.

2.5. Comparisons with other studies

We compared our PCr kinetics results to those of several studies that incorporated similar protocols. Comparisons were made using relative changes to resting [PCr] to avoid confusion over assumed resting metabolite levels.

2.6. Statistical analyses

Although trials were separated by at least 7 days, because of the lack of published information regarding the washout period of *R rosea* and because subjects were randomly given placebo vs *R rosea*, we included treatment order as a factor in our analyses. We compared results for TTE between treatments and treatment orders and compared RPE during exercise and PCr after exercise between treatments, times (0, 2.5, 5, 10, 15, and 20 minutes of recovery), and treatment orders in Greenhouse-Geisser repeated-measures analyses of variances. Analysis of variance assumptions of homoscedasticity and normality were tested and met.

[PCr] during recovery from exercise was plotted against time and fit with a monoexponential function (Y = [top − bottom][1 − exp(−kX)] + bottom) to attain a rate constant (k). The initial PCr resynthesis rate ($PCrrate_i$) was determined by calculating the amount of PCr resynthesized in the first second of recovery by using the exponential equation and multiplying that quantity by 60 to obtain $PCrrate_i$ in millimoles per kilogram per minute [10]. Paired-samples t test was used to compare constants and rates. An α level of .05 was used to denote significance for all statistical analyses.

Table 2
TTE between treatments and treatment order (n = 12)

	P-R	R-P
R	10.56 ± 0.46	10.31 ± 0.96
P	10.83 ± 0.58	10.44 ± 0.38

No significant differences were found at any level.

3. Results

Subject mean age was 29.92 ± 4.51 years, and mean height and weight were 1.84 ± 0.07 m and 89.58 ± 12.05 kg, respectively. All 12 subjects successfully completed both exercise trials. Fig. 2 provides an example of the ^{31}P spectrum throughout one entire 35-minute trial. However, the MRS signal for one *R rosea* trial was faulty and unusable. Because this was a repeated-measures design, the same subject's placebo trial MRS data were not used either. Therefore, n = 12 for TTE and RPE data, whereas n = 11 for phosphate data.

Rating of perceived exertion, shown in Table 1, increased over time for both treatments. However, there were no significant differences observed between treatments, nor did treatment order have a significant effect. Time to exhaustion (Table 2) did not differ between treatments and was not

Table 1
RPE ± SD for both treatments over time (n = 12)

	Time (min)				
	2	4	6	8	10
R	7.09 ± 0.70	10.91 ± 1.22	13.73 ± 1.56	16.09 ± 1.81	18.18 ± 1.54
P	7.09 ± 0.83	11.09 ± 1.30	13.55 ± 1.29	16.09 ± 1.76	18.10 ± 1.29

RPE for each time was significantly different than that for all other times for both treatments (P < .05). RPE between R and P was not significantly different at any time. R indicates *R rosea*; P, placebo.

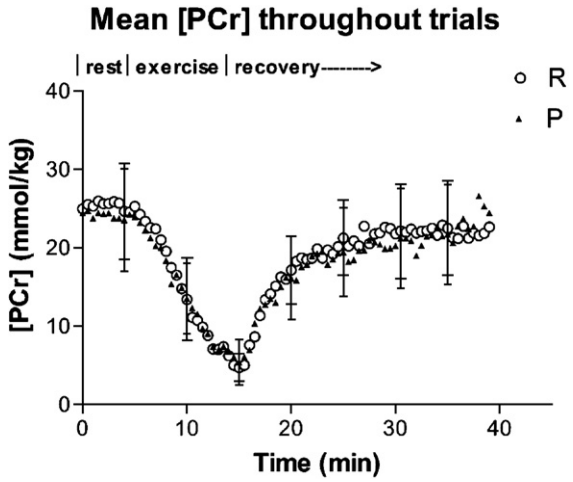

Fig. 3. [PCr] for both treatments for entire rest/exercise/recovery session.

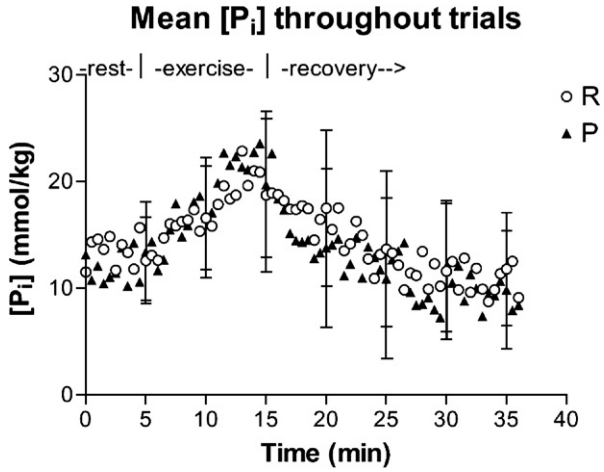

Fig. 5. Mean [P_i] for both treatments for entire rest/exercise/recovery session.

affected by treatment order. Mean TTE for the placebo trials was 10.48 ± 0.68 minutes, whereas mean TTE for the *R rosea* trials was 10.60 ± 0.36 minutes. Fig. 3 displays [PCr] means for both treatments for entire rest/exercise/recovery session and is intended to give a perspective on PCr kinetics during all 3 test phases. However, because exercise times varied (9.5-11.0 minutes), specific data points shown in this figure differ slightly and are less accurate than those shown in Fig. 4. Fig. 4 displays the data for [PCr] recovery for both treatments. Time "0" is the time that exercise stopped for each subject. There was no significant difference in rate constants, $k_P = 0.3956 \pm 0.2238$ and $k_R = 0.3726 \pm 0.1515$. Likewise, $PCrrate_i$ between trials was not significantly different: $PCrrate_i$ was 6.37 ± 0.60 mmol/kg per minute for *R rosea* and 7.11 ± 0.86 mmol/kg per minute for placebo. Figs. 5 and 6 illustrate concentrations of P_i and ATP, respectively, for both treatments throughout the entire rest/exercise/recovery session. There were no differences between treatments for either of those variables. Table 3 provides [PCr] at specific times throughout recovery. [PCr] increased significantly for both treatments from time 0 to 2.5 to 5 minutes. However, there were no significant differences observed between treatments at any time nor did treatment order have any significant effect on [PCr] between treatments.

Muscle pH (Fig. 7) did not differ between treatments. Muscle pH at the 30-second scan immediately after exhaustion was 6.69 ± 0.27 for *R rosea* and 6.71 ± 0.30 for placebo. Please note that bars representing SD are included in only 4 to 5 representative cases for all graph plots to improve readability. Table 4 displays PCr kinetics results along with those from similar studies.

4. Discussion

The primary finding from this investigation is that ingestion of *R rosea* failed to influence exercise performance

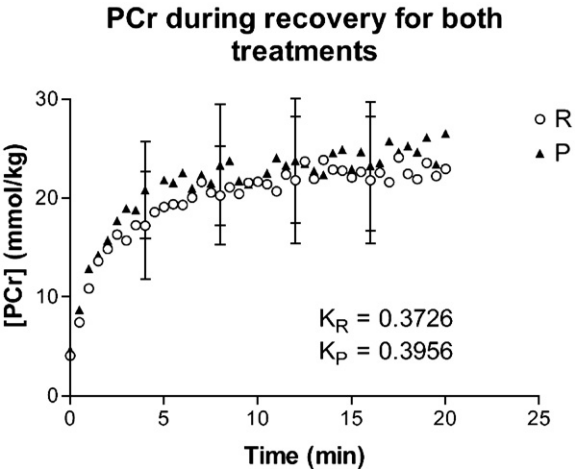

Fig. 4. [PCr] recoveries for both treatments (n = 11). R indicates *R rosea*; P, placebo.

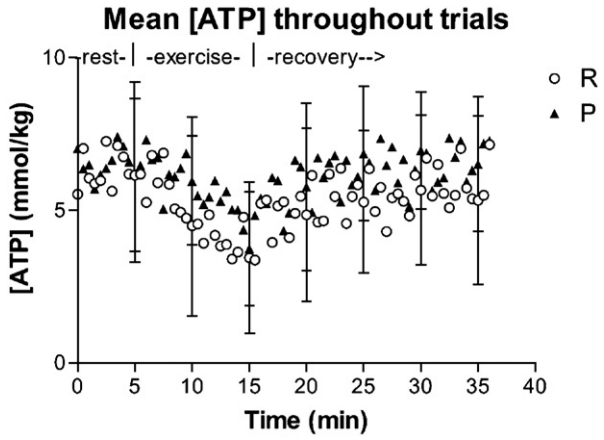

Fig. 6. Mean [ATP] for both treatments for entire rest/exercise/recovery session.

Table 3
PCr (mmol/kg) ± SD at rest and at specific times throughout recovery (n = 11)

	Time (min)					
	Rest	0.0	2.5	5.0	10.0	15.0
R	24.63 ± 6.45	4.07 ± 2.94	16.32 ± 5.53	19.10 ± 4.37	21.67 ± 5.68	22.28 ± 6.35
P	25.31 ± 6.12	4.64 ± 1.77	16.78 ± 6.52	21.33 ± 6.45	21.74 ± 4.66	22.93 ± 5.87

[PCr] at time = 0.0 differed from that at all other times for both treatments ($P < .05$). [PCr] at time = 2.5 differed from that at all other times for both treatments ($P < .05$). [PCr] between R and P was not significantly different at any time.

(as measured by TTE), perceived exertion, or muscle phosphate kinetics. These findings support those of Colson et al [16] and Earnest et al [17] who tested the effect of an herbal blend primarily composed of *Cordyceps sinensis* and *R rosea* on cycling exercise and found that it failed to impact performance or any associated physiologic variable, including heart rate, $V\dot{O}_2$, and lactate and ventilation thresholds. However, our results are at odds with the conclusions of other investigators [3,7,8] who reported observing an ergogenic effect of *R rosea* ingestion.

Abidov et al [7] reported significantly higher postswim [ATP] in rats after 6 days of *R rosea* supplementation. We saw no evidence of such an effect. Resting, during-exercise, and recovery ATP and PCr levels did not differ between treatment groups at any time. One potential reason for the discrepancy could be the difference in dosages. The Abidov et al rats ingested 50 mg/kg per day. Matching that dosage would have resulted in our subjects receiving more than 4000 mg/d. We were not comfortable giving such a large dose because of unlikely but potential central nervous system stimulation actions. However, our dosage far exceeded the manufacturer's recommended amount and was 100% to 400% greater than that used in most other human studies [3,8,16,17]. Only Wing et al [6] administered a higher dosage (1778 mg/d) to human subjects. Whereas Abidov et al physically assayed ATP content, we used ^{31}P MRS to determine ATP turnover. Of course, it is well established that ^{31}P MRS accurately reflects ATP turnover from mitochondrial respiration [18,19]. Based on our results, *R rosea* does not affect ATP turnover during or after exercise.

Rhodiola rosea ingestion also failed to impact perceived exertion levels during exercise. DeBock et al [8] found a significantly higher TTE during an incremental cycle ergometry test for subjects who had received a single 200-mg dose of *R rosea* than for those who received a placebo. They speculated the difference was due to increased β-endorphin synthesis, transport, or receptor activity that allowed subjects to tolerate a higher intensity of exercise. Their supposition was based on 2 Russian studies [20,21] that reported increased opioid activity in rats after *R rosea* administration. The results of the current study refute that thesis. Our subjects failed to note any comfort or exertion difference between treatments during the exercise trials at any time.

Admittedly, there were some potential limitations to our ability to observe an effect of *R rosea* on our measured variables. Because of the size of the magnet bore, we isolated the forearm, particularly the palmaris longus and flexor carpi radialis. This is in contrast to the larger muscle masses used in swimming [7] and cycling [3,8] studies that observed an effect. It is possible that the primary ergogenic action of *R rosea* is to reduce central fatigue. Such an action would likely not be observed in our test of an isolated small muscle group. However, it should be noted that other studies that used cycling tests [16,17] failed to observe an effect of *R rosea*.

Other potential limitations stem from the fact that phosphate kinetics may be significantly affected by pH [13], fiber type [22], and oxygen availability [23]. Therefore, subject characteristics of aerobic capacity and fiber type distribution, muscle(s) tested, and intensity and duration of exercise can alter phosphate responses. However, because the current study used a crossover design, subject characteristics were not a limitation. Nor, obviously, were there differences in exercise protocols between treatments. Lastly, pH immediately after exhaustion was not different between treatments. However, because resistance training improves phosphate kinetics during exercise and recovery, it is possible that although *R rosea* ingestion did not alter phosphate kinetics in the resistance-trained men used in this protocol, it may, in fact, alter phosphate kinetics in untrained subjects.

Because of the wide variation of protocols and subjects that have been used in previous research and the factors influencing phosphate kinetics mentioned above, it is

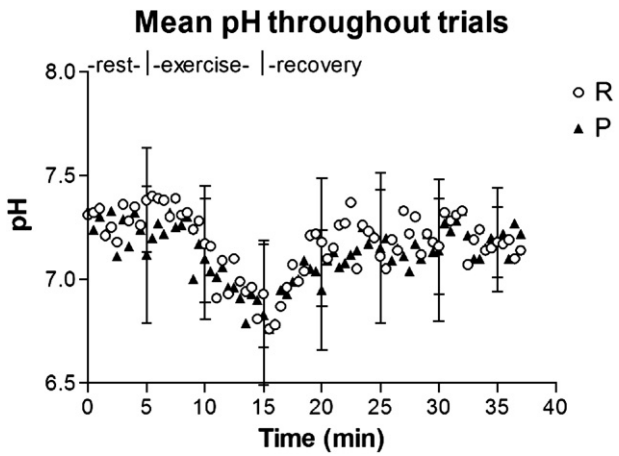

Fig. 7. Mean muscle pH throughout entire trial.

Table 4
Comparisons of PCr kinetics: multiple studies

Author(s)	Protocol	Subjects	PCr			Lowest pH
			End exercise	5 min recovery	10 min recovery	
Walker (this study)	11 min incremental forearm	Trained	0.25	0.74	0.81	6.70
McCann et al [11]	250 s forearm light	Untrained	0.77	1.00	NA	7.01
McCann et al [11]	250 s forearm heavy	Untrained	0.33	0.88	NA	6.92
Roussel et al [12]	6 min forearm HF	Untrained	0.34	0.89	0.95	6.45
Roussel et al [12]	6 min forearm low frequency	Untrained	0.61	0.95	0.98	6.83
Arnold et al [13]	4.5 min forearm light	NA	0.43	0.94	1.00	6.88
Arnold et al [13]	2.5 min forearm heavy	NA	0.26	0.77	0.90	6.23
Park et al [14] [a]	18 min incremental forearm	Elite	0.42	0.85	NA	6.94
Park et al [14] [a]	18 min incremental forearm	Untrained	0.37	0.74	NA	6.68
Brosseau et al [15]	3 × 1 min forearm at 60% MVC	Untrained	0.16	0.86	0.97	6.25

PCr values were expressed as a fraction of [PCr] at rest. NA indicates not available; MVC, maximal voluntary contraction.
[a] Recovery measured at 3 minutes, not 5.

difficult to compare phosphate kinetics in this study with those observed in other studies. Another factor contributing to this difficulty is the mathematical function used to define PCr recovery rate. Previous studies have used various monoexponential, biphasic (linear and exponential), and linear (over initial 15-60 seconds of recovery) functions in this effort. McMahon and Jenkins [24], in a recent review, concluded that PCr recovery is best described by a monoexponential function when pH has not been significantly reduced but that because the latter stages of PCr recovery are affected by a significant reduction in pH, a biexponential function is a better fit in such circumstances. We chose to use a monoexponential function to define PCr recovery after fitting data with both monoexponential and biexponential functions and finding significantly higher R^2 values and lower and Sy.x values with the monoexponential fit. Despite these confounds to direct comparisons, some general comparisons may still be needed to validate the results of the current study and to provide further insight into the factors governing phosphate kinetics. To avoid the confusion introduced by potentially differing [ATP] assumptions and different functions used to analyze rates, our comparisons were of relative changes in PCr.

Our exercise protocol reduced [PCr] to approximately 25% of rest. This is in line with the results of studies of similar muscles and with similar durations and/or intensities to include the high-frequency (HF) group in the study of Roussel et al [12] and the heavy group in the study of Arnold et al [13], although [PCr] in the elite runners in the study by Park et al [14] only fell to 42% of resting despite a longer duration protocol. The difference in endurance capacity between our subjects and theirs is the most likely reason for the discrepancy. It is logical to conclude that the lower exercise intensities, as demonstrated by their higher minimum pHs, in the Roussel et al low-frequency protocol, McCann et al [11] light-intensity protocol, and Arnold et al light-intensity protocol caused their end exercise [PCr] to be substantially higher and recoveries to be faster than those for higher-intensity protocols. Our subjects' [PCr] at 5 minutes of recovery was similar to that of the heavy group of Arnold et al and the control (nonelite) group of Park et al. The apparent outlier was the Roussel et al HF group. This is surprising, as the low pH (6.45) attained by the Roussel et al HF group would have been expected to delay PCr recovery. Our subjects' PCr recovery at 10 minutes of recovery appears to be slightly less complete than others'. A potential explanation for these 2 discrepancies could stem from postural position differences between studies. Postural differences could affect oxygen delivery. Our subjects maintained their seated exercise posture with their arm extended laterally at nearly 90° for a passive recovery. Unfortunately, most studies have not provided a precise description of posture during exercise and recovery. For the studies included within these comparisons, only Arnold et al [13] described posture. Their subjects lay on a bed with arms abducted at 90° during exercise and recovery. An investigation as to the potential effects of postural differences on PCr recovery may be warranted. Specific to the current study, there were no postural differences between treatments.

Because of the validity, sensitivity, and high temporal resolution of our methods, we remain confident of our ability to observe differences in our measured variables between treatments if they were to exist. Therefore, we conclude that short-term *R rosea* ingestion does not affect incremental wrist flexion exercise performance, perceived exertion during such exercise, or muscle phosphate kinetics during or after such exercise in resistance-trained men. Whether *R rosea* might affect other physiologic parameters associated with exercise or other subject populations remains to be investigated.

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