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QUERCETIN EFFECTS ON WEIGHT GAIN AND CALORIC INTAKE IN EXERCISED RATS

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ABSTRACT: Quercetin is a flavonoid which activates oxidative metabolism. Quercetin may reduce weight gain by decreasing feed efficiency. The present study aims to evaluate weight gain, caloric intake and feed efficiency in exercised and sedentary rats supplemented with quercetin. Wistar rats were divided into four groups: quercetin-exercise training (QT), quercetin-sedentary (QS), placebo-exercise training (PT) and placebo-sedentary (PS). Rats were exercised and/or orally supplemented with quercetin (25 $mg \cdot kg^{-1}$ on alternate days) during six weeks. Weight gain of the QT group decreased when compared with the PT and PS groups. Exercised groups increased cumulative caloric intake during the experimental period. The QT group rats also reduced their feed efficiency when compared with the QS and PS groups. These results suggest that quercetin is not able to decrease weight gain because no differences were found between placebo and quercetin condition either in the sedentary or in the training condition.

KEY WORDS: **flavonoids; body weight; training; feed efficiency.**

INTRODUCTION

Flavonoids are a large family of phenolic compounds or polyphenols. Flavonols are the most common of these phenolic compounds with a daily intake ranging from 20 mg to 35 mg [19]. One of the most common flavonols is quercetin. It is mostly found in onions, which contain up to 1.2 $g \cdot kg^{-1}$, and in most plant foods in quantities of 15-30 $mg \cdot kg^{-1}$ of fresh produce [18]. Quercetin is currently under study because it may have anti-inflammatory and antioxidant effects [22]. Quercetin has been proposed as an ergogenic supplement due to its capacity to increase aerobic exercise performance [9,10,17], because it may increase oxidative metabolism [9]. Moreover, quercetin may also decrease adiposity [1]. However, quercetin's effects on weight gain (WG) differ between studies. While one study performed by Rivera et al. [28] reported lower WG in obese rats supplemented with quercetin, no effect of quercetin on WG was found in lean rats [3,27]. Thus, it seems that quercetin may exert its anti obesity effects on obese rather than lean rats.

It is important to study new strategies to prevent the growth of obesity and related diseases which is expected in the coming years [30]. Exercise seems to be a powerful tool to face obesity problems. However, when studies performed on a rat model are reviewed, the data are contradictory. Resistance training decreased body weight [2]; moreover, high intensity and moderate exercise training may reduce WG [4,8,20,21]. However, other researchers have not found any effect of exercise on WG [6,11,12]. But given that exercise or dietary treatment alone is less effective than the combination of exercise plus dietary treatment to reduce WG [7], it can be suggested that quercetin supplementation during exercise will be more effective to reduce WG. In addition, some polyphenols are thought to decrease body weight when supplemented during exercise [29]. We hypothesize that quercetin combined with exercise will decrease WG in rats.

When WG is evaluated, caloric intake (CI) and feed efficiency must also be assessed [27]. Feed efficiency is the ability to transform the calories into body weight [24]. Thus, the aim of the present study was to assess the ability of quercetin to diminish WG in both sedentary and trained rats. The secondary aim was to find out any effect of quercetin on CI and feed efficiency in order to achieve deeper conclusions. Finally, given that quercetin intake can increase the weight of some organs such as the liver [3], the third goal was to assess long-term quercetin intake on muscle, heart and liver weight.

MATERIALS AND METHODS

Design. During the experimental period, rats had free access to water and maintenance chow (Table 1). Rats were weighed twice a week at the same hour, and food intake was recorded daily. Feed efficiency was calculated as previously described in the literature [26]: WG (g) $\cdot$CI (Kcal)$^{-1}$.

TABLE 1. CALORIE COMPOSITION OF THE MAINTENANCE CHOW

Macronutrients	
Energy Density (Kcal$\cdot$g^{-1})	2,9
Calories from Protein (%)	20
Calories from Fat (%)	13
Calories from Carbohydrates (%)	67

At the end of the treatment, and 48 hours after any exercise, the rats were anaesthetized with pentobarbital and were bled by cannulation of the aorta. All experiments were conducted according to ethical standards in sport and exercise science research [14].

Animals

The experiment was carried out on 33 young male inbred Wistar rats (Janvier, Fr), distributed into four groups: quercetin+exercise training (QT, n=9), placebo+exercise training (PT, n=8), quercetin+sedentary (QS, n=8), and placebo+sedentary (PS, n=8). Initial groups comprised nine rats, but three rats, from PT, QS and PS respectively, died during the first week. Animals were placed for eight weeks in individual cages in a thermoregulated (21 ± 2°C), well-ventilated room, with relative humidity ranging from 40% to 60%.

Exercise and quercetin supplementation

After the two weeks allowed for acclimation to experimental conditions, treadmill training took place five days a week for six weeks (on Panlab Treadmills for five rats, LE 8710R). The rats ran at a constant speed of 44 cm$\cdot$s^{-1} at an angle of 10 degrees. The rats ran for 20 minutes the first two days, and for 25 minutes the third day. Training duration was increased by five minutes every two days. The rats ran for 80 minutes on the last day of the fifth week and also throughout the last week of training [5].

The rats were supplemented with quercetin (QU995; Quercegen Pharma, Newton, MA), via gavage, on alternate days throughout the experimental period. A dose of 25 mg$\cdot$kg^{-1} diluted in a 1% solution of methylcellulose was used. Quercetin dose and supplementation length used in the present study were chosen because in a preliminary study we found <3-fold increase in plasma quercetin (unpublished data). Moreover, this dosage was found to activate oxidative metabolism [9].

Statistical analyses

Results are presented as mean and standard deviation. A repeated-measures ANOVA was used to analyse between-group differences within six weeks of study. Weight, CI and feed efficiency were included as dependent variables, and exercised groups as an independent variable. To analyse the results at the end of the study (haematological parameters, WG, cumulative CI and final feed efficiency), a one-way ANOVA was used, using the groups of the study as an independent variable. When the effect was significant ($P < 0.05$) a post-hoc analysis was performed (Bonferroni). Analyses were performed using the Statistical Package for Social Sciences (SPSS, v. 19.0 for Windows; SPSS, Chicago).

RESULTS

The results of the twelve measurements of weight during the six weeks of study, and WG of each group are presented in Figure 1. The ANOVA for repeated measures revealed that the QT group weighed less than the PS ($P = 0.018$) and QS groups ($P = 0.038$) from the third and the fourth weeks respectively (Fig. 1A). After the experimental period, the weight of the QT group rats was significantly lower than the QS ($P = 0.030$) and PS ($P = 0.006$) groups. There were no statistically significant differences between

TABLE 2. FINAL HAEMATOLOGICAL PARAMETERS AND ORGAN RELATIVE WEIGHT

	QT	PT	QS	PS	QT vs. PT	QT vs. QS	QT vs. PS	PT vs. QS	PT vs. PS	QS vs-PS
					p - value					
HGB (g/L)	13.66 ± 2.47	13.47 ± 1.80	12.68 ± 2.06	13.38 ± 1.98	ns	ns	ns	ns	ns	ns
HCT (%)	45.42 ± 6.03	42.81 ± 5.99	38.18 ± 6.54	40.80 ± 6.16	ns	ns	ns	ns	ns	ns
Quad R (g)	0.0069 ± 0.0007	0.0070 ± 0.0005	0.0062 ± 0.0010	0.0070 ± 0.0005	ns	ns	ns	ns	ns	ns
Quad L (g)	0.0066 ± 0.0006	0.0066 ± 0.0012	0.0072 ± 0.0008	0.0064 ± 0.0009	ns	ns	ns	ns	ns	ns
Liver (g)	0.0249 ± 0.0023	0.0217 ± 0.0022	0.0211 ± 0.0027	0.0209 ± 0.0017	p<0.05	p<0.02	p<0.01	ns	ns	ns
Brain (g)	0.0055 ± 0.0004	0.0053 ± 0.0002	0.0053 ± 0.0004	0.0053 ± 0.0002	ns	ns	ns	ns	ns	ns
Heart (g)	0.0031 ± 0.0001	0.0029 ± 0.0002	0.0028 ± 0.0002	0.0028 ± 0.0001	ns	p<0.02	p<0.01	ns	ns	ns

Note: Values are means (± SD). QT - quercetin+exercise training, PT - placebo+exercise training, QS - quercetin+sedentary, PS - placebo+sedentary, HGB - haemoglobin, HCT - hematocrit, quad L and R - quadriceps left and right. ns - not statistically significant

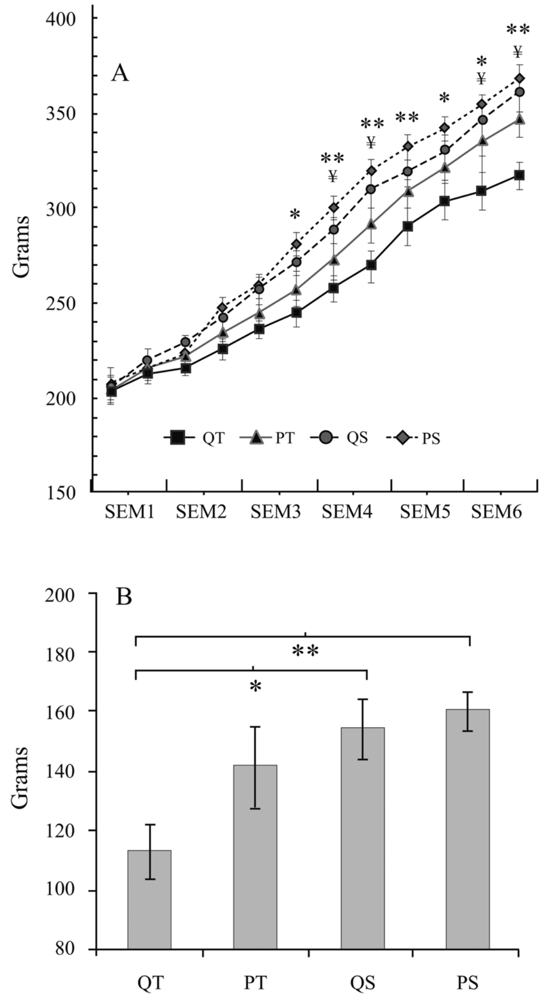

FIG. 1. WEIGHT EVOLUTION DURING THE 6 WEEKS OF STUDY (A) AND WEIGHT GAIN (B) IN EACH GROUP.
Note: Data are presented as the mean ± SD. * P<0.05. ** P<0.01 in QT vs PS (A) and in weight gain (B). ¥ P<0.05 in QT vs QS

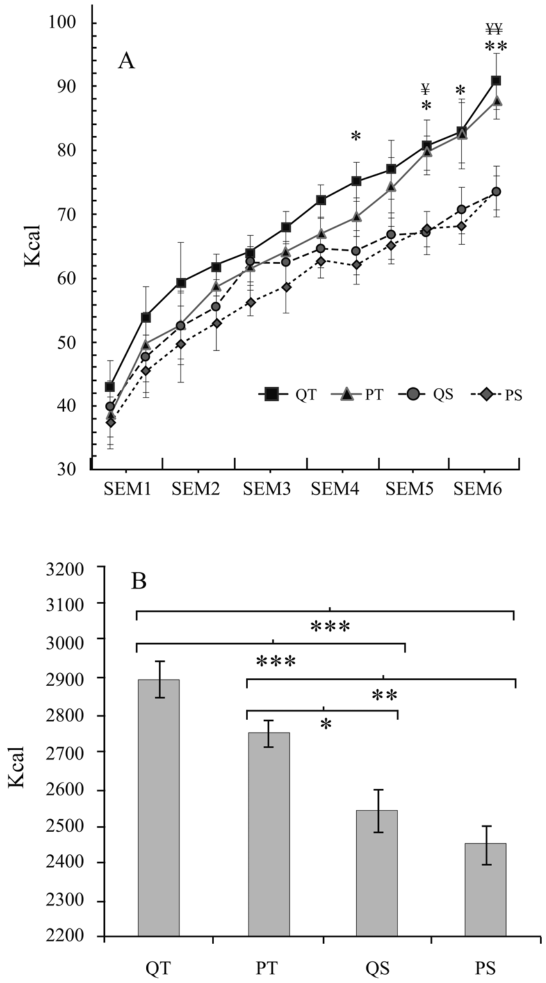

FIG. 2. CALORIC INTAKE (CI) EVOLUTION (KCAL). SAMPLE OBTAINED ON THE SAME DAYS THAT THE RATS WERE WEIGHED (A) AND CUMULATIVE CI (B).
Note: Data are presented as the mean ± SEM *P<0.05 and **P<0.01 in QT vs PS, and ¥ P<0.05, ¥¥ P<0.01 in QT vs QS for fig. 3A. * P<0.05, ** P<0.01 and ***P<0.001 for fig. 3B.

the weights of QT and PT rats in any of the measured intervals (P> 0.05). Moreover, the one-way ANOVA analysis performed on the WG data revealed a lower weight in the QT than in the QS (P = 0.012) and PS (P = 0.009) groups. There were no significant differences in WG between the QT and PT groups (Fig. 1B).

The relative weight of organs (organ weight/total weight) and final haematocrit (HCT) and haemoglobin (HGB) results are presented in Table 2. Data were analysed using a one-way ANOVA. The QT group achieved a higher relative liver weight than the other groups (P = 0.042 compared with PT, P = 0.011 compared with QS, and P = 0.007 compared with PS). The relative weight of the heart was also higher in the QT group when compared with QS (p = 0.015) and PS (p = 0.008). There were no significant differences between groups in hypertrophy rates of right or left quadriceps muscle and of brain (P> 0.05). No differences were found either in HGB or HCT between the study groups, nor in running distance between trained groups (data not shown).

A sample of twelve measurements of food intake, obtained on the same days that the rats were weighed, and the cumulative CI of six weeks are presented in Figure 2. The ANOVA for repeated measures revealed that the QT group had a higher intake than the PS group (P = 0.029) from week four, and than the QS group (P = 0.05) from week five (fig. 2A). At the end of the study daily food intake of the QT group showed higher levels (P <0.01) when compared with the QS and PS groups. No significant differences were found between the QT and PT groups on any day (P> 0.05). The one-way ANOVA revealed that cumulative CI was significantly higher in the QT group when compared with the QS and PS groups (Ps <0.001), and in the PT group when compared with the QS (P = 0.041) and PS groups (P = 0.002) (Fig. 2B).

Results of feed efficiency and total efficiency are presented in Figure 3. The analysis of repeated measures ANOVA performed on the results of feed efficiency did not find statistically significant differences between groups in any of the measurements (P>0.05) (Fig. 3A). However, total feed efficiency revealed a low-

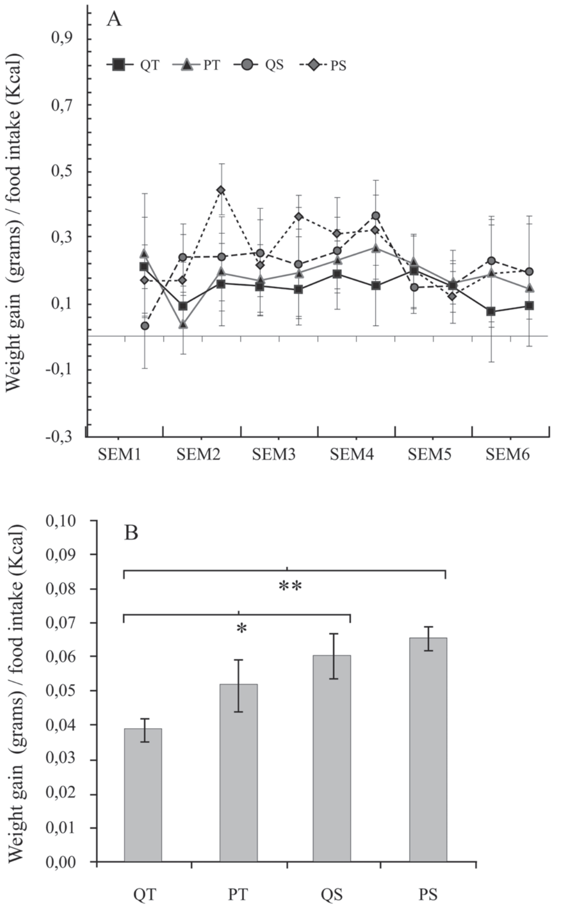

FIG. 3. FEED EFFICIENCY EVOLUTION DURING EXPERIMENTAL PERIOD (A) AND TOTAL FEED EFFICIENCY (B).
Note: Data presented as mean ± SEM * P<0.05, ** P<0.01

er rate in QT (0389 ± 0.010 Kcal) when compared with QS (0.051 ± 0.021 kcal, P = 0.045) and PS (0.060 ± 0.018, P = 0.009). There were no significant differences among the other comparisons (P> 0.05) (fig. 3B).

DISCUSSION

Taken as a whole, the results indicate that six weeks of exercise did not reduce body WG in lean rats fed with maintenance caloric chow. Although there was a lower WG in the QT group when compared with QS and PS groups, no effect was found between quercetin and placebo groups. Moreover, feed efficiency was lower in the QT group than in the QS and PS groups, but no quercetin effect was also found. It must be highlighted that exercise increased CI in both supplemented and non-supplemented groups. Moreover, when quercetin was supplemented during exercise training, the heart and liver became heavier.

In the coming years there will be a rising prevalence of obesity and related diseases [30], and it is therefore necessary to explore new strategies to avoid this problem. Polyphenols are under study as dietary compounds to decrease body weight [21]. Although it appears that polyphenols may hamper WG, quercetin seems to have a greater effect in obese rats than in lean ones [28]. Previous data have shown that polyphenol intake during exercise decreases body weight [25,29]. Some researchers, moreover, support the theory that both diet and exercise have to be controlled to reduce WG [7]. However, our results are not as clear as in previous experiments performed with mixed polyphenols. Although it seems that quercetin supplementation during six weeks of exercise training could decrease WG when compared with both sedentary groups, we believe that this effect must be attributed to exercise rather than to quercetin, because neither in the sedentary nor in the training condition is quercetin able to decrease WG when compared to placebo.

Feed efficiency measures the animal's ability to transform the calories into body weight [24]. The results of the present study show that the QT group had a lower feed efficiency than the QS and PS groups. But no differences in feed efficiency were found between the QT and PT groups, nor between the QS and PS groups. Moreover, the same results were obtained for CI and feed efficiency; in fact, the QS group had higher CI and lower feed efficiency than the QS and PS groups. Contrary to the results reported by others [2,12], our results show that exercise training increases CI in a rat model. Quercetin was supposed to be an activator of oxidative metabolism [9] and it also may inhibit adipogenesis [1]. But taken together, our data show that quercetin is not able to decrease either weight gain or feed efficiency as hypothesized, because no differences were found between placebo and the quercetin group. However, it seems that exercise impairs WG when caloric intake is increased, probably by inducing a lower feed efficiency.

In addition, our results show that the relative weight of the liver is higher in the QT group when compared to the other groups. Azuma et al. [3] described the same effect in the liver with a toxic dose of over 315 $mg \cdot kg^{-1} \cdot d^{-1}$. Thus, it is possible that long-term quercetin supplementation during exercise training may become toxic, but at the present stage we cannot reach further conclusions and more studies are needed. In addition, relative heart weight was higher in QT when compared to QS and PS, but no differences were found between placebo and quercetin condition. These data suggest that, as previously described [16], the increase in relative heart weight observed in the QT group may be an adaptation to exercise. Moreover, muscle weight results confirmed the difficulty of finding muscle hypertrophy with endurance training [13]. However, it can be stated that quercetin supplementation during exercise has a greater effect on central organs, such as heart or liver, than in peripheral organs such as muscle.

CONCLUSIONS

Our results show that quercetin supplementation is not able to decrease WG either in exercised or in sedentary rats. Moreover, no effect of quercetin was found when CI and feed efficiency were assessed. On the other hand, WG and feed efficiency are lower in the QT group. But given that these statistical differences were not found when compared to the PT group and that there is a higher CI induced by exercise training, we believe that exercise and not quercetin is responsible for the lower WG and feed efficiency found when QT is compared to PS and QS. In addition, when liver weight was assessed, it was greater in the QT group when compared with the other groups. But more studies are needed to reach further conclusions on this topic.

Conflict of interest: The authors declare no conflicts of interest.

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