ORIGINAL ARTICLE

Dietary Supplement with a Combination of Rhodiola Crenulata and Ginkgo Biloba Enhances the Endurance Performance in Healthy Volunteers*

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ABSTRACT **Objective:** To determine whether the ingestion of a herbal supplement called Rhodiola-Gingko Capsule (RGC) would enhance the endurance performance of healthy volunteers and change relevant hormones in a favorable manner. **Methods:** Seventy healthy male volunteers (age ranges from 18 to 22 years old) were randomly assigned to RGC group (35 cases, each capsule containing 270 mg herbal extracts, 4 capsules per day) or placebo group (35 cases, equivalent placebo preparation) for 7 weeks using computer-produced digital random method. The endurance performance, serum testosterone and cortisol levels were measured at the baseline and the endpoint. **Results:** Sixty-seven subjects (34 in the RGC group and 33 in the placebo group) completed a 7-week treatment. The RGC group displayed a significantly greater baseline-to-endpoint increase in maximal oxygen uptake (VO_{2max}) than placebo group in both absolute (P=0.020) and relative values (P=0.023). At the endpoint, the serum cortisol level was unchanged in the RGC group compared with the baseline, but it was significantly elevated in the placebo group (P<0.05). The endpoint ratio of testosterone to cortisol, a surrogate for overtraining and fatigue in endurance exercises, was also indifferent compared with the baseline in the RGC group, but significantly decreased in the placebo group (P<0.05). **Conclusion:** The combined herbal supplement of Rhodiola and Gingko could improve the endurance performance by increasing oxygen consumption and protecting against fatigue.

KEY WORDS herbal supplement, endurance, maximal oxygen uptake, cortisol, testosterone, clinical trial

A major challenge of contemporary sports medicine is to maintain and improve athletic performance in training and competition. For this purpose, researchers have paid great attention to herbal medicines purporting to possess physical and mental performance-enhancing potentials in ancient pharmacopoeias(1). Meanwhile, a growing number of herbal supplements for improving strength and endurance performance have been introduced to athletes in various sports(1). However, the efficacy and safety of most such supplements have not yet been evaluated with rigorous trial protocols(1,2). Rhodiola and *Ginkgo biloba* are two representative plants having ergogenic and adaptogenic effects, and numerous the single or the combined herbal products prepared have been available commercially(3-5).

Rhodiola is a high-altitude growing plant and there are about 200 species, including *R. rosea* and *R. crenulata*(4,6). Salidrosides are major bioactive constituents identified from the plant and frequently used as references for determination of the quality of the preparations(4,6). Rhodiola is traditionally used by local people to vitalize energy, enhance the work performance, alleviate physical and psychological stress, and prevent mountain sickness(4,5,7). Indeed, animal studies have shown that administration with *R. rosea* and *R. crenulata* extracts prolonged the duration of exhaustive swimming of rats(4,8). However, these effects of Rhodiola preparations have not yet been well confirmed in human subjects, as evidenced by apparently inconsistent results reported in previous studies(9-18). On the other hand, *Ginkgo biloba* also has been extensively used for athletic performance-enhancing purpose(19). Also it is used as a memory enhancer for cognitive impairment and dementia(3,20). Several studies have shown that *Ginkgo biloba* supplements could effectively prevent acute mountain sickness(21,22) and improve maximal

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and pain-free walking distance in patients with intermittent claudication(23), although similar effects were not observed in patients with peripheral arterial disease(24,25). The beneficial effects of *Ginkgo biloba* products are believed to be associated with the actions of their bioactive constituents (mainly flavonoid glycosides) in protecting against the deformation of erythrocytes and modulating energy synthesis(19).

These observations have led to the hypothesis that dietary supplements with a combination of *Rhodiola crenulata* and *Ginkgo biloba* could yield superior endurance performance by improving oxygen consumption and protecting against fatigue. To test this hypothesis, a double-blinded, randomized, placebo-controlled study was designed to determine whether the ingestion of a combination preparation of the two herbs called Rhodiola-Gingko Capsule (RGC) would improve the endurance performance and relevant hormones surrogate in healthy volunteers.

METHODS

Subjects and Estimation of the Sample Size

The study was conducted in Shanghai University of Sports from November 2007 to January 2008 and the protocol was approved by Medical Ethical Committee of the University Orthopaedics and Traumatology Hospital in conformity with the Declaration of Helsinki and its subsequent amendment. The written informed consent was obtained from each subject before entering the study. College male students who met the following criteria were recruited in the study: (1) aged from 18 to 22 years old; (2) had moderate-intensity exercises in a regular manner; and (3) whose maximal oxygen uptake (VO_{2max}) and body mass index (BMI) were 47-75 mL/(min·kg) and 18.5-26.0 respectively. The excluded from this study were those who had unstable medical conditions, or a history of alcohol, or substance abuse within 1 year prior to the study, or allergies to herbal medicines or were currently under herbal or conventional medications.

The present study was intended to detect a minimum 25% difference between RGC and placebo-ingested groups in the baseline-to-endpoint change of VO_{2max}, with a power (1-β) = 90% and a two-side level of α = 0.05. Nearly 70 subjects were needed with the consideration of 15% dropouts. So a total of 70 subjects were recruited for the study. Seventy subjects selected from 480 candidates were randomly and equally assigned to the placebo group or RCG group in the ratio of 1:1 using computer-produced digital random method, 35 subjects in each group. One subject assigned to placebo was removed from data analysis because his age (only 17 years old) did not reach the criterion. Two subjects allocated to RCG were excluded due to his BMI value (26.4), higher than the criterion and incomplete endurance exercise tests, respectively. Over 83% participants in each group reported that they had 1-2 h exercises and 6-8 h sleep daily during the study. Almost all the participants of the two groups defined as their dietary pattern for mixed vegetable and meat. There were no significant differences in terms of age, height, body weight, or BMI between the two groups (Table 1).

Table 1. Demographic Characteristics of Subjects ($\bar{x} \pm s$)

Group	Case	Age (year)	Height (cm)	Weight (kg)	BMI
Placebo	34	20.0 ± 1.3	175.7 ± 4.6	67.2 ± 7.1	21.7 ± 1.7
RGC	33	19.9 ± 1.0	174.7 ± 4.5	65.2 ± 6.1	21.3 ± 1.9
P value		0.748	0.367	0.223	0.379

Preparation of RGC and Placebo

The RGC preparation and equivalent placebo used in the study were specifically manufactured by Integrated Chinese Medicine Holdings Ltd., Hong Kong, China. For RGC preparation (batch number: 071001), the extraction of *Rhodiola crenulata* and *Ginkgo biloba* leaves in a ratio of 9:1 in dry weight were processed according to Pharmacopoeia of the People's Republic of China, 2005 Edition(26). The extracted powder was encapsulated into dark orange, nontransparent capsules each containing 270 mg mixed extractives. The placebo (batch number: 071002) was prepared with specific starchy powder having similar taste and smell in capsules, identical to the active capsules in shape, size, and color.

Since salidrosides and flavonoids are major constituents of *Rhodiola crenulata* and *Ginkgo biloba*(4,6,19) respectively, the contents of the two constituents contained in the active capsules measured with high-performance liquid chromatography (HPLC) were 23.80 mg/g and 12.55 mg/g extracted powder respectively, much higher than the requirements of the Pharmacopoeia(26). Heavy metals, contaminants and adulterants were tested by the China Doping Control

Center of the National Research Institute of Sports Medicine at the State Sport General Administration and all substances tested were undetectable.

Study Design and Procedures

The participants were received RGC or placebo supplement in a double-blinded fashion for 7 weeks. All the participants were required to come to the dispensing center to take 4 capsules per day (2 after breakfast and 2 after supper) by swallowing with water but not biting or chewing under dispensers' witness and capsule counts taken were recorded in the log for calculating the compliance. Adverse events and blinding adequacy were examined with an end-of-study questionnaire.

Endurance Exercise Tests

The tests consisting of a 30-s fixed workload test and a maximal incremental test were conducted at the baseline and the endpoint. The subjects were instructed to avoid strenuous exercises for 24 h before each test session and arrived at the exercise testing laboratory in the rested and fully hydrated state. Food, caffeine, and alcohol intake were prohibited for 3 h before testing. The laboratory was maintained at 19-21 ℃ of room temperature under 40%-60% of relative humidity during the exercise testing. Each subject was tested at the same time of testing days in the baseline and the endpoint to control circadian and diurnal influences.

The 30-s fixed workload test was conducted on a cycloergometer (Monark 834, Varberg, Sweden) to measure parameters associated with the power output as previously described[27]. Briefly the test started with a warm-up without workload, through which 150-160 beat/min of heart rate was required to be achieved (3-5 min). Following this warm-up, subjects performed maximal cycling exercise with a fixed workload equal to 75% of body weight for 30 s. Maximal power output (W_{max}), minimum power output (W_{min}), mean power output (W_{mean}) and drop rate of the power output (W_{drop}) were measured based on a 5-s interval data record.

About 30 min after the completion of the fixed workload test, the subjects started the maximal incremental test. Time to exhaustion (Te) and absolute VO_{2max} were directly measured in the test, and the relative VO_{2max} was calculated with body weight divided by absolute VO_{2max}. The test was conducted on a motorized treadmill running machine (h/p/cosmos, Germany) using a standard Bruce Protocol[28]. Briefly the slope of the treadmill was set at 10% with a speed of 1.7 m/h in the initial 3 min of the test. The two parameters were then increased by 2% and by 0.5-0.9 m/h every 3 min, respectively. The gas exchange of subjects' breath was analyzed continuously using an automatic gas exchange analyzer (Max Ⅱ, USA) through a facemask. The heartbeat was measured using a wireless heart rate monitoring method (Polar, Sweden). The test was stopped and Te and VO_{2max} were recorded till any two of the following maximal criteria occurred as previously described[27]: VO_2 plateau, respiratory exchange ratio (RER) > 1.15, or heart rate > 180 beat/min; or when the subject was exhausted and could not maintain the imposed treadmill speed.

Determination of Serum Testosterone and Cortisol Concentrations

Resting cortisol and the ratio of testosterone to cortisol are valid indices in reflecting overtraining and fatigue during exercises[29,30]. In order to detect the effects of the supplement on these hormone indices, two 8 mL blood samples were collected under the resting condition in the morning (7:00-8:00 AM) before meals at the baseline and the endpoint respectively. Sera was immediately separated and stored at -80 ℃ for assay. Serum concentrations of testosterone and cortisol were measured using radioimmunoassay and the ratio of testosterone to cortisol was calculated. In order to exclude inter-assay variations, all samples were processed in one batch with the same assay kit under the same condition.

Statistical Analysis

Baseline-to-endpoint changes in endurance variables were used for statistical analysis. Baseline variables were analyzed using Student *t*-test. Two-way repeated measure analysis of variance (ANOVA) was used to detect time-by-treatment interactions, treatment and time effects. Students-Newman-Keuls method was further applied to detect differences between the two groups if interactions reached a significant level. Data were expressed as mean ± standard deviation. All tests were two-sided and statistical significance was defined as $P<0.05$.

RESULTS

General Condition

The mean compliance rate exceeded 96%

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during the 7-week study. The blinding adequacy was high, with 83% placebo-ingested and 88% RGC group who did not know which capsule they took or guessed wrongly.

Effects on Endurance Exercise Parameters

The baseline endurance exercise variables were similar between the two groups. Significant time-by-treatment interactions were observed on baseline-to-endpoint changes in absolute VO_{2max} (F=3.817, P=0.024) and relative VO_{2max} (F=3.616, P=0.030), but not on Te (F=2.908, P=0.093), W_{max} (F=0.001, P=0.966), W_{min} (F=0.067, P=0.796), W_{mean} (F=0.021, P=0.886), and W_{drop} (F=2.563, P=0.114) (Table 2). Moreover, both treatment and time factors had significant effects on baseline-to-endpoint changes in absolute VO_{2max} (treatment: F=5.692, P=0.020; time: F=11.043, P=0.001) and relative VO_{2max} (treatment: F=5.461, P=0.023; time: F=9.840, P=0.003). Post hoc between-group comparisons further revealed that RGC group had a significantly greater baseline-to-endpoint increase in absolute and relative VO_{2max} (P<0.001).

Effects on Fatigue-Related Hormone Indices

The effects on serum testosterone, cortisol levels and their ratios were shown in Figure 1. The two groups of subjects had similar baseline of testosterone (t=0.329, P=0.743), cortisol (t=1.189, P=0.239), and ratio (t=1.758, P=0.083). ANOVA analysis revealed significant time-by-treatment interactions on cortisol (F=10.120, P=0.002) and the ratio (F=6.422, P=0.014), but not testosterone (F=0.359, P=0.551). The time factor had significant effects on cortisol (F=10.845, P=0.002) and the ratio (F=5.096, P=0.027), but the treatment factor did not (cortisol: F=0.411, P=0.524; ratio: F=0.034 P=0.855). Post hoc between-group comparisons further showed that the endpoint cortisol level was significantly higher and the ratio was significantly lower than baseline values in the placebo group ($P\leqslant$0.029), but the two indices were unchanged at the endpoint from baseline in the RGC group ($P\geqslant$0.294).

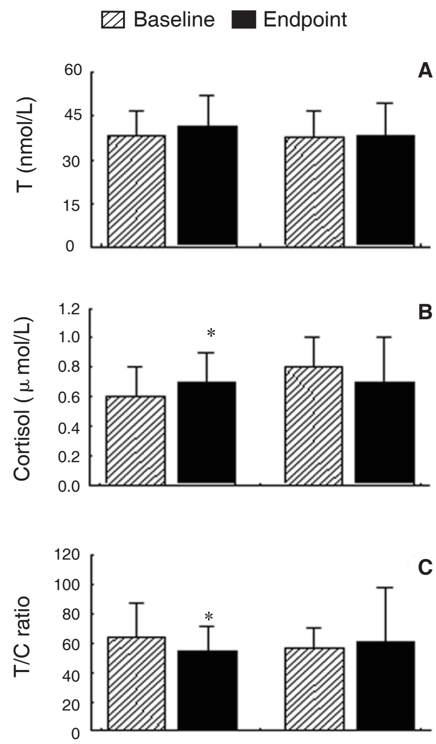

Figure 1. Effects of 7-week Supplement with Placebo and RGC on Testosterone, Cortisol, and T/C Ratio from Baseline to Endpoint

Notes: A: testosterone (T); B: cortisol (C); C: T/C ratio; *P< 0.05, compared to the baseline values

Incidence of Adverse Events

There were 9 subjects (4 in placebo and 5 in RGC) who experienced transient sleepiness in the initial phase of treatment. No other adverse events were reported.

Table 2. Effects of 7-week Supplement with Placebo and RGC on Changes in Endurance Exercise Tests in Healthy Volunteers ($\bar{x}\pm s$)

Group	Case	Item	Te (s)	Absolute VO_{2max} (mL/min)	Relative VO_{2max} (mL/min)	W_{max} (W/kg)	W_{min} (W/kg)	W_{mean} (W/kg)	W_{drop} [W/(s•kg)]
Placebo	34	Baseline	801.6±71.7	4141.8±415.8	62.0±6.1	10.1±1.7	5.8±0.9	7.7±0.7	0.2±0.1
		Endpoint	791.8±55.0	4188.2±384.5	62.4±5.0	10.1±1.5	5.5±0.8	7.5±0.9	0.2±0.1
		Change	-9.7±38.2	46.3±449.5	0.4±6.4	0.0±1.6	-0.3±1.0	-0.2±0.7	0.0±0.2
RGC	33	Baseline	794.1±65.1	3951.3±461.8	59.5±6.5	10.0±0.8	5.5±0.9	7.6±0.5	0.1±0.1
		Endpoint	804.4±50.3	4233.1±480.6	63.4±4.6	10.1±1.2	5.2±0.3	7.4±0.5	0.2±0.1
		Change	10.3±46.2	281.8±350.9*	3.9±5.2*	0.0±1.5	-0.3±1.0	-0.2±1.0	0.0±0.1

Note: *P<0.05, compared with the placebo group

DISCUSSION

The present study represents a methodologically rigorous investigation evaluating safety and efficacy of the herbal supplement prepared from a combination of *Rhodiola crenulata* and *Ginkgo biloba* in improving the endurance exercise performance. In order to heighten the sensitivity of the study protocol, a highly uniform population was defined, characterized by the same gender, similar demographic, exercise, dietary and sleep patterns. The study protocol also showed the high validity in the maintenance of blind conditions (⩾83%) and adherence (>96%).

In the present study, we found that the ingestion of RGC for 7 weeks resulted in the significant greater increase of both absolute and relative VO_{2max} compared with the placebo, although the time to exhaustion and power output indices were unaffected, indicating the effectiveness of RGC in improving the endurance performance. Moreover, the present study demonstrated that, while the placebo group displayed the significantly increased blood cortisol and the significantly decreased ratio of testosterone to cortisol under the resting condition, the two hormone indices remained unchanged in the RGC group. It is well-known that cortisol excess and a decreased ratio of testosterone to cortisol represent valid surrogates for overtraining and fatigue in endurance exercises[(29,30)]. Therefore, the study results suggest that RGC may possess a capacity against fatigue caused by overtraining and the enhancement of the endurance performance may be associated with this protective effect to increase oxygen consumption.

The previous studies also have shown similar effects of the single herbal preparation of *R. rosea* in increasing pulmonary ventilation and physical capacities[(4)]. However, unlike the previous studies[(4)], the present study used the combination formula of *R. crenulata* and *Gingko biloba*. While various *Ginkgo biloba* preparations, especially the standardized extract EGb 761, have been shown to be effective in improving memory[(3,20)], several studies have demonstrated that treatment with *Ginkgo biloba* extracts also enhanced physical performance by increasing walking distances and times in the patients with intermittent claudication[(23,31)]. Moreover, like Rhodiola preparations, pretreatment with *Gingko biloba* extracts significantly reduces the incidence and severity of acute mountain sickness[(21,22,32)]. Based on these observations, it might be postulated that the significant improvement on both absolute and relative VO_{2max} observed in the RGC group in the present study seems to be, at least in part, attributed to additive or synergic effects of *Ginkgo biloba.*

Nevertheless, there have been several studies failing to achieve positive outcomes with the single or the combined preparations of *R.* rosea on endurance exercise tests, hypoxemia, and oxidative stress[(10,14,18)]. Despite difficulties in comparing the results of the present study with the previous studies, apparent differences in species of Rhodiola, supplement formula, duration of treatment, definition of population, and size of samples should be taken into account in explaining the discrepancy of the results.

Although little is known about the mechanisms of exercise-performance enhancing actions of most herbal supplements[(1)], *in vitro* studies have shown that pretreatment with Rhodiola extracts, the major constituent salidroside, and *Ginkgo biloba* extract (EGb 761) can effectively protect against the damage of human erythrocytes induced by various oxidative stresses[(33-38)]. More interestingly, the treatment with *R. crenullata* extract can activate the synthesis and resynthesis of ATP in mitochondria and stimulate reparative energy processes after intense exercise in the rat skeletal muscles[(39)]. Thus, the increased oxygen consumption produced by RCG supplement observed in the present study may be related to its protection of erythrocytes and the maintenance of energy synthesis.

In addition, there was no incidence of significant adverse events occurring during the study, except transient sleepiness experienced in few subjects. The quality of RGC preparation used in the present study also met the requirements. Despite these, some limitations of the current study should be addressed. Firstly, the sampling frame was restricted to young healthy males, who obviously have distinctive physical and psychological characters. Whether the effects of RGC observed in the present study could also be achieved in other populations, particularly in females and elders, may need to be further examined. A recent study has failed to observe positive effects of *Ginkgo biloba*-containing dietary supplement on cognitive functions in healthy older adults[(40)]. Secondly, although single-point peak cortisol and the ratio of testosterone to cortisol measured in the morning can basically reflect the endurance-related status[29,30], the multiple-point measurement could represent the changing course of hormones and may deserve to be further investigated.

In summary, the present findings have provided evidence supporting the use of *Rhodiola crenulata* and *Ginkgo biloba* combined supplement for improving the endurance performance by increasing oxygen consumption and protecting against fatigue.

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