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RESEARCH ARTICLE

ANTI-FATIGUE AND ERGOGENIC EFFECT OF *ROUREA COCCINEA* SCHUM. AND THONN. (CONNARACEAE) ETHANOLIC EXTRACT IN RATS

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ABSTRACT

Plants are recognized today as natural medicinal sources and some are used as ergogenic aids because of their antioxidant properties. *Rourea coccinea* is one of the most widely used plants in African traditional medicine. Studies have demonstrated its antioxidant and anti-inflammatory properties. The aim of this study is to evaluate the potential beneficial effect of supplementation of *R. coccinea* ethanolic extract on anti-fatigue and ergogenic functions following intense endurance exercise. Male Wistar rats divided into three groups (n = 10) were given distilled water, ethanolic extract of *R. coccinea* (Rc) at 400 mg/kg (Rc-400) and 800 mg/kg (Rc-800) per day orally for 16 days. The effects on physical performance and anti-fatigue of the extract were evaluated after physical tests by measuring the time of swimming until exhaustion, and the level of biomarkers associated with fatigue such as blood glucose, blood lipids, creatine kinase (CK), lactate dehydrogenase (LDH), aspartate transaminase (AST) and alanine transaminase (ALT). The results showed that the 400 and 800 mg/kg extract significantly increased swimming time compared to the control group. Rats in the extract treated groups showed a decrease in the level of AST, ALT and CK after physical activity compared to the control group. Blood glucose was significantly increased with the treated groups. In lipid profile, total cholesterol, triglyceride and HDL levels were not significantly altered in Rc treated groups; however, Rc extract decreased the LDL level significantly. Overall, these results suggest that the ethanolic extract of *R. coccinea* possesses anti-fatigue effects and increases physical performance in rats. Therefore, supplementation of *R. coccinea* may be beneficial for improving physical performance and combating muscle fatigue.

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INTRODUCTION

Fatigue is defined as the inability to maintain power and strength, which impairs physical performance. Excessive physical load, insufficient rest and mental stress or pressure are the factors responsible for physiological fatigue. There are two types of fatigue, central fatigue and peripheral or physical fatigue. Central fatigue could be caused or mediated by altered levels of histamine, 5-HT (serotonin), 5-hydroxyindoleacetic acid (5-HIAA), related neurotransmitter pathways, hormones, and exercise-induced cytokines (Huang *et al*., 2015; Yamamoto *et al*., 2012). According to the exhaustion theory, a decrease in major energy sources, such as glucose, muscle and liver glycogen and the accumulation of metabolites such as lactic acid, ammonia, inorganic phosphate due to intense physical exercise are factors responsible for physical fatigue (Morales-Alamo *et al*., 2015; Westerblad *et al*., 2002). The radical theory suggests that intense exercise can produce an imbalance between the body's oxidation system and its antioxidation system.

The accumulation of reactive-free radicals will put the body in a state of oxidative stress and bring injury to the body by attacking large molecules and cell organs. The mechanisms and cellular systems responsible for oxidative stress include mitochondria, leucocytes, and ischemia-reperfusion, and recovery from exercise-induced fatigue requires damage repair and elimination of the accumulated metabolic products (Wang *et al*., 2008; You *et al*., 2011). Antioxidant supplementation is a common practice among both professional athletes and amateur sportspersons, and the market offering various nutrient supplements is immense (Maughan *et al*., 2007). Although these products have been touted as a means of preventing exercise-induced oxidative damage and enhancing performance, consistent evidence of their efficacy is lacking (Peternelj and Coombes, 2011). Complementation and/or supplementation with antioxidants prior to exercise may enhance antioxidant status and decrease tissue damage resulting from oxidative stress during exercise (Mastaloudis *et al*., 2004). It has been suggested that antioxidant supplementation may improve performance by reducing oxidative stress on muscle contractile and structural proteins, thereby limiting inflammation and the tiring effects of exercise (Scholten and Sergeev, 2013). Although

the majority of surveys have noted lower levels of stress biomarkers at the end of aerobic training, the effectiveness of using antioxidant supplements to suppress exercise-induced oxidative stress is clear (Bloomer *et al*., 2006).

Most antioxidant supplementation studies on human performance have been conducted using vitamins A, C, and E, but these antioxidant drugs have side effects. Several studies have shown that supplementation with natural antioxidant products including plants fights fatigue and improves physical performance without health risks (Chen *et al*., 2022; Lamou *et al*., 2016). *Rourea coccinea* (syn. *Byrsocarpus coccineus*) Schum. and Thonn. (Connaraceae) is a climbing shrub, used in ethnomedicine in West Africa for the treatment of various ailments: muscle and rheumatic pain, primary and secondary infertility (Adjanohoun *et al*., 1986), wound, swelling, tumors, venereal diseases, dysentery (Akindele *et al*., 2010). Scientific studies conducted on *Rourea coccinea* have shown it's anti-inflammatory and antioxidant activities as well as it's richness in polyphenols and flavonoids (Dosseh *et al*., 2015). However, the anti-fatigue effect and exercise performance of *R. coccinea* have not been reported. The aim of this study is to evaluate the potential beneficial effect of supplementation of the ethanolic extract of *R. coccinea* on anti-fatigue and ergogenic functions following intense endurance exercise.

MATERIALS AND METHODS

Plant materials: Matured roots of *Rourea coccinea* were collected around the campus of University of Lome in April 2022 and authenticated by the botanist at the Department of Botany ("Université de Lome"). A voucher specimen is deposited in the Herbarium of the department under reference Number Togo 15887. The root bark was dried under air-conditioning and powdered. The powder (100 g) was extracted with continuous agitation in ethanol 95° (1000 mL) for 72 h. The extraction yield of dried extract was approximately 12,5 %.

Experimental animals: Male Wistar rats weighing 140 to 160 g were used. These animals, produced by the Department of Physiology/Pharmacology of University of Lome, were kept under natural environmental conditions with a 12 h light and dark cycle and had free access to food and water. After 1 week of acclimatization, rats were randomly divided into Three (03) groups of 10 animals each. The first group (control) received distilled water (10 ml/kg), the second and third groups received, respectively *Rourea coccinea* (Rc) at 400 (Rc-400) and 800 (Rc-800) mg/kg. Animals were daily treated orally (p.o.) for 16 days. All animal procedures were performed after approval from the Ethics Committee of University of Lome (Togo) and in accordance with the recommendations of the proper care and use of laboratory animals.

Weight-Loaded Swimming Test: A weight-loaded swimming test in the rats was performed to evaluate the exercise endurance time based on the previous report (Huang *et al*., 2012). After 16 days of Rc supplementation, five rats of each group were selected randomly, a lead sheet (5% equivalent to individual body weight) was attached to the tail of each rat. Swimming was performed in plastic water tank (90 cm tall and radius 45 cm), filled with water to 40 cm water depth and maintained at ambient temperature. The rats were considered exhausted when they failed to rise to the surface of the water to breathe after 7 s. Swim time to exhaustion was evaluated as the index of exercise performance.

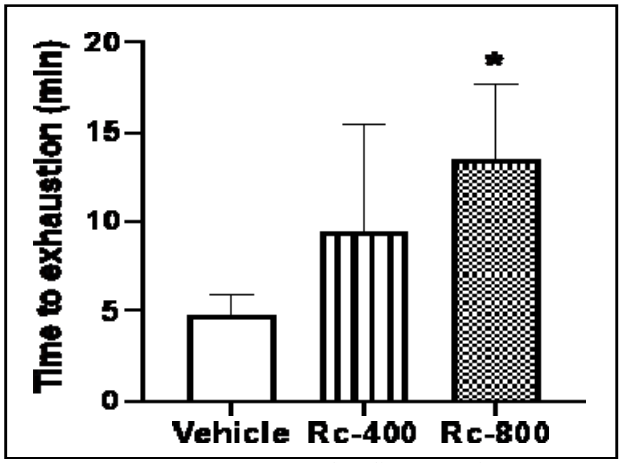
Biochemical Parameters Associated with Fatigue: To assess the anti-fatigue effect of *R. coccinea* root bark in rats, fatigue-related biochemical parameters were measured. After 1 hour of the last Rc extract administration, the last five rats of each group were allowed for a swimming test for 15 min without weight. The blood sample was collected after swimming exercise from retro-orbital sinus of rats, serum was separated by centrifugation and used to analyze fatigue-associated biochemical parameters, such ALT, AST, Creatine Kinase, Lactate Dehydrogenase, Alkaline Phosphatase, Glucose, Total Cholesterol, HDL and LDL Cholesterol, Triglycerides using an autoanalyzer (Hitachi 7060, Hitachi, Tokyo, Japan).

Evaluation of antioxidant activity by the FRAP (Ferric Reducing Antioxidant Power) method: A portion of the serum collected from the rats that swam for 15 minutes is used for the FRAP test. The antioxidant power of serum was determined by measuring its ability to reduce Fe^{3+} into Fe^{2+} by FRAP assay (Nair *et al*., 2007). Briefly, 300 µl of a daily working reagent (prepared by mixing 25 mL of acetate buffer at 300 mM; 2.5 ml of Fe^{3+}-tripyridyl-s-triazine (Fe^{3+} - TPTZ) at 10 mM in 40 mM of HCl and 2.5 ml of FeCl-6H_2O at 20 mM was mixed with 10 µl of serum sample and 30 µl of distilled water. The change in absorbance at 593 nm was measured against blank after 10 min of incubation using Genesys 10S UV-Vis Spectrophotometer, USA. Aqueous solutions of FeSO4.7H2O was used for calibration with a concentration range (0 – 2000 µM) and antioxidant power was expressed as µM.

Statistical analysis: The results are expressed as mean ± standard error of mean (M ± SEM). Data were analysed by one-way analysis of variance followed by Tukey post-hoc test. Results were considered to be significant at $P< 0.05$. All statistical analyses were carried out using GraphPad Prism 8 (GraphPad Software Inc., CA, USA).

RESULTS

Weight-Loaded Swimming Test: The exercise endurance in rats administered the vehicle, Rc-400 and Rc-800 were 4.86±0.47, 9.43 ±2.69 and 13.51±1.87 min, respectively, as shown in Figure 1. Swimming time increased dose-dependent in the treated groups compared to the control group. The swimming time of the Rc-800 was significantly higher ($P < 0.05$) compared to the control group.



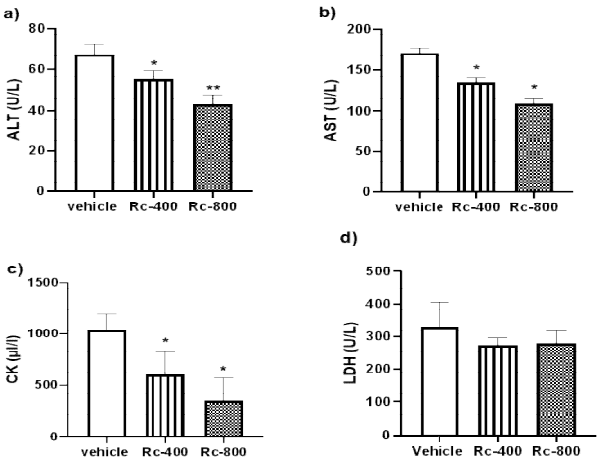
Data are mean ± SEM, (n = 5); Rc-400: ethanolic extract of *R. coccinea* at dose of 400mg/kg; Rc-800: *R. coccinea* extract at dose of 800mg/kg; *: P < 0.05 significant difference from control (ANOVA at a factor followed by Tukey multiple comparison test).

Figure 1. **Effect of Rc on performance in swimming exercise.**

Effect of Rc Extract on Biochemical Markers Associated with Fatigue: The status of peripheral fatigue can be evaluated by important biochemical indicators, including, ALT AST, CK, LDH, and Serum glucose, blood lipids, after exercise (Wu *et al*, 2013; Huang *et al*., 2015).

Effect of Rc extract supplementation on exercise-induced lesion indicators: Results showed that ALT values of treated groups were significant decreased: Rc-400 and Rc-800 groups were respectively, 63.180 ± 2.262 U/L ($P< 0.05$) and 55.320 ± 1.854 U/L ($P< 0.001$), as compared to control, 43.060 ± 2.027 U/L (Figure 2a). Serum AST levels were lower with Rc-400 (134.50 ± 2.16 U/L), Rc-800 (108.92 ± 3.19 U/L), respectively, (all $P < 0.05$), than vehicle treatment (170.42 ± 2.95) (Figure 2b). CK values for the control, Rc-400 and Rc-800

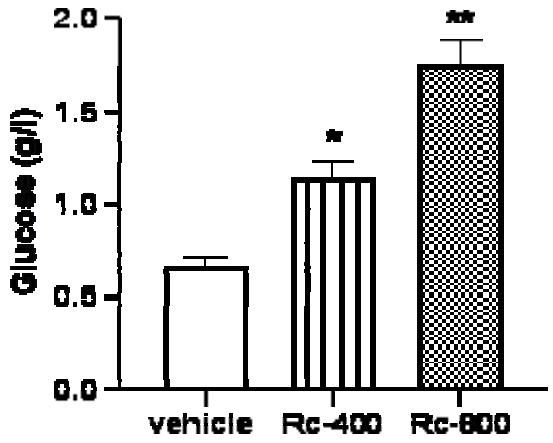
groups, are respectively, 1037.3±68.974, 604.40±103.092, 348.950±98.608 U/L. Significant decrease in CK levels with both doses compared to the control (P<0.05) (Figure 2c). LDH values of treated groups did not differ significantly from control, levels of control, Rc-400 and Rc-800 groups were respectively, 329.75 ± 13,61, 273.25 ± 9,848 and 279.5 ± 17,873 U/L (Figure 2d).



Data are mean ± SEM (n = 5), Rc: *Rourea coccinea*. a) ALT: alanine aminotransferase, b) AST: aspartate aminotransferase, c) CK: creatine kinase, d) LDH: lactate dehydrogenase, * *P< 0.05*; ** *P< 0.001* significant difference as compared to control.

Figure 2. Effect of extract supplementation on exercise-induced lesion indicators

Effect of extract supplementation on serum glucose: We assessed the supplementation effect of *Rourea coccinea* on serum glucose; glucose being the energy source of muscles during exercise. The glucose values of the control groups, Rc-400 and Rc-800 are 0.665±0.027, 1.139±0.044, 1.752±0.058 g/l respectively (Figure 3). There is a significant increase in glucose levels in the treated groups compared to the control group (Rc-400, P<0.05 and Rc-800, P<0.001).

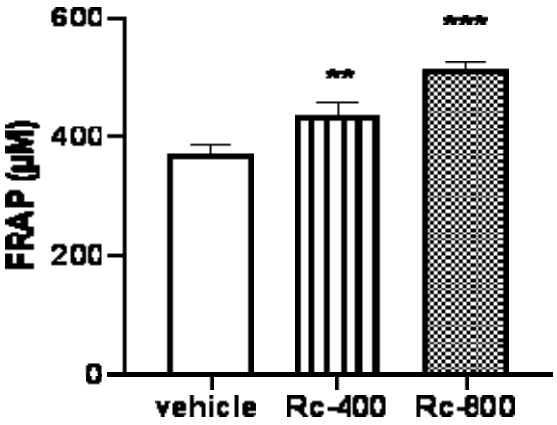


Data are mean ± SEM (n = 5). Rc: *Rourea coccinea*; *: *P<0.05* significant difference from control; **: *P<0.001* significant difference as compared to control (one-way ANOVA followed by Tukey multiple comparison test)

Figure 3. Effect of extract supplementation on glucose level

Effect of extract supplementation on other biochemical parameters: We assessed the effect of *Rourea coccinea* supplementation on other biochemical parameters such as total cholesterol, low-density lipids (LDL), high-density lipids (HDL) and triglycerides. The values of these parameters are summarized in Table 1. Total cholesterol, HDL, cholesterol and triglycerides show no significant difference in the treated groups compared to the control group (P0.05). On the other hand, there is a significant difference in LDL in the Rc-800 group compared to the control for P<0.001.

Effect of supplementation on antioxidant activity by the FRAP method: To determine the antioxidant power of *Rourea coccinea* supplementation, we performed the FRAP test. The values of the different concentrations of the control groups, Rc-400 and Rc-800 are respectively 373.454±6.073, 438.449±9.224, 516.976±4.711 µM. There is a significant increase in Fe^{2+} concentrations in the treated groups compared to the control group.



Data are mean ± SEM (n=5). Rc: *Rourea coccinea*; FRAP: ferric reducing antioxidant power. **: significant difference from control for P<0.001, ***: significant difference from control for P<0.0001.

Figure 4. Effect of ethanolic extract of R. coccinea on FRAP values in serum in treated rats

Table 1. Effect of extract supplementation on Total cholesterol, HDL, LDL, and triglycerides

Parameters	Groups		
	Control	Rc-400	Rc-800
TC (mg/dL)	59.3±0,04	52.7±0.02	59.4±0.06
HDL (mg/dL)	32.22±3.19	34.84±2.41	44.82±3.54
LDL (mg/dL)	18.2±0.01	15.2±0.02	10.3±0.02**
TG (mg/dL)	74.9±0.09	63.3±0.02	56.4±0.04

Data are mean ± SEM (n = 5). TC: Total cholesterol, Rc: *Rourea coccinea*, HDL: high-density lipoprotein, LDL: low-density lipoprotein, **: significant difference from the control for P<0.001 (one-way ANOVA followed by the Tukey multiple comparison test).

DISCUSSION

Oxidative stress plays a role in exhaustion during physical exercise. Studies have shown that supplementation with antioxidant substances has a beneficial effect on physical performance. *R. coccinea* is a plant used in African traditional medicine whose studies have shown its antioxidant and anti-inflammatory properties. In the literature, the anti-fatigue and exercise performance effect of this plant have not been reported. We aimed to evaluate the potential beneficial effects of *R. coccinea* supplementation on fatigue and ergogenic function after physical challenge in rats. The effects on physical and anti-fatigue performance of *R. coccinea* ethanolic extract were evaluated after physical tests by measuring swimming time to exhaustion, the level of certain fatigue-associated biomarkers such as blood glucose, blood lipids, creatine kinase (CK), lactate dehydrogenase (LDH), transaminases (AST, ALT) and lipoproteins. *R. coccinea* supplementation dose-dependently increased endurance and significantly decreased ALT, AST, and CK levels after physical challenge. Serum glucose, an important energy source for exercise, was significantly increased. *R. coccinea* improved total blood antioxidant potential in treated rats. In sports science, endurance exercise is typically assessed using two different models of aerobic exercise, including treadmill running and the swimming test in animals. The treadmill test forces experimental animals to run in an increasing gradient of speed or slope by negative motivation (e.g. electric shock), until exhaustion (Huang *et al*., 2008).

The other swimming test involves loading a mass equivalent to a percentage of body weight at the tail for an exhaustive swim based on the animal's survival instinct (Huang *et al*., 2012). Dawson and Horvath (1970) reported that swimming has advantages over the treadmill because it promotes more vigorous exercise than when rats are left alone. Improving exercise endurance time is the key manifestation of the anti-fatigue effect of a drug or natural compound. In our current study, administration of *R. coccinea* for 16 days significantly improved the swimming time of the treated rats compared to the control. Administration of phytochemicals such as resveratrol, capsaicin and curcumin has been shown to improve swimming endurance time in untrained animal models (Hsu *et al*., 2016; Huang *et al*., 2015; Wu *et al*., 2013). Supplementation with pulp and leaf extract of *Adansonia digitata* also improved swimming time in rats (Kpatcha *et al*., 2016). In addition to swimming tests, blood biochemical parameters are also used as markers of fatigue. Energy expenditure is also an important issue to maintain exercise capacity. Glucose is produced from tissue glycogen in the liver and muscles and released into the blood as a source of energy (Liu *et al*., 2015). Intensive exercise has a high energy demand and consumes glucose from tissue glycogen and increases its concentration in the blood (Liu *et al*., 2014). *Rourea coccinea* extract at 400 mg/kg and 800 mg/kg significantly increased serum glucose levels compared to the control group. This suggests that *R. coccinea* increases exercise performance by providing and/or maintaining high blood glucose levels. These results are comparable to those of Lee *et al*. (2021) who found elevated post-exercise serum glucose levels after 4-week supplementation with combined green tea of soy-isolated protein in ICR mice. For exhaustive exercise, several indicators are used to evaluate muscle and liver injury, such as CK, LDH, AST, and ALT (Huang *et al*., 2008; Luo *et al*., 2019). In the current study, rats in treated groups showed decrease levels of these different parameters except LDH. Therefore, supplementation with *R. coccinea* is expected to improve muscle and liver damage induced by an acute exercise test in rats. Our results confirm the hepatoprotective effect of *R. coccinea* (Akindele *et al*., 2010). *R. coccinea* supplementation did not have a significant effect on blood lipids such as, Total Cholesterol, HDL cholesterol and Triglycerides levels as compared to the control. But LDL levels was significantly decrease in Rc-800 treated group. This suggests that supplementation with *R. coccinea* inhibits the accumulation of fat in tissues and could possibly reduce the risk of cardiovascular damage associated with exercise. Physical exercise increases the production of free radicals related to increased oxygen consumption and causes oxidative stress (Alessio, 1993). There are several mechanisms and systems responsible for the production of free radicals during exercise: electron leakage in the respiratory chain, the xanthine dehydrogenase / oxidase system activated during ischemia-reperfusion, and the activation of post exercise pro-inflammatory processes that purify tissues damaged during exercise and responsible for delayed onset muscle pain (Lee *et al*., 2002). Increasing the serum antioxidant status has been suggested as a possible method of reducing the risk of many chronic diseases. In this study, the reducing power of *R. coccinea* was evaluated by the FRAP method. The reducing power in the serum of rats administered with *R. coccinea* is significantly high compared to the control. This suggests that *R. coccinea* could counteract the production of exercise-induced free radicals by intervening at the level of the various mechanisms responsible for the production of these ROS.

CONCLUSION

Our data suggest that the ethanolic extract of *R. coccinea* may increase the swimming time to exhaustion of test animals, as well as increase plasma glucose, and decrease liver and muscle injury markers such us ALT, AST and CK. These results indicate that *R. coccinea* has anti-fatigue activity and can elevate exercise performance. These activities could be, due to the antioxidant properties of the plant. Although the exact bioactive phytocompounds and detailed anti-fatigue mechanisms of *R. coccinea* remain to be elucidated, this study provides science-based evidence to support that *R. coccinea* could be a promising anti-fatigue agent and an ergogenic aid.

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