Running Economy and Maximal Oxygen Consumption After 4 Weeks of Oral *Echinacea* Supplementation

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Abstract

Whitehead, MT, Martin, TD, Scheett, TP, and Webster, MJ. Running economy and maximal oxygen consumption after 4 weeks of oral *Echinacea* supplementation. *J Strength Cond Res* 26(7): 1928–1933, 2012—The purpose of this investigation was to determine the effects of 4 weeks of oral *Echinacea* (ECH) supplementation on erythropoietin (EPO), red blood cell (RBC) count, running economy (RE), and $\dot{V}O_2$max. Twenty-four men aged 24.9 ± 4.2 years, height 178.9 ± 7.9 cm, weight 87.9 ± 14.6 kg, body fat 19.3 ± 6.5% were grouped using a double-blind design and self-administered an 8,000-mg·d^{-1} dosage of either ECH or placebo (PLA) in 5 × 400 mg × 4 times per day for 28 days. Blood samples were collected and analyzed for RBCs and EPO using automated flow cytometery and enzyme-linked immunosorbent assay. Maximal graded exercise tests (GXTs) were administered to measure $\dot{V}O_2$max, RE, and heart-rate responses. Analysis of variance was used to determine statistically significant differences ($P \leq 0.05$). The EPO increased significantly in ECH at 7 days (ECH: 15.75 ± 0.64, PLA: 10.01 ± 0.73 mU·ml^{-1}), 14 days (ECH: 18.88 ± 0.71, PLA: 11.02 ± 0.69 mU·ml^{-1}), and 21 days (ECH: 16.06 ± 0.55, PLA: 9.20 ± 0.55 mU·ml^{-1}). $\dot{V}O_2$max increased significantly in ECH (ECH: 1.47 ± 1.28, PLA: −0.13 ± 0.52%). Running economy improved significantly in ECH as indicated by a decrease in submaximal $\dot{V}O_2$ during the first 2 stages of the GXT (stage 1: ECH −1.50 ± 1.21, PLA 0.60 ± 1.95%; stage 2: ECH −1.67 ± 1.43, PLA 0.01 ± 1.03%). These data suggest that ECH supplementation results in significant increases in EPO, $\dot{V}O_2$max, and running economy.

Key Words nutrition, exercise physiology, exercise performance, supplement

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Introduction

Echinacea (ECH) is a herbal supplement derived from the North American Purple Coneflower plant that is generally used as a nonspecific immunostimulant. Evidence from animal models (11,22) and cell cultures (6,21,26) indicates that ECH supplementation may also stimulate the production of erythroid growth factors, induce erythropoiesis, and increase the oxygen transport capacity of the blood. *Echinacea* supplementation in humans (3,200 g·d^{-1} for 30 days) resulted in a 5% "nonsignificant" increase in maximal oxygen consumption ($\dot{V}O_2$max) in untrained subjects (27). Another investigation reported that ECH supplementation (1,000 mg·d^{-1} for 42 days) resulted in an increase in the number and size of red blood cells (RBCs), hemoglobin (Hb), and hematocrit in an animal model (22). One explanation to account for the *Echinacea*-induced erythrocythemia and $\dot{V}O_2$max is an increase in serum erythropoietin (EPO) and other erythropoietic growth factors.

Red blood cells develop from stem cells after stimulation by several growth factors including EPO, interleukin-3, and granulocyte macrophage–colony-stimulating factor. Red blood cell production is thought to be regulated within limits such that an adequate concentration of RBCs is maintained to provide sufficient tissue oxygenation while simultaneously not promoting excessive hemoconcentration. The accepted mechanism for the regulation of EPO production is based on oxygen concentration of the blood and is increased by any condition that results in a decrease in the quantity of oxygen transported in the blood to the tissues.

Evidence indicates that an increase in circulating RBCs (hypercythemia) can result in improved exercise economy during submaximal cycling and running (16,23). An improvement in running economy (RE) has been defined as a reduction in the energy cost of submaximal running evaluated through the measurement of oxygen consumption during steady-state exercise (16,23). Potential mechanisms for improved submaximal RE ensuing from hypercythemia are an increase in the quantity of adenosine triphosphate (ATP) produced per mole of oxygen consumed, a decrease in the amount of ATP

necessary for running at a given speed, or a combination of both mechanisms (16,23). A secondary adaptation resulting from hypercythemia is a reduction in the heart rate (HR) for a given submaximal running speed. An increase in the oxygen transport capacity of the blood could result in a reduction in the cardiac output required for a given submaximal running speed. Because cardiac output is the product of HR and stroke volume, a decrease in HR might occur subsequent to an increase in the oxygen transport capacity of the blood.

To date, no studies have been performed with recreationally trained human subjects that have evaluated the effects of oral ECH supplementation on oxygen transport capacity and uptake during submaximal exercise. Thus, the purpose of this investigation was to determine the effects of 4 weeks of oral ECH supplementation on serum EPO, RBC, $\dot{V}O_2$max, and RE as evaluated by $\dot{V}O_2$ and HR responses during submaximal treadmill running in human subjects.

Methods

Experimental Approach to the Problem

The objective of this investigation was to determine whether oral ECH supplementation would result in an increase in EPO and a resultant improvement of oxygen use capacity. To this end, a total of 24 participants were grouped and supplemented with either ECH or placebo (PLA) for 28 consecutive days. The first 12 participants in each cohort were randomly assigned, whereas participants 13–24 were grouped in a balanced manner based on baseline RBC count by an individual not involved in the data collection for this project to prevent initial between-groups differences in hematological parameters. The study design and timetable of measurements are presented in Figure 1. Data for this study were collected between March and June. The participants were asked to abstain from strenuous physical activity, alcohol, and caffeine for 48 hours before all the testing sessions. The participants first reported to the laboratory to complete preliminary testing before beginning supplementation that included a blood sample for group assignment; 3-day diet and physical activity recall; measurement of height, mass, body composition; and a graded exercise testing familiarization session. The participants were asked to repeat patterns obtained from diet and physical activity recall each week for the 3 days before data collection and not to make any deviations from normal diet and physical activity patterns during the course of the study. Seven days later, the participants came to the laboratory and had a blood sample taken, performed a graded exercise test (GXT) protocol, and were given supplements to take for the next 7 days. The subjects then reported to the laboratory weekly for the next 3 weeks and had subsequent blood samples taken and were given supplements for the next week. After the 28 days of supplementation, the participants reported to the laboratory at approximately the same time of the day to complete the testing, which included a final blood sample and GXT. Blood samples were analyzed for EPO and RBC, and submaximal and maximal $\dot{V}O_2$ responses were measured during the GXTs. All the variables were analyzed between the groups during each of the 4 weeks of the supplementation period.

		Day of Protocol				
Measurement	Preliminary Testing	0	7	14	21	28
Graded Exercise Testing Familiarization Session	•					
Supplementation		•	•	•	•	•
Daily Supplementation Log			•	•	•	•
Blood Collection	•	•	•	•	•	•
Graded Exercise Test Protocol		•				•
3-day Diet Recall	•					
Dietary Control		•	•	•	•	•
Physical Activity Recall	•					
Physical Activity Control		•	•	•	•	•

Figure 1. Study design and timetable of measurement.

Subjects

Twenty-four apparently healthy male students between the ages of 18 and 30 years were recruited to participate in this investigation. Participant characteristics are presented in Table 1. Height was measured with a stadiometer, body mass was measured with an electronic balance, and body composition was measured with dual energy x-ray absorptiometry (Prodigy Lunar, G.E. Medical Systems, Madison, WI, USA). All the participants were verified as being recreationally active (i.e., $\geq$30 minutes 3 d·wk^{-1}); not currently taking any medications or dietary supplements; or using tobacco in any form; and free from signs, symptoms, or known cardiovascular or metabolic diseases. All the subjects were carefully informed about the possible risks and benefits of the study, and all the subjects signed a written informed consent form before participation in the study. The Human Subjects Protection Review Committee of the University of Southern Mississippi approved the study.

Table 1. Mean ± *SE* for all the participants in PLA and ECH supplementation groups.*

Descriptive	PLA ($n = 12$)	ECH ($n = 12$)
Age (y)	24.9 ± 3.6	25.2 ± 1.4
Height (cm)	180.3 ± 2.0	177.5 ± 2.0
Mass (kg)	93.5 ± 14.7	82.4 ± 12.7
Body fat (%)	19.8 ± 7.4	18.7 ± 5.7
$\dot{V}O_2max$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	40.7 ± 1.3	43.8 ± 1.7

*PLA = placebo; ECH = *Echinacea*.

Procedures

Participants self-administered an oral dose of either 8,000 $mg \cdot d^{-1}$ of *Echinacea* (*Echinacea Purpurea*, Puritan's Pride, Oakdale, NY, USA) or PLA (wheat flour) and a multivitamin (Equate Complete Multi-Vitamin, Perrigo Consumer Healthcare, Allegan, MI, USA) for 28 consecutive days. Multivitamins were orally self-administered immediately after waking and to ensure adequate dietary intake of vitamins and minerals according to the National Academy of Sciences Dietary Reference Intake. Each participant orally self-administered five 400-mg capsules on 4 separate occasions during the course of each day according to the following schedule: (a) immediately after waking, (b) with lunch, (c) midafternoon, and (d) with the evening meal. This dosage and regimen are similar to those of protocols used in previous research (2,27,29). The ECH supplement used in this study was provided by the manufacturer and is commercially available as an over-the-counter nutritional supplement. Each participant was provided with a known quantity of either ECH or PLA and daily supplementation log to document the time and dosage for each self-administration on a weekly basis. Both the daily supplementation log and any unused dosages were returned to the investigators to document adherence to the dosage protocol on a weekly basis.

Baseline blood samples were collected on day 0 for comparison to subsequent samples taken on days 7, 14, 21, and 28 during the supplementation period. Whole-blood samples were collected and analyzed for RBC count, whereas serum samples were collected, processed, and stored for analyses of EPO. Each sample was collected between 0600 and 0900 hours after a 12-hour fast. Each subject was scheduled for blood collection at the same time ±30 minutes for all the visits to the laboratory to control for the influence of circadian rhythm. Before collection of each blood sample, an 18-g indwelling cannula (JELCO®, Johnson and Johnson Medical, Arlington, TX, USA) was placed in a superficial forearm vein and kept patent with a saline flush. The participants were then required to rest in a seated position for 30 minutes to allow for stabilization of body fluids. The first 3 ml of each sample was discarded, and then 15 ml was collected with 5 and 10 ml separated into ethylenediaminetetraacetic acid and serum tubes, respectively.

Whole-blood samples were analyzed for RBC count using flow cytometery (Gen·S™ System 2 Hematology Workstation, Beckman Coulter, Fullerton, CA, USA). Serum samples were allowed to clot for 20 minutes at room temperature and then centrifuged for 10 minutes at 5,000 rpm and 4°C. The separated samples were then decanted into 2.5-ml polyethylene storage tubes and frozen at −80°C until the completion of data collection.

Serum samples were analyzed in duplicate for EPO using enzyme-linked immunosorbent assay (ELISA) and analyzed on a VersaMax™ microplate reader and accompanying software (SoftMax Pro v4.3, Molecular Devices, Sunnyvale, CA, USA). Each participant's duplicate samples were analyzed from the same ELISA kit (DEP00, R&D Systems, Minneapolis, MN, USA). Sensitivities and intra-assay coefficient of variations for EPO (0.6 $mIU \cdot ml^{-1}$ and 2.78%, respectively, DEP00, R&D Systems, Minneapolis, MN, USA) were determined by following respective manufacturers' directions.

Table 2. Mean ± *SE* for red blood cells and erythropoietin at baseline (day 0), 1 week (day 7), 2 weeks (day 14), 3 weeks (day 21), and 4 weeks (day 28) for PLA and ECH supplementation groups.*

Variable	Day	PLA ($n = 12$)	ECH ($n = 12$)
Red blood cells ($\times 10^{12} \cdot L^{-1}$)	0	4.78 ± 0.04	4.70 ± 0.07
	7	4.69 ± 0.03	4.71 ± 0.12
	14	4.71 ± 0.04	4.72 ± 0.10
	21	4.77 ± 0.06	4.71 ± 0.08
	28	4.73 ± 0.07	4.78 ± 0.10
Erythropoietin ($mU \cdot ml^{-1}$)	0	10.63 ± 0.68	12.37 ± 0.87
	7	10.02 ± 0.72	17.79 ± 1.52†‡
	14	10.46 ± 0.91	20.21 ± 1.43†‡
	21	8.64 ± 0.81	16.84 ± 2.17†‡
	28	9.54 ± 0.98	10.32 ± 0.51

*PLA = placebo; ECH = *Echinacea*.
†Significantly different from PLA.
‡Significant differences from premeasure within the group.

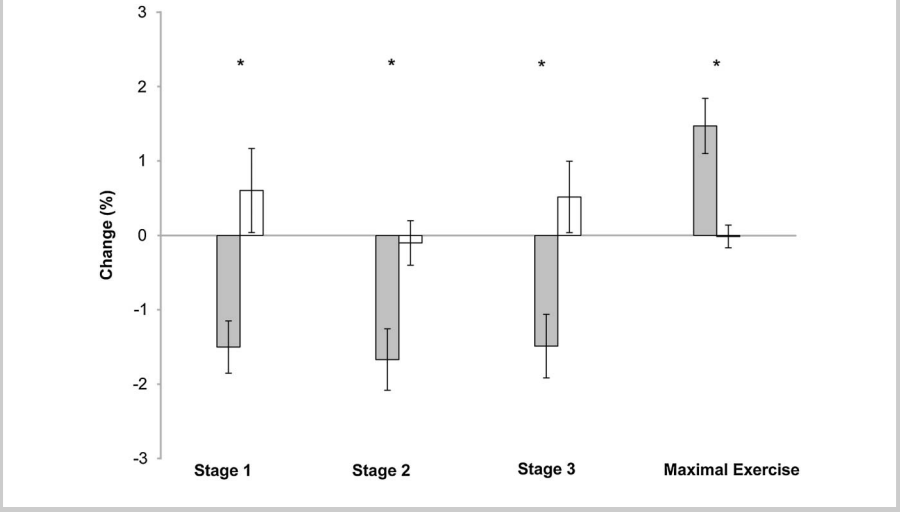

Figure 2. Percent change in submaximal and maximal oxygen consumption in the placebo (gray) and *Echinacea* (white) supplementation groups. Significant differences between groups are as indicated.

Graded exercise tests were performed on a motorized treadmill before and after the supplementation period. Graded exercise tests were continuous and consisted of multiple 3-minute stages. After a warm-up at 2.5 miles·h^{-1}, the speed was increased to 5 miles·h^{-1} (stage 1) and 6 miles·h^{-1} (stage 2). Thereafter, the treadmill speed remained constant at 6 miles·h^{-1}, and the grade was increased by 3% (stage 3) until volitional fatigue. During each GXT, expired gases were analyzed continuously with open-circuit spirometry (Max-1, Physiodyne, Qougue, NY, USA), and $\dot{V}O_2$max was determined during the final minute of the test. Running economy was evaluated through submaximal $\dot{V}O_2$ and HR responses averaged during the final minute of the first 3 stages of each GXT. Heart rate was measured continuously via telemetry (Polar Electro Incorporated, Port Washington NY, USA).

Statistical Analyses

Repeated measures analysis of variance (ANOVA) was performed to determine significant main effects between the groups and across time for RBC count, EPO, $\dot{V}O_2$, and HR. Post hoc analyses were performed for all the variables that exhibited significant main effects using independent samples *t*-tests. A 1-way ANOVA was performed to determine the differences across time within each group that exhibited significant main effects and was followed with Bonferroni adjusted multiple comparisons. Significance for all analyses was set at $p \leq 0.05$ for this study.

Results

Mean replacement was used to extrapolate data for a single time point for RBC count because of loss of viability of one sample. The means for RBC count and serum EPO concentration obtained at each time point are presented in Table 2. There were no significant main effects detected between the groups for RBC ($p = 0.881$). Repeated measures ANOVA indicated significant between-subject effects for EPO ($p < 0.001$). Results of independent sample *t*-tests indicated that the ECH group had a significantly greater serum EPO as compared with that of the PLA group on days 7 ($p < 0.001$), 14 ($p < 0.001$), and 21 ($p = 0.002$). One-way ANOVA revealed a significant difference in the means within the ECH group with respect to EPO ($p < 0.001$). Within-group multiple comparisons indicated that EPO was significantly greater than the premeasure on days 7, 14, and 21 ($p = 0.007$, <0.001, and $= 0.003$, respectively).

The $\dot{V}O_2$max observed during a maximal GXT was found to be significantly greater in the ECH group as compared with that in the PLA group after supplementation ($p < 0.001$). A significantly lower submaximal $\dot{V}O_2$ was observed in the ECH group as compared with that in the PLA group after supplementation during GXT stages 1–3 ($p = 0.005$, 0.006, and 0.005, respectively). Data for submaximal $\dot{V}O_2$ and $\dot{V}O_2$ observed during GXT after supplementation are depicted in Figure 2. Submaximal HR was not significantly different after supplementation during GXT stages 1, 2, or 3.

Discussion

The results of this investigation demonstrated a significant increase in serum EPO attributable to oral supplementation with *Echinacea* in human subjects and improvements in RE and $\dot{V}O_2$max. Mechanistically, an increase in serum EPO is known to induce the maturation and proliferation of RBCs and prevent apoptosis in existing RBCs. Erythropoietin is also purported to have potentially beneficial effects on the endothelium including antiapoptotic, mitogenic, and angiogenic activities (25). The separate or combined effects of these mechanisms can result in an increase in the oxygen transport and delivery capacity of the blood.

The increases in serum EPO reported in this investigation are similar to the results from previously reported research demonstrating an increase in serum EPO after exposure to hypoxia through a "live-high, train-low" regimen (7). The stimulus used to induce the increase in serum EPO in these "live-high, train-low" investigations was 28 days spent living at a moderate altitude of 2,500 m while training at 1,250 m above sea level (7). Chapman et al. (7), reported a significant

30% increase in serum EPO (12.5 $mU \cdot ml^{-1}$ at baseline vs. 16.2 $mU \cdot ml^{-1}$ after 14 days at altitude) in the responder group (13.7 at baseline vs. 15.4 $mU \cdot ml^{-1}$ after 14 days at altitude), and in the nonresponder group that returned to baseline values after 28 days at sea level. The increases in serum EPO in the present investigation are similar to the previous results from several researchers who implemented hypoxic protocols in both magnitude and response pattern with respect to time (1,7,28). Hypoxia is considered to be the primary stimulus for increased serum EPO (3,8–10). The oxygen-dependent increase in EPO attributable to hypoxia is thought to be mediated by tumor suppressor protein Von Hipple Lindau (20) and transcription factor complex hypoxia-inducible factor-1α (24). The EPO response appears to vary with the magnitude of hypoxic exposure; specifically, a higher altitude (4,500 m) will typically induce a larger circulating EPO response as compared with a moderate (1,900 m) altitude (3). The similarity of the present results to those previously reported with altitude-induced hypoxia indicates that the observed EPO response was physiologically plausible despite the lack of hypoxic stimulus. There was a lack of statistically detectable changes in RBCs despite the significant increase in serum EPO. This phenomenon has been previously observed with intermittent altitude (2,650-m) exposure for 8–11 hours per night for 5 nights (1) and intermittent hyperbaric hypoxia (4,000–5,500 m) (13).

The second major finding from this investigation was that 4 weeks of oral ECH supplementation resulted in a significant improvement in RE as evidenced by lower $\dot{V}O_2$ during submaximal exercise. Because this is the first investigation to report this finding, there are no other data available for corroboration; therefore, the comparison of results will be limited to investigations implementing altitude exposure. Chronic exposure of trained cyclists to altitude (21 days at 6,194 m) has been shown to lower submaximal $\dot{V}O_2$ by approximately 7–10% (16). Likewise, runners exposed to altitude have demonstrated a 3.3% decrease in submaximal $\dot{V}O_2$ while running at 14, 16, and 18 $km \cdot h^{-1}$ (23). Additional support for a decrease in submaximal $\dot{V}O_2$ comes from an investigation that examined the effects of a 21-day mountain climbing expedition to 6,194 m on the submaximal steady state $\dot{V}O_2$. These investigators found a reduced steady state $\dot{V}O_2$ during 2-leg kicking exercise at 0 and 50 W after exposure to altitude (19). Previous research studies have also reported that RE has been shown to improve independent of changes in Hb mass, ventilation, respiratory exchange ratio, and HR (23). One of the possible explanations for the mechanism to explain the improvement in RE observed in altitude studies is that a decrease in the use of available oxygen by muscle tissue occurs, specifically, an increase in the glycolytic contributions to ATP synthesis (17,18). This mechanism does not seem likely given that a reduction in lactate production (4) and the lowered blood (14) and muscle lactate concentration (15) reported with acclimatization to chronic altitude exposure. A second explanation for the observed lower $\dot{V}O_2$ during submaximal exercise after acclimatization to chronic hypoxia is an increase in the exploitation of available oxygen (17,18) that increases the reliance on carbohydrate use for oxidative phosphorlyation (16,23). Several researchers have suggested a shift toward increased dependence on glucose metabolism and away from fatty acids under hypoxic conditions might be beneficial because glucose is a more efficient fuel in terms of generating ATP per mole oxygen consumed (5,12,16). A third postulated mechanism for this adaptation is a reduced energy need of one or more of the processes involved in excitation and contraction (16,23). The results of this investigation cannot be explained by these mechanisms because chronic exposure to hypoxia was not implemented to induce the observed increase in serum EPO. In this case, a plausible mechanism for the observed increase in RE in this investigation is an increase in the oxygen transport capacity of the blood subsequent to an increase in serum EPO induced by ECH supplementation. Previously reported data from our laboratory demonstrated a "nonsignificant" increase in RBC, which although not statistically significant might be physiologically important (29); however, the exact mechanism for the improvement in RE in this investigation remains unclear.

The present investigation demonstrated a significant improvement in $\dot{V}O_2max$ after 4 weeks of ECH supplementation as compared with PLA supplementation as evaluated by percent change. This is the first report of a significant increase in $\dot{V}O_2max$ associated with ECH supplementation. Because *Echinacea* is generally considered to be a nonspecific immunostimulant, research using this supplement as an intervention has been limited to investigations related to immune function. To date, the only study that implemented exercise testing along with ECH supplementation reported that 4 weeks of oral supplementation in humans resulted in a "nonsignificant" increase in $\dot{V}O_2max$ (27).

In summary, evidence from this investigation indicates that oral supplementation with 8,000 $mg \cdot d^{-1}$ of ECH for 4 weeks results in an increase in serum EPO but not a significant increase in RBC. Additionally, the observed increase in EPO was followed by an increase in $\dot{V}O_2max$ and RE as indicated by a decrease in submaximal $\dot{V}O_2$. These data suggest that supplementation with ECH results in an increase EPO, $\dot{V}O_2max$, and RE independent of a significant increase in RBC.

Practical Applications

Echinacea supplementation for 4 weeks resulted in a significant increase in EPO and a concomitant improvement in submaximal and maximal oxygen consumption during running. *Echinacea* as a nutritional supplement may offer a viable means for aerobic athletes to increase oxygen consumption and subsequently improve performance.

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REFERENCES

1. Ashenden MJ, Gore CJ, Dobson GP, Boston TT, Parisotto R, Emslie KR, Trout GJ, and Hahn AG. Simulated moderate altitude elevates serum erythropoietin but does not increase reticulocyte production in well-trained runners. *Eur J Appl Physiol* 81: 428–435, 2000.
2. Berg A, Northoff H, Konig D, Weinstock C, Grathwohl D, Parnham MJ, Stuhlfauth I, and Keul J. Influence of Echinacin (EC31) treatment on the exercise-induced immune response in athletes. *J Clin Res* 1: 367–380, 1998.
3. Berglund B. High-altitude training. Aspects of haematological adaptation. *Sports Med* 14: 289–303, 1992.
4. Brooks GA, Butterfield GE, Wolfe RR, Groves BM, Mazzeo RS, Sutton JR, Wolfel EE, and Reeves JT. Decreased reliance on lactate during exercise after acclimatization to 4,300 m. *J Appl Physiol* 71: 333–341, 1991.
5. Brooks GA, Butterfield GE, Wolfe RR, Groves BM, Mazzeo RS, Sutton JR, Wolfel EE, and Reeves JT. Increased dependence on blood glucose after acclimatization to 4,300 m. *J Appl Physiol* 70: 919–927, 1991.
6. Burger RA, Torres AR, Warren RP, Caldwell VD, and Hughes BG. Echinacea-induced cytokine production by human macrophages. *Int J Immunopharmacol* 19: 371–379, 1997.
7. Chapman RF, Stray-Gundersen J, and Levine BD. Individual variation in response to altitude training. *J Appl Physiol* 85: 1448–1456, 1998.
8. Fisher JW. Control of erythropoietin production. *Proc Soc Exp Biol Med* 173: 289, 1983.
9. Fisher JW. Erythropoietin: Physiologic and pharmacologic aspects. *Proc Soc Exp Biol Med* 216: 358–369, 1997.
10. Fisher JW. Erythropoietin: Physiology and pharmacology update. *Exp Biol Med* 228: 1–14, 2003.
11. Goel V, Chang C, Slama JV, Barton R, Bauer R, Gahler R, and Basu TK. Alkylamides of Echinacea purpurea stimulate alveolar macrophage function in normal rats. *Int Immunopharmacol* 2: 381–387, 2002.
12. Gore CJ, Hahn AG, Aughey RJ, Martin DT, Ashenden MJ, Clark SA, Garnham AP, Roberts AD, Slater GJ, and McKenna MJ. Live high: train low increases muscle buffer capacity and submaximal cycling efficiency. *Acta Physiol Scand* 173: 275–286, 2001.
13. Gore CJ, Rodriguez FA, Truijens MJ, Townsend NE, Stray-Gundersen J, and Levine BD.Increased serum erythropoietin but not red cell production after 4 wk of intermittent hypobaric hypoxia (4,000-5,500 m). *J Appl Physiol* 101: 1386–1393, 2006.
14. Grassi B, Marzorati M, Kayser B, Bordini M, Colombini A, Conti M, Marconi C, and Cerretelli P. Peak blood lactate and blood lactate vs. workload during acclimatization to 5,050 m and in deacclimatization. *J Appl Physiol* 80: 685–692, 1996.
15. Green HJ, Roy B, Grant S, Hughson R, Burnett M, Otto C, Pipe A, McKenzie D, and Johnson M. Increases in submaximal cycling efficiency mediated by altitude acclimatization. *J Appl Physiol* 89: 1189–1197, 2000.
16. Green HJ, Sutton JR, Wolfel EE, Reeves JT, Butterfield GE, and Brooks GA. Altitude acclimatization and energy metabolic adaptations in skeletal muscle during exercise. *J Appl Physiol* 73: 2701–2708, 1992.
17. Hochachka PW. Mechanism and evolution of hypoxia-tolerance in humans. *J Exp Biol* 201: 1243–1254, 1998.
18. Hochachka PW, Gunga HC, and Kirsch K. Our ancestral physiological phenotype: An adaptation for hypoxia tolerance and for endurance performance? *Proc Natl Acad Sci U S A* 95: 1915–1920, 1998.
19. MacDonald MJ, Green HJ, Naylor HL, Otto C, and Hughson RL. Reduced oxygen uptake during steady state exercise after 21-day mountain climbing expedition to 6,194 m. *Can J Appl Physiol* 26: 143–156, 2001.
20. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, and Ratcliffe PJ. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* 399: 271–275, 1999.
21. Mishima S, Saito K, Maruyama H, Inoue M, Yamashita T, Ishida T, and Gu Y. Antioxidant and Immuno-Enhacning Effects of Echinacea purpurea. *Biol Pharm Bull* 22: 1004–1009, 2004.
22. O'Neill W, McKee S, and Clarke AF. Immunological and haematinic consequences of feeding a standardised Echinacea (Echinacea angustifolia) extract to healthy horses. *Equine Vet J* 34: 222–227, 2002.
23. Saunders PU, Telford RD, Pyne DB, Cunningham RB, Gore CJ, Hahn AG, and Hawley JA. Improved running economy in elite runners after 20 days of simulated moderate-altitude exposure. *J Appl Physiol* 96: 931–937, 2004.
24. Semenza GL. Hypoxia-inducible factor 1: Master regulator of O2 homeostasis. *Curr Opin Genet Dev* 8: 588–594, 1998.
25. Smith KJ, Bleyer AJ, Little WC, and Sane DC. The cardiovascular effects of erythropoietin. *Cardiovasc Res* 59: 538–548, 2003.
26. Stimpel M, Proksch A, Wagner H, and Lohmann-Matthes ML. Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant Echinacea purpurea. *Infect Immun* 46: 845–849, 1984.
27. Szolomicki S, Samochowiec L, Wojicki J, and Drozdzik M. The influence of active components of Eleutherococcus on cellular defence and physical fitness in man. *Phytother Res* 14: 30–35, 2000.
28. Wehrlin JP, Zuest P, Hallen J, and Marti B. Live high-train low for 24 days increases hemoglobin mass and red cell volume in elite endurance athletes. *J Appl Physiol* 100: 1938–1945, 2006.
29. Whitehead MT, Martin TD, Scheett TP, and Webster MJ. The effect of 4 wk of oral echinacea supplementation on serum erythropoietin and indices of erythropoietic status. *Int J Sport Nutr Exerc Metab* 17: 378–390, 2007.