Yerba Mate and chlorogenic acid reduce anxiety and cognitive deficits caused by detraining in mice

Yerba Mate y ácido clorogénico reducen ansiedad y déficits cognitivos causados por el desentrenamiento en ratones

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Abstract

Objective: This study aimed to investigate whether the administration of Yerba Mate (YM) and one of its bioactive components, chlorogenic acid, can reverse detraining-induced negative behavioral changes in mice.
Methodology: Mice were randomly assigned to five experimental groups (n=10): a sedentary group, a trained group, a detraining group, a detraining group treated with yerba mate, and a detraining group treated with chlorogenic acid. The trained group underwent a swimming training regimen for 8 weeks (5 days/week, 60 min/day), while the detraining groups completed the same swimming program for 4 weeks before discontinuing exercise for the subsequent 4 weeks. Mice were weighed weekly throughout the treatment period. After 8 weeks, the subjects were tested in a series of behavioral assays, including the open field test, object recognition task, light-dark box, and tail suspension test.
Results: Significant differences were observed in the relative weight of epididymal fat between the detraining group and the other experimental groups. Physical activity was shown to promote an antidepressant effect in trained mice; however, prolonged detraining eliminated this effect. Additionally, detraining led to increased anxiety-like behavior compared to the trained group and impaired memory relative to both the sedentary and trained mice. Interestingly, these detraining-induced deleterious effects were partially reversed by treatment with yerba mate or chlorogenic acid. No differences were found in the open field test. Conclusions: Yerba mate and chlorogenic acid partially reverse the behavioral changes and cognitive decline associated with detraining.

Keywords

Anxiety; chlorogenic acid; depression; memory; yerba mate.

Resumen

Objetivo: En el presente estudio, investigamos si la administración de Yerba Mate (YM) y uno de sus componentes bioactivos, el ácido clorogénico, son capaces de revertir los cambios de comportamiento negativos inducidos por el desentrenamiento
Metodología: Para este propósito, los animales fueron divididos aleatoriamente en cinco grupos experimentales (n=10): el grupo sedentario, el grupo entrenado, el grupo de desentrenamiento, el grupo de desentrenamiento tratado con yerba mate y el grupo de desentrenamiento tratado con ácido clorogénico. El grupo entrenado fue sometido a un entrenamiento de natación durante 8 semanas (5 días/semana, 60 min/día), mientras que los grupos de desentrenamiento realizaron el mismo programa de natación durante 4 semanas y luego discontinuaron el ejercicio por 4 semanas. Los animales fueron pesados semanalmente durante el tratamiento. Después de 8 semanas, los sujetos se sometieron a una batería de pruebas de comportamiento, incluyendo: campo abierto, tarea de reconocimiento de objetos, caja de luz-oscuridad y prueba de suspensión de la cola
Resultados: Hubo cambios significativos en el peso relativo de la grasa epididimal entre el grupo de desentrenamiento y los otros grupos experimentales. También se demostró que la actividad física promovió un efecto antidepresivo en los ratones entrenados. Sin embargo, el desentrenamiento prolongado elimina este efecto. Además, el desentrenamiento causa un aumento en el comportamiento similar a la ansiedad en comparación con el grupo entrenado y un deterioro de la memoria en comparación con los ratones sedentarios y entrenados. Curiosamente, estos efectos perjudiciales inducidos por el desentrenamiento son parcialmente revertidos por el tratamiento con yerba mate o ácido clorogénico. No se observó ninguna diferencia en la prueba de campo abierto.
Conclusiones: Por lo tanto, la yerba mate y el ácido clorogénico revierten parcialmente los cambios de comportamiento y el deterioro cognitivo causados por el desentrenamiento.

Palabras clave

Ácido clorogénico; ansiedad; depresión; yerba mate.

Introduction

Since Ancient Greece, physical activity has been recognized for its benefits to human health(Paffenbarger et al., 2001). According to the World Health Organization, the physical activity can be defined as any bodily movement generated by skeletal striated muscles and requiring energy expenditure(*Physical activity*, n.d.). Numerous scientific studies show that regular physical activity reduces the risk of chronic diseases, among which are: obesity, diabetes mellitus, sarcopenina, cardiovascular disorders, osteoporosis and cancer(Ahmed et al., n.d.; Carbone et al., 2019; Mctiernan et al., 2019; Pinheiro et al., 2020; Rodrigues da Conceição et al., 2024; Gómez Chávez et al., 2022; Orba-Pinheiro et al., 2024; Corvos-Hidalgo et al., 2024). Nevertheless, physical activity during adulthood reduces the prevalence of psychiatric disorders, such as anxiety and depression disorders, as well as preventing and/or delaying the progression of neurodegenerative diseases, such as dementia and Alzheimer's disease(DIshman et al., 2021; Huang et al., 2022; McDowell et al., 2019; Pisani et al., 2021).

However, prolonged interruption of training, known as detraining, reduces the benefits induced by the training protocol in both animals and humans(Mazzucatto et al., 2014; Tavassoli et al., 2022). This phenomenon is well characterized especially in former athletes, who become more susceptible to weight gain and increased body fat percentage after training interruption(Izquierdo-Gabarren et al., 2010). In addition to the negative metabolic effects, there are studies that demonstrate that detraining is also detrimental to muscle function and cardiovascular adaptation(Chen et al., 2022; Murach et al., 2020; Petek et al., 2022). However, there are few studies that assess the impacts of detraining on mental health and memory.

Based on these assumptions, some strategies have been carried out in order to reduce the deleterious consequences of detraining, such as: caloric restriction and supplementation with nutraceuticals(Friedman et al., 2018; Teich et al., 2017). An elegant study published by Teich and his colleagues found that the curcuma treatment is able to partially reverse weight gain, body fat percentage and glucose intolerance in rats underwent to detraining(Teich et al., 2017). In this context, due to its thermogenic and antioxidant properties, yerba mate (YM) could potentially be used to reduce the impacts of detraining. YM is a plant native to South America, naturally found in Argentina, Paraguay, Uruguay and Brazil, known worldwide and consumed in the form of mate, tereré and mate tea(Bracesco et al., 2011). Several bioactive, phenolic compounds such as chlorogenic acid, methylxanthines and saponins have been associated with several beneficial effects on human health, such as: improvement of the lipid and glycemic profile, modulation of human antioxidant enzymes, as well as thermogenic effect, showing potential to assist in the weight loss(Riachi & De Maria, 2017).

As there are few studies on the impacts of detraining on affective behaviors and memory in both humans and animal models, we investigated if the administration of yerba mate and one of its bioactive componentes, chlorogenic acid, are able to reverse the behavioral changes negative induced by detraining.

Method

Plant and CGA (Chlorogenic Acid)Preparation

Both Claudio Kovaleski and Silvio Kovaleski producers from the “Ervateira Chiru” (Chapecó, SC, Brazil) provided YM leaves. Dried and roasted YM was roasted at 180oC for 10 min as previously reported. More details with respect to the plant can be found in elsewhere(Riachi et al., 2018). Roasted YM infusion was prepared as follows: Boiling distilled water (500 mL) was added to the plant (8.751 g), mixed, capped and filtered under gravity after 15 min based on previous study(Coelho et al., 2019). The concentration de YM infusion to be administrated to the mouse was as follows: Take into account the average weight of both a human being and a mouse, 70 Kg and 46 g, respectively, a final volume of 0.3285 mL was obtained to gavage administration. Concentration of 26.285 mg mL-1 was adjusted to a volume of 0.1 mL to reduce the stress of the mice during gavage.

The content of CGA (0.896 mg mL-1 YM infusion) in the YM used in the present study was described previously elsewhere(Coelho et al., 2019). An aqueous solution of CGA standard was prepared and 0.1 mL of this solution was administrated via gavage. This volume contained approximately 0.0716 mg of standard CGA which paralleled with CGA value found in the volume of YM administrated to mice.

Animal Experimental Design

Fifty male Swiss Webster mice of 90 days old (~40 g) derived from the Barra Mansa University Center colony were used in this study. After an acclimatization period of 15 days, the mice were housed in plastic cages (30 x 19 x 13 cm). All animals used in this work were housed at a controlled temperature (20 ±2 °C) with daily exposure to a 12 h light-dark cycle and free access to water and commercial rodent diet (Presence ®).

The animals were randomly divided in five experimental groups (n =10). The sedentary (SED) group was composed by animals that were never underwent to physical activity. The trained (TRN) group was represented by the subjects that were submitted to physical activity for 8 weeks, whereas the detrained group was composed by the animals that were submitted to physical activity for 4 weeks, followed by another 4 weeks of detraining. After 4 weeks of experiment, the animals of SED and TRN groups were treated with 0.9% saline by the gavage method. According to the treatments that were submitted, the detrained group was subdivided into 3 groups

a) Detraining (DET) Group. After 30 days of experiment, the animals were treated with 0.9% saline by the gavage method.

b) Detraining Treated with Yerba Mate (DET+YM) Group: animals that were submitted to physical activity for 4 weeks, followed by another 4 weeks of detraining. After the training period, the animals were treated with 200mg/ml yerba mate by the gavage method.

c) Detraining Treated with Chlorogenic Acid (DET+CA) Group: animals that were submitted to physical activity for 4 weeks, followed by another 4 weeks of detraining. After the training period, the animals were treated with 2mg/ml chlorogenic acid by the gavage method.

Animals from trained and detraining groups were submitted to a progressive adaptive swimming training of three days (first day - 25 min, second day - 30 min and third day – 45 min). After adaptative training, a chronic swimming protocol was carried out as follow: 30 min for first week, 45 min for second week and 60 min for the following weeks(de Souza et al., 2021). After this period, the trained group continued to be submitted to the exercise protocol for another four weeks. Glass aquarium at 31°±1°C was used for swimming.

The animals were weighed weekly during treatment. After 8 weeks, the subjects underwent a battery of behavioral tests, including: open field, object recognition task light-dark box, tail suspension test. At the end of experimental design, in all cases, the mice were anesthetized by an injection of thiopental (90 mg/Kg, i.p.) and euthanized by decapitation. After euthanasia, the epididymal adipose tissue was dissected and weighed.

Ethics committee

This investigation was carried out according to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No.85-23, revised 1996) and the protocol was approved by Animal Experimental Ethics Committee of the "Barra Mansa University Center" (Barra Mansa, RJ, Brazil) under number 001/2022.

Behavioral tests

The tests were performed at one-day interval, and the order of tests within the battery was determined according to the progressive degree of invasiveness. Except for the object recognition test, all testing was performed between 7 and 13 a.m. During each test, the experimenter remained outside the testing room. Each test was recorded, and behavior parameters were analyzed by at least two observers.

Open Field Test

Each mouse was placed individually in the center of a white acrylic cage (30 cm × 30 cm × 15 cm) and allowed to explore the cage for five minutes. During this time, number of squares crossed, number of rearing (standing on hind legs with paws pressed against the wall of the arena), time of grooming, time in the center zone and center ratio (center distance to total distance ratio) were assessed. At the end of testing, the number of fecal pellets was also counted, and the arena was cleaned with a 10% ethanol solution. In this test, locomotor activity is indicated by the total distance traveled in the apparatus, while the vertical activity is assigned by the number of rearing. Concerning defecation, this parameter appeared, under some circumstances, to represent an emotional behavior. Lastly, anxiety-like responses were linked to time in the center zone and center ratio, whereas grooming time indicates higher stress responsiveness(Roth & Katz, 1980; Walsh & Cummins, 1976; Prut & Belzung, 2003; Dos-Santos et al., 2023).

Object recognition task

We used the open-field apparatus as the context to perform this experimental protocol. That way, each animal was introduced in the apparatus in the absence of objects or another behavioral stimulus for 5 minutes, for just 1 day. On the day after the end of the habituation period, the animals were subjected to a training session for memory acquisition. Two cell culture flasks filled with sand (A1 and A2) were placed at opposite corners of the apparatus used for the test. Thus, each animal was positioned individually in the arena center, and the familiarization session was stopped when there has been a 20 s exploration of both objects and when a 10 min period is over. After 6 hours, the animals were exposed again to the test context for object recognition. In this step used to assess the ability of them to retain information, it was used as a familiar object (A3) and a new object (B), a tower of bulding bricks. As in the training session, the retention test also lasted 5 minutes(Leger et al., 2013).

It is noteworthy that between each animal tested, the apparatus and the objects were properly sanitized with alcohol 70% to counteract any olfactory clue. Moreover, the exploration was only considered when the animals put the nose at up to 2 cm towards objects. Any other kind of physical contact, such as to lean, or climb over objects, was not considered as exploration. The basic measurements were the time spent by rats in exploring each object during the retention test. From this basic value, absolute and relative discrimination index could be calculated. The variable e is the total time spent investigating both objects during the retention test. The absolute discrimination index depicts the absolute difference in exploitation between the new and the familiar objects. The relative discrimination index index shows the proportion of e devoted to the novel object(Akkerman et al., 2012).

Light-Dark Box Test

The animals were individually placed in an acrylic cage (45 cm × 27 cm × 27 cm) unequally divided into two chambers by a black partition containing a small opening. Two-thirds of this chamber was illuminated (200 lux), and the remaining section was closed and dark. Mice were placed inside the dark side and allowed to freely move between the two chambers for 5 min. During this time, the time spent on the light side, number of transitions and latency to first entry into the light side was recorded. In this test, these parameters are associated with anxiety-like behavior (Crawley & Goodwin, 1980).

Tail Suspension Test

In this protocol, the mice were suspended 100 cm above the stand by adhesive tape placed approximately 1 cm from the tip of the tail. The test was videotaped for five minutes. During this period, the time of immobility and latency to the first immobility episode were evaluated. The immobility assumes a low resilience, and consequently, a high level of depression-like behavior (Porsolt, Le Pichon, & Jalfre, 1977).

Statistical analysis

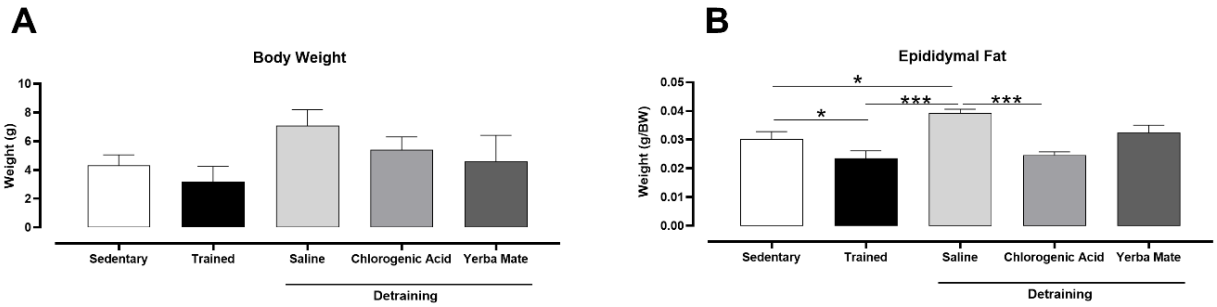
All results are presented as the means ± SE. The assumption of normal data distribution was assessed with the Shapiro-Wilk test. If the data did pass the normality test, parametric comparisons were performed. In this case, we used one-way ANOVA combined with Tukey Post Hoc test. Grubbs' test was used for detecting outliers. Differences were considered statistically significant when $p < 0.05$. GraphPad Prism 8 statistical software (La Jolla, CA, USA) was used for all statistical analyses.

Results

Body Weight Gain and Epididymal Adipose Tissue Weight

Although we did not verify differences in body weight gain (Figure 1A), there were significant changes in the epididymal fat relative weight between the experimental groups [F (4, 44) = 8.28, p < 0.001]. According to the Tukey post hoc test, the TRN mice had lower relative weight of epididymal fat when compared to the SED group. In addition, DET group had a higher relative weight of epididymal fat when compared to the other groups (Figure 1B).

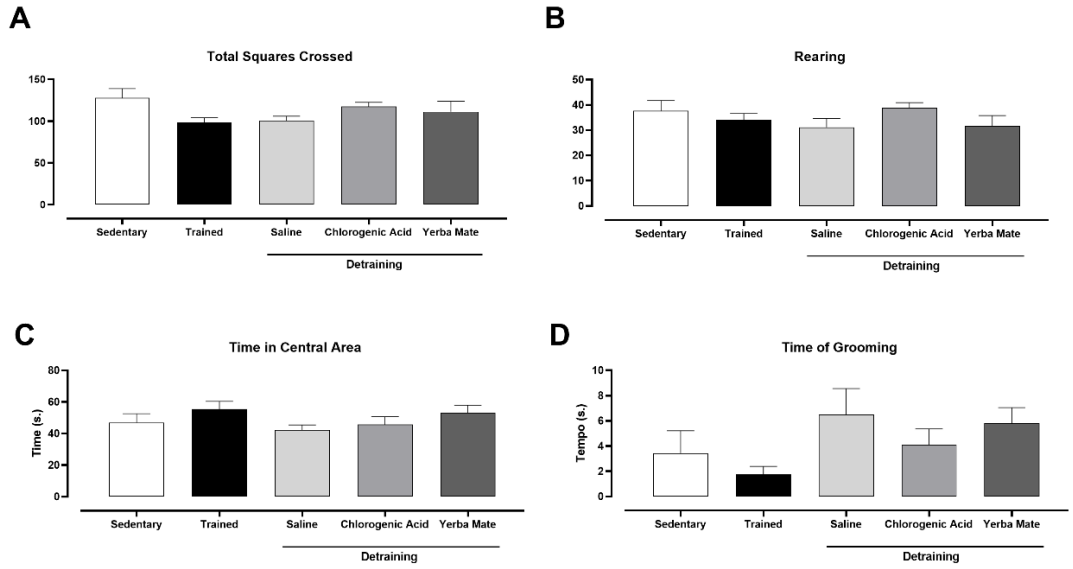
Figure 1. Figure 1 shows body weight (A) and epididymal fat relative weight (B) of trained and detraining mice. The detraining groups were treated with saline, chlorogenic acid or yerba mate. The trained mice had lower relative weight of epididymal fat when compared to the sedentary group. There were significant changes in the epididymal fat relative weight between detraining mice treated with saline and the other experimental groups. * represents p < 0.05 and ***, p < 0.001. Data represent the mean ± standard error of the mean. n=10.



Behavioral Analysis

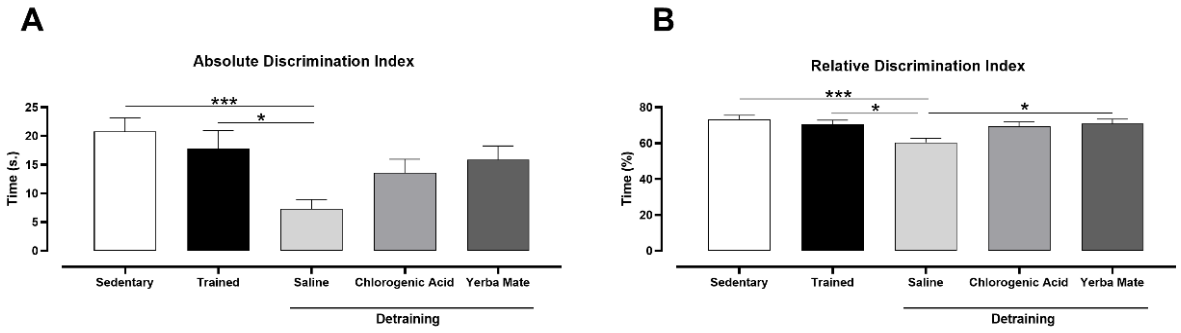
In the open field test, no significant differences were found either in parameters related to anxiety-like behavior or in those associated with exploration (Figure 2).

Figure 2. Figure 2 shows the behavioral parameters of the open field test test in trained and detraining mice. The detraining groups were treated with saline, chlorogenic acid or yerba mate. In this protocol, no differences were observed between the experimental groups. Data represent the mean ± standard error of the mean. n=10.



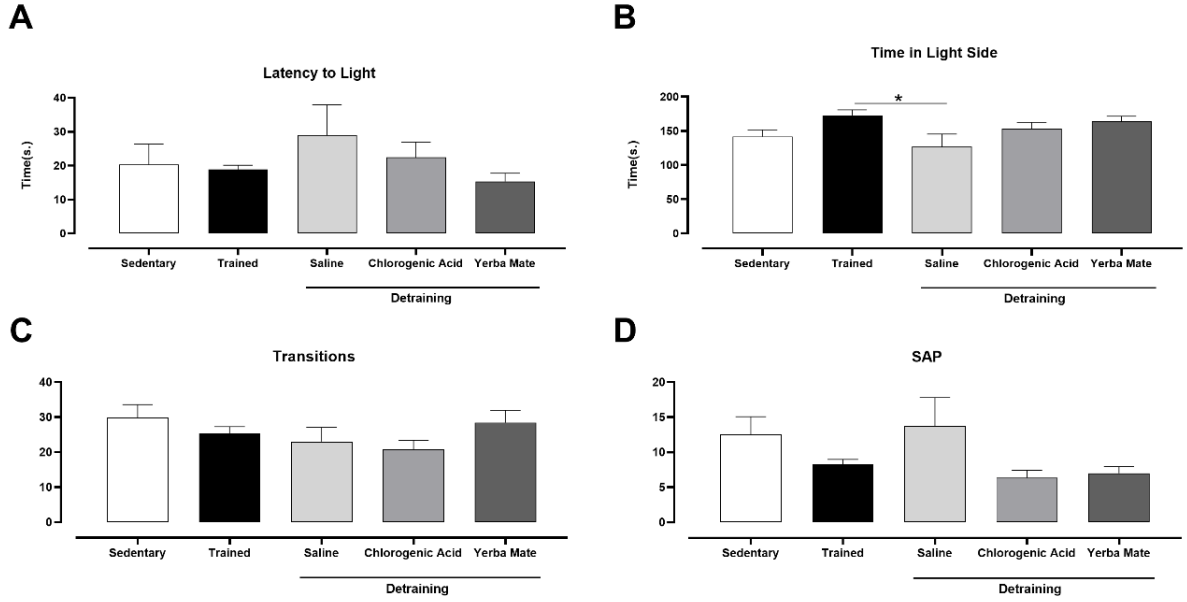
In the object recognition task, it was demonstrated significative changes in the absolute [F (4, 43) = 4.09, p = 0.006] and the relative [F (4, 42) = 4.27, p = 0.005] discriminative indexes between experimental groups (Figure 3). According to the Tukey post hoc test, the absolute discriminative index was lower in the DET group than in the SED and DET group. The treatment with yerba mate or chlorogenic acid partially reversed this alteration in the DET groups. The relative discriminative index was also lower in the DET group than in the SED and TRN group. In this variable, the yerba mate treatment reversed totally the mnemonic deficit. No difference was observed in the total exploration time of the objects.

Figure 3. Figure 3 shows the behavioral parameters of the object recognition task in trained and detraining mice. The detraining groups were treated with saline, chlorogenic acid or yerba mate. In this protocol, it was verified a cognitive impairment in the detraining group treated with saline 0,9%. The treatment with yerba mate fully reversed this mnemonic deficit. * represents p < 0.05 and ***, p < 0.001. Data represent the mean ± standard error of the mean. n=10.



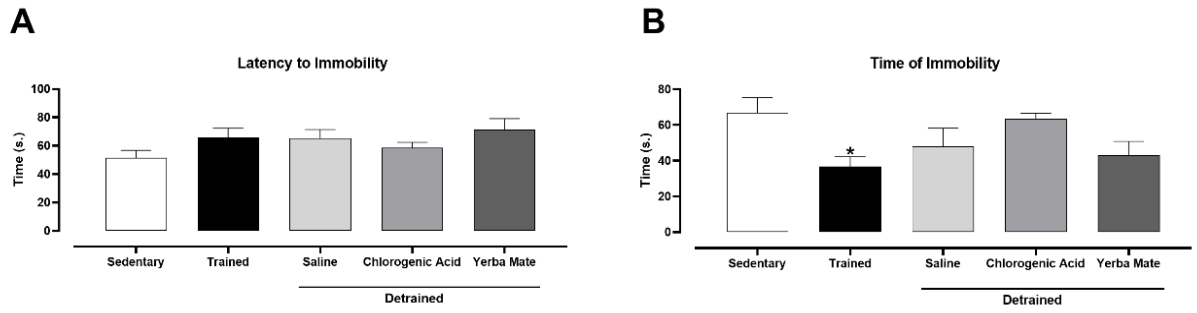
We also recorded interesting data in the light-dark box paradigm (Figure 4). In this test, we observed a significant difference in the time spent in the light side [F (4, 37) = 2,691, p = 0.04]. According to the Tukey post hoc test, the TRN group had an increased time in the light side than DET group (14.6 ± 0.79 s. vs. 20.7 ± 1.65 s., p = 0.002). No difference was observed in the other parameters.

Figure 4. Figure 4 shows the behavioral parameters of the light-dark box test in trained and detraining mice. The detraining groups were treated with saline, chlorogenic acid or yerba mate. In this protocol, it was verified anxiety-like behavior in the detraining group. treated with saline 0,9%. The treatment with yerba mate or chlorogenic acid partially reversed this anxiety-like behavior. * represents p < 0.05. Data represent the mean ± standard error of the mean. n=10.



Regarding tail suspension test (Figure 5), we verified a significant difference in time of immobility [F (4, 40) = 3,06, p = 0.02]. According to the Tukey post hoc test, the TRN group had a decreased time of immobility when compared with SED group (36.6 ± 5.53s. s. vs. 67 ± 8.37 s., p = 0.04).

Figure 5. Figure 5 shows the behavioral parameters of the tail suspension test in trained and detraining mice. The detraining groups were treated with saline, chlorogenic acid or yerba mate. In this protocol, it was verified antidepressant behavior in the trained group. * represents $p < 0.05$. Data represent the mean ± standard error of the mean. n=10.



Discussion

According to our results, although there were no statistical differences in weight gain, the DET group had a higher relative weight of epididymal fat compared to the SED, TRN and the DET +CA groups. According to Sertié and co-authors, the physical detraining is correlated with increased glucose transport and oxidation in periepididymal white adipose tissue in rats. Probably, this increased glucose oxidation rate allowed an increase in energy supply for triacylglycerol synthesis(Sertié et al., 2015). This process might be related to the increases in tissue-specific insulin sensitivity(Sertie et al., 2013). CGA treatment reverses this effect since it induced lipolysis, upregulated AMPK and browning gene expression and downregulated peroxisome proliferator-activated receptor γ (PPARγ) at both transcriptional and protein levels(Vasileva et al., 2020). In general, these actions are similar to exercise training-induced irisin in browning of white fat.

It was also shown that physical activity promoted an antidepressant effect in male mice. However, the prolonged detraining abolishes this effect. Additionally, detraining causes an increase in anxiety-like behavior and a memory impairment when compared to the trained group. Interestingly, these deleterious effects induced by detraining are partially reversed by treatment with yerba mate or chlorogenic acid. To explain these results, we have three non-mutually exclusive hypotheses: the activation of hippocampal BDNF-tyrosine kinase B (TrkB) signaling, the irisin levels and the cholinergic function augmentation.

BDNF is a neurotrophic that is essential to the growth, differentiation, survival and synaptogenesis of neurons in brain regions involved in emotional and cognitive function(Miranda et al., 2019). This neurotofin binds to the TrkB receptor and the p75 neurotrophins receptor (p75NTR), with a higher affinity for TrkB(Colucci-D'amato et al., 2020). Activation of p75NTR promotes apoptotic and neurodegenerative processes, while activation of TrkB induces protective and anti-apoptotic effects(S. Der Chen et al., 2017; Kraemer et al., 2014). Lower levels of BDNF are related to cognitive deficit and depressive state in patients with psychiatric or neurodegenerative disorders(Bawari et al., 2019; Castrén & Monteggia, 2021; Lima Giacobbo et al., 2019; Ventriglia et al., 2013; Zuccato & Cattaneo, 2009). In this context, physical activity induces an increase in the BDNF levels in both healthy and depressed patients. This effect depends on the intensity, duration and type of physical activity(Pedersen, 2019; Schmolesky et al., 2013). Thereby, in our study, we believe that antidepressant effects induced by swimming training may be related to activation of the BDNF-TrkB pathway in the hippocampus. These results are consistent with other studies that have already been published.

On the other hand, as mentioned above, the detraining abolished the antidepressant effects induced by the swimming training. Moreover, the detraining promoted memory capability impairment and anxiogenic effects when compared to TRN group. These results are similar to those published by Radak and colleagues (2006). According this group, detraining reduces BDNF levels and cognitive enhancement induced by swimming training(Radak et al., 2006). Similarly, it was also verified that abrupt interruption of prolonged spontaneous exercise decrease expression of mRNA encoding BDNF and TrkB in certain hippocampal areas in rats(Widenfalk et al., 1999). Thereby, a disruption of BDNF-TrkB signaling could explain the negative effects caused by the detraining.

The present work also raises the reasons by which yerba mate and one of its main constituents, chlorogenic acid, are able to reverse the negative effects promoted by detraining. Both in vivo animal experiments and in vitro cell experiments have shown have shown that chlorogenic acid is able to activate the BDNF-TrkB pathway(Liu et al., 2020; Yao et al., 2019). According Zhao and coworkers, the chlorogenic acid inhibits the serotonin transporter and indoleamine 2,3-dioxygenas. These actions increase the bioavailability at synaptic clefts of serotonin. Consequently, there is activation cAMP-CREB-BDNF signaling pathway and reduction of chronic restraint stress-induced prefrontal cortex injury and depression-like behavior in rats(Zhao et al., 2022). Possibly, these chlorogenic acid actions could explain the reversal of the anxiogenic effect and the cognitive deficit induced by the detraining. Further studies will also be needed to explain the chlorogenic acid and yerba mate actions on the expression and activity of plasmins responsible for the conversion of pro-BDNF to BDNF.

In recent years, it has been discovered that some actions promoted by physical activity are induced by a myokine called irisin. This myokine is mainly produced by skeletal muscle after exercise and exposure to cold, and its gene expression is mediated by the transcription factor PGC-1α(Flori et al., 2021; Perakakis et al., 2017). The irisin levels is positively correlated with antidepressant effects, working memory, hippocampal BDNF levels and hippocampal cell proliferation(Pesce et al., 2021). Based on this premise, the administration of irisin-neutralizing antibody abolishes the cognitive improvement and the increase in BDNF levels induced by exercise in mice underwent to physical inactivity. Thus, the beneficial actions caused by exercise could be induced by irisin. Interestingly, Souza and colleagues found that the administration of roasted yerba mate increases irisin levels in sedentary mice(de Souza et al., 2021). In this context, in our work, the reversal of the harmful effects of detraining caused by the yerba mate or chlorogenic acid treatment could also be related to the modulation of irisin levels.

Finally, we need to highlight that acetylcholine is an important neuromodulator involved with memory and learning. It is well known that acute exercise increases cholinergic input in the cortex and hippocampus (Kurosawa et al., 1993). Moreover, the chronic exercise prevented the loss of cholinergic inputs in the hippocampus in aged mice(Xu et al., 2019). The swimming training also decreased AChE activity in the medial prefrontal cortex and hippocampus and, consequently, improvements in learning and memory(Farzi et al., 2019). Similarly, chlorogenic acid also inhibits cholinesterase activity. According Know and coworkers, the chlorogenic acid prevents scopolamine-induced amnesia by inhibiting acetylcholinesterase and reducing free radicals in the hippocampus and prefrontal cortex of mice(Kwon et al., 2010). Therefore, the cognitive function improvement in the detraining group treated with chlorogenic acid and yerba mate can be explained by the modulation of the cholinergic system.

To explain the reversal of anxiogenic behavior in the detrained animals treated with yerba mate, we must resort to a work published by Santos and colleagues. According to this group, the chronic treatment with hydroethanolic extract of Ilex paraguariensis promotes anxiolytic effects in Swiss mice. According to the authors, the same dose capable of inducing anxiolytics, also promote increased activity of acetylcholinesterase in the hippocampus(Santos et al., 2015). Such results are consistent with data obtained in the literature, in which acetylcholinesterase knockout mice have anxiogenic behavior, characterized by a lower percentage of permanence in the open arms in the elevated plus maze test(Mineur et al., 2013). Thus, it is also possible that the anxiolytic actions of *Ilex paraguariensis* may be explained by its modulation in cholinergic pathways associated with the affective behaviors.

Conclusions

In conclusion, based on our results, yerba mate and chlorogenic acid partially reverse the behavioral changes and cognitive decline caused by detraining. Further studies will be necessary to demonstrate the molecular mechanisms related to the beneficial actions of chlorogenic acid and yerba mate, especially those involving the BDNF- TrkB signaling. In addition, although the actions of chlorogenic acid and yerba mate are similar, we need to emphasize that the protective properties of the whole extract of Ilex paraguariensis against detraining are the result of the combined effects of all its natural antioxidant compounds, and not only of the properties of chlorogenic acid.

The findings of the study on the effects of yerba mate and chlorogenic acid during detraining have significant practical implications, underscoring the importance of maintaining a regular physical activity program to prevent adverse outcomes such as weight gain and compromised mental health. Incorporating natural supplements like yerba mate may serve as an effective strategy to mitigate the negative impacts of exercise interruption, benefiting both physical and mental health.

For future research, it is crucial to explore the biological mechanisms underlying the beneficial effects of yerba mate and chlorogenic acid, as well as to conduct longitudinal studies in human populations to validate the results observed in animal models. Analyzing the effectiveness of different dosages and assessing combined approaches involving exercise, diet, and supplementation may reveal synergies that promote both mental and physical health, contributing to more effective integrated interventions. These research directions are fundamental for enhancing our understanding of the effects of detraining and associated nutritional interventions.

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References

Ahmed, H., Blaha, M., Nasir, K., … J. R.-T. A. journal of, & 2012, undefined. (n.d.). Effects of physical activity on cardiovascular disease. *Elsevier*. Retrieved January 24, 2023, from https://www.sciencedirect.com/science/article/pii/S0002914911027597?casa_token=YJ16Chw9c-cAAAAA:UjX2_nf0Xd1G1NMGTMAEXmXVC37PfWH8VF2f79EHTZbNFrGSoWHaBSPFOlYD_usWM8KRsi105h8

Akkerman, S., Blokland, A., Reneerkens, O., van Goethem, N. P., Bollen, E., Gijselaers, H. J. M., Lieben, C. K. J., Steinbusch, H. W. M., & Prickaerts, J. (2012). Object recognition testing: Methodological considerations on exploration and discrimination measures. *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2012.03.022

Bawari, S., Tewari, D., Argüelles, S., Sah, A. N., Nabavi, S. F., Xu, S., Vacca, R. A., Nabavi, S. M., & Shirooie, S. (2019). Targeting BDNF signaling by natural products: Novel synaptic repair therapeutics for neurodegeneration and behavior disorders. In *Pharmacological Research* (Vol. 148). https://doi.org/10.1016/j.phrs.2019.104458

Bracesco, N., Sanchez, A. G., Contreras, V., Menini, T., & Gugliucci, A. (2011). Recent advances on Ilex paraguariensis research: Minireview. In *Journal of Ethnopharmacology* (Vol. 136, Issue 3). https://doi.org/10.1016/j.jep.2010.06.032

Carbone, S., Del Buono, M. G., Ozemek, C., & Lavie, C. J. (2019). Obesity, risk of diabetes and role of physical activity, exercise training and cardiorespiratory fitness. In *Progress in Cardiovascular Diseases* (Vol. 62, Issue 4). https://doi.org/10.1016/j.pcad.2019.08.004

Castrén, E., & Monteggia, L. M. (2021). Brain-Derived Neurotrophic Factor Signaling in Depression and Antidepressant Action. In *Biological Psychiatry* (Vol. 90, Issue 2). https://doi.org/10.1016/j.biopsych.2021.05.008

Chen, S. Der, Wu, C. L., Hwang, W. C., & Yang, D. I. (2017). More insight into BDNF against neurodegeneration: Anti-apoptosis, anti-oxidation, and suppression of autophagy. In *International Journal of Molecular Sciences* (Vol. 18, Issue 3). https://doi.org/10.3390/ijms18030545

Chen, Y. T., Hsieh, Y. Y., Ho, J. Y., Lin, T. Y., & Lin, J. C. (2022). Two weeks of detraining reduces cardiopulmonary function and muscular fitness in endurance athletes. *European Journal of Sport Science*, *22*(3). https://doi.org/10.1080/17461391.2021.1880647

Coelho, G. C., Riachi, L. G., Marcellini, P. S., & De Maria, C. A. B. (2019). Yerba Mate Consumption Effect on the Total Concentration of Creatine Phosphokinase in Healthy Volunteers from the Age of 50. *European Journal of Medical and Health Sciences*, *1*(3). https://doi.org/10.24018/ejmed.2019.1.3.58

Colucci-D'amato, L., Speranza, L., & Volpicelli, F. (2020). Neurotrophic factor bdnf, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. In *International Journal of Molecular Sciences* (Vol. 21, Issue 20). https://doi.org/10.3390/ijms21207777

Corvos-Hidalgo, C., Melendez-Gallardo, J., Pintos-Toledo, E., Silveira, A., & Souza-Marabotto, F. (2024). Ejercicio físico y diabetes mellitus tipo 1: Una revisión narrativa (Physical exercise and type 1 diabetes mellitus: A narrative review). *Retos*, 51, 159–166. https://doi.org/10.47197/retos.v51.99366

Crawley, J., & Goodwin, F. K. (1980). Preliminary report of a simple animal behavior model for the anxiolytic effects of benzodiazepines. *Pharmacology, Biochemistry and Behavior, 13*(2), 167-170. https://doi.org/10.1016/0091-3057(80)90067-2

de Souza, V. L., Stutz, E. T. G., De S. F. Pehrson, M. E., Coelho, G. C., Netto, C. C., & de Maria, C. A. B. (2021). Ilex paraguariensisA. St.-Hil. (Yerba Mate) Differently Regulates the Lipid Mobilization and, Irisin and Lactate Levels in Sedentary and Chronic Swimming Mice. *European Journal of Medical and Health Sciences*, *3*(6). https://doi.org/10.24018/ejmed.2021.3.6.1088

Dos-Santos, R. C., Silva-Almeida, C., Marinho, B. G., Conceição, R. R., Côrtes, W. S., Ahmed, R. G., & Laureano-Melo, R. (2023). Perinatal N(G)-Nitro-L-arginine methyl ester administration decreases anxiety- and depression-like behaviors in adult mice. *Einstein (São Paulo), 21*, eAO0302. https://doi.org/10.31744/einstein_journal/2023AO0302

DIshman, R. K., McDowell, C. P., & Herring, M. P. (2021). Customary physical activity and odds of depression: A systematic review and meta-analysis of 111 prospective cohort studies. In *British Journal of Sports Medicine* (Vol. 55, Issue 16). https://doi.org/10.1136/bjsports-2020-103140

Farzi, M. A., Sadigh-Eteghad, S., Ebrahimi, K., & Talebi, M. (2019). Exercise Improves Recognition Memory and Acetylcholinesterase Activity in the Beta Amyloid-Induced Rat Model of Alzheimer's Disease. *Annals of Neurosciences*, *25*(3). https://doi.org/10.1159/000488580

Flori, L., Testai, L., & Calderone, V. (2021). The "irisin system": From biological roles to pharmacological and nutraceutical perspectives. In *Life Sciences* (Vol. 267). https://doi.org/10.1016/j.lfs.2020.118954

Friedman, M. A., Szczepankiewicz, R. P., & Kohn, D. H. (2018). Combined mineral-supplemented diet and exercise increases bone mass and strength after eight weeks and maintains increases after eight weeks detraining in adult mice. *PLoS ONE*, *13*(9). https://doi.org/10.1371/journal.pone.0204470

Gómez Chávez, L. F. J., Cortés Almanzar, P., Rodríguez Melchor, V. Z. del C., Salazar Pérez, J. I., & Gómez Chávez, M. Y. (2022). Actividad física y cáncer: una revisión bibliométrica 2016-2021 [Physical activity and cancer: A bibliographic review 2016-2021]. *Retos, 45*, 622–627. https://doi.org/10.47197/retos.v45i0.92728

Huang, X., Zhao, X., Li, B., Cai, Y., Zhang, S., Wan, Q., & Yu, F. (2022). Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: A systematic review and network meta-analysis. In *Journal of Sport and Health Science* (Vol. 11, Issue 2). https://doi.org/10.1016/j.jshs.2021.05.003

Izquierdo-Gabarren, M., De Txabarri Expósito, R. G., De Villarreal, E. S. S., & Izquierdo, M. (2010). Physiological factors to predict on traditional rowing performance. *European Journal of Applied Physiology*, *108*(1). https://doi.org/10.1007/s00421-009-1186-3

Kraemer, B. R., Yoon, S. O., & Carter, B. D. (2014). The biological functions and signaling mechanisms of the p75 neurotrophin receptor. *Handbook of Experimental Pharmacology*, *220*. https://doi.org/10.1007/978-3-642-45106-5_6

Kurosawa, M., Okada, K., Sato, A., & Uchida, S. (1993). Extracellular release of acetylcholine, noradrenaline and serotonin increases in the cerebral cortex during walking in conscious rats. *Neuroscience Letters*, *161*(1). https://doi.org/10.1016/0304-3940(93)90143-9

Kwon, S. H., Lee, H. K., Kim, J. A., Hong, S. I., Kim, H. C., Jo, T. H., Park, Y. I., Lee, C. K., Kim, Y. Bin, Lee, S. Y., & Jang, C. G. (2010). Neuroprotective effects of chlorogenic acid on scopolamine-induced amnesia via anti-acetylcholinesterase and anti-oxidative activities in mice. *European Journal of Pharmacology*, *649*(1–3). https://doi.org/10.1016/j.ejphar.2010.09.001

Leger, M., Quiedeville, A., Bouet, V., Haelewyn, B., Boulouard, M., Schumann-Bard, P., & Freret, T. (2013). Object recognition test in mice. *Nature Protocols*. https://doi.org/10.1038/nprot.2013.155

Lima Giacobbo, B., Doorduin, J., Klein, H. C., Dierckx, R. A. J. O., Bromberg, E., & de Vries, E. F. J. (2019). Brain-Derived Neurotrophic Factor in Brain Disorders: Focus on Neuroinflammation. In *Molecular Neurobiology* (Vol. 56, Issue 5). https://doi.org/10.1007/s12035-018-1283-6

Liu, D., Wang, H., Zhang, Y., & Zhang, Z. (2020). Protective effects of chlorogenic acid on cerebral ischemia/reperfusion injury rats by regulating oxidative stress-related nrf2 pathway. *Drug Design, Development and Therapy*, *14*. https://doi.org/10.2147/DDDT.S228751

Mazzucatto, F., Higa, T. S., Fonseca-Alaniz, M. H., & Evangelista, F. S. (2014). Reversal of metabolic adaptations induced by physical training after two weeks of physical detraining. *International Journal of Clinical and Experimental Medicine*, *7*(8).

McDowell, C. P., Dishman, R. K., Gordon, B. R., & Herring, M. P. (2019). Physical Activity and Anxiety: A Systematic Review and Meta-analysis of Prospective Cohort Studies. In *American Journal of Preventive Medicine* (Vol. 57, Issue 4). https://doi.org/10.1016/j.amepre.2019.05.012

Mctiernan, A., Friedenreich, C. M., Katzmarzyk, P. T., Powell, K. E., Macko, R., Buchner, D., Pescatello, L. S., Bloodgood, B., Tennant, B., Vaux-Bjerke, A., George, S. M., Troiano, R. P., & Piercy, K. L. (2019). Physical Activity in Cancer Prevention and Survival: A Systematic Review. In *Medicine and Science in Sports and Exercise* (Vol. 51, Issue 6). https://doi.org/10.1249/MSS.0000000000001937

Mineur, Y. S., Obayemi, A., Wigestrand, M. B., Fote, G. M., Calarco, C. A., Li, A. M., & Picciotto, M. R. (2013). Cholinergic signaling in the hippocampus regulates social stress resilience and anxiety- and depression-like behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(9). https://doi.org/10.1073/pnas.1219731110

Miranda, M., Morici, J. F., Zanoni, M. B., & Bekinschtein, P. (2019). Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. In *Frontiers in Cellular Neuroscience* (Vol. 13). https://doi.org/10.3389/fncel.2019.00363

Murach, K. A., Mobley, C. B., Zdunek, C. J., Frick, K. K., Jones, S. R., McCarthy, J. J., Peterson, C. A., & Dungan, C. M. (2020). Muscle memory: myonuclear accretion, maintenance, morphology, and miRNA levels with training and detraining in adult mice. *Journal of Cachexia, Sarcopenia and Muscle*, *11*(6). https://doi.org/10.1002/jcsm.12617

Orba-Pinheiro, C. J., Gama Linhares, D., Lima dos Santos, L., Pereira Salustiano Mallen da Silva, G. C., Maria Almeida de Figueiredo, N., Eduardo Jofré-Saldía, E., Oliveira Barros dos Santos, A., Brandão Pinto de Castro, J., & Gomes de Souza Vale, R. (2024). Prescripción de ejercicio físico para mujeres posmenopáusicas con osteopenia u osteoporosis basada en una revisión sistemática de ensayos clínicos aleatorizados [Prescription of physical exercise for postmenopausal women with osteopenia or osteoporosis based on a systematic review of randomized clinical trials]. *Retos, 52*, 647–656. https://doi.org/10.47197/retos.v52.102439

Paffenbarger, R. S., Blair, S. N., & Lee, I. M. (2001). A history of physical activity, cardiovascular health and longevity: the scientific contributions of Jeremy N Morris, DSc, DPH, FRCP. *International Journal of Epidemiology*, *30*(5), 1184–1192. https://doi.org/10.1093/IJE/30.5.1184

Pedersen, B. K. (2019). Physical activity and muscle–brain crosstalk. In *Nature Reviews Endocrinology* (Vol. 15, Issue 7). https://doi.org/10.1038/s41574-019-0174-x

Perakakis, N., Triantafyllou, G. A., Fernández-Real, J. M., Huh, J. Y., Park, K. H., Seufert, J., & Mantzoros, C. S. (2017). Physiology and role of irisin in glucose homeostasis. In *Nature Reviews Endocrinology* (Vol. 13, Issue 6). https://doi.org/10.1038/nrendo.2016.221

Pesce, M., Fratta, I. La, Paolucci, T., Grilli, A., Patruno, A., Agostini, F., Bernetti, A., Mangone, M., Paoloni, M., Invernizzi, M., & de Sire, A. (2021). From exercise to cognitive performance: role of irisin. In *Applied Sciences (Switzerland)* (Vol. 11, Issue 15). https://doi.org/10.3390/app11157120

Petek, B. J., Groezinger, E. Y., Pedlar, C. R., & Baggish, A. L. (2022). Cardiac effects of detraining in athletes: A narrative review. In *Annals of Physical and Rehabilitation Medicine* (Vol. 65, Issue 4). https://doi.org/10.1016/j.rehab.2021.101581

Physical activity. (n.d.). Retrieved January 24, 2023, from https://www.who.int/news-room/fact-sheets/detail/physical-activity

Pinheiro, M. B., Oliveira, J., Bauman, A., Fairhall, N., Kwok, W., & Sherrington, C. (2020). Evidence on physical activity and osteoporosis prevention for people aged 65+ years: a systematic review to inform the WHO guidelines on physical activity and sedentary behaviour. In *International Journal of Behavioral Nutrition and Physical Activity* (Vol. 17, Issue 1). https://doi.org/10.1186/s12966-020-01040-4

Pisani, S., Mueller, C., Huntley, J., Aarsland, D., & Kempton, M. J. (2021). A meta-analysis of randomised controlled trials of physical activity in people with Alzheimer's disease and mild cognitive impairment with a comparison to donepezil. In *International Journal of Geriatric Psychiatry* (Vol. 36, Issue 10). https://doi.org/10.1002/gps.5581

Porsolt, R. D., Le Pichon, M., & Jalfre, M. (1977). Depression: A new animal model sensitive to antidepressant treatments. *Nature, 266*(5604), 730-732. https://doi.org/10.1038/266730a0

Prut, L., & Belzung, C. (2003). The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: A review. *European Journal of Pharmacology, 463*(1-3), 3-33. https://doi.org/10.1016/s0014-2999(03)01272-x

Radak, Z., Toldy, A., Szabo, Z., Siamilis, S., Nyakas, C., Silye, G., Jakus, J., & Goto, S. (2006). The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. *Neurochemistry International*, *49*(4). https://doi.org/10.1016/j.neuint.2006.02.004

Riachi, L. G., & De Maria, C. A. B. (2017). Yerba mate: An overview of physiological effects in humans. In *Journal of Functional Foods* (Vol. 38). https://doi.org/10.1016/j.jff.2017.09.020

Riachi, L. G., Simas, D. L. R., Coelho, G. C., Marcellini, P. S., Ribeiro da Silva, A. J., & Bastos de Maria, C. A. (2018). Effect of light intensity and processing conditions on bioactive compounds in maté extracted from yerba mate (Ilex paraguariensis A. St.-Hil.). *Food Chemistry*, *266*. https://doi.org/10.1016/j.foodchem.2018.06.028

Rodrigues da Conceição, R., Laureano-Melo, R., da Silva Almeida, C., Cenélia Matos da Silva, A., Luiz Bezerra da Silveira, A., Vidal Linhares, R., Porto Marassi, M., Akemi Sato, M., Giannoco, G., Costa e Silva, G., & Côrtes, W. (2024). El entrenamiento isométrico promueve cambios en la acetilcolinesterasa y la fuerza muscular [Isometric training promotes changes in acetylcholinesterase and muscle strength]. *Retos, 55*, 72–77. https://doi.org/10.47197/retos.v55.103877

Roth, K. A., & Katz, R. J. (1979). Stress, behavioral arousal, and open field activity: A reexamination of emotionality in the rat. *Neuroscience & Biobehavioral Reviews, 3*(4), 247-263. https://doi.org/10.1016/0149-7634(79)90012-5

Santos, E. C. S., Bicca, M. A., Blum-Silva, C. H., Costa, A. P. R., dos Santos, A. A., Schenkel, E. P., Farina, M., Reginatto, F. H., & de Lima, T. C. M. (2015). Anxiolytic-like, stimulant and neuroprotective effects of Ilex paraguariensis extracts in mice. *Neuroscience*, *292*. https://doi.org/10.1016/j.neuroscience.2015.02.004

Schmolesky, M. T., Webb, D. L., & Hansen, R. A. (2013). The effects of aerobic exercise intensity and duration on levels of brain- derived neurotrophic factor in healthy men. *Journal of Sports Science and Medicine*, *12*(3).

Sertie, R. A. L., Andreotti, S., Proença, A. R. G., Campana, A. B., Lima-Salgado, T. M., Batista, M. L., Seelaender, M. C. L., Curi, R., Oliveira, A. C., & Lima, F. B. (2013). Cessation of physical exercise changes metabolism and modifies the adipocyte cellularity of the periepididymal white adipose tissue in rats. *Journal of Applied Physiology*, *115*(3). https://doi.org/10.1152/japplphysiol.01272.2012

Sertié, R. A. L., Andreotti, S., Proença, A. R. G., Campaña, A. B., & Lima, F. B. (2015). Fat gain with physical detraining is correlated with increased glucose transport and oxidation in periepididymal white adipose tissue in rats. *Brazilian Journal of Medical and Biological Research*, *48*(7). https://doi.org/10.1590/1414-431X20154356

Tavassoli, H., Heidarianpour, A., & Hedayati, M. (2022). The effects of resistance exercise training followed by de-training on irisin and some metabolic parameters in type 2 diabetic rat model. *Archives of Physiology and Biochemistry*, *128*(1). https://doi.org/10.1080/13813455.2019.1673432

Teich, T., Pivovarov, J. A., Porras, D. P., Dunford, E. C., & Riddell, M. C. (2017). Curcumin limits weight gain, adipose tissue growth, and glucose intolerance following the cessation of exercise and

caloric restriction in rats. *Journal of Applied Physiology*, *123*(6). https://doi.org/10.1152/japplphysiol.01115.2016

Vasileva, L. V., Savova, M. S., Amirova, K. M., Balcheva-Sivenova, Z., Ferrante, C., Orlando, G., Wabitsch, M., & Georgiev, M. I. (2020). Caffeic and chlorogenic acids synergistically activate browning program in human adipocytes: Implications of AMPK-and PPAR-mediated pathways. *International Journal of Molecular Sciences*, *21*(24). https://doi.org/10.3390/ijms21249740

Ventriglia, M., Zanardini, R., Bonomini, C., Zanetti, O., Volpe, D., Pasqualetti, P., Gennarelli, M., & Bocchio-Chiavetto, L. (2013). Serum brain-derived neurotrophic factor levels in different neurological diseases. *BioMed Research International*, *2013*. https://doi.org/10.1155/2013/901082

Walsh, R. N., & Cummins, R. A. (1976). The open-field test: A critical review. *Psychological Bulletin, 83*(3), 482-504.

Widenfalk, J., Olson, L., & Thorén, P. (1999). Deprived of habitual running, rats downregulate BDNF and TrkB messages in the brain. *Neuroscience Research*, *34*(3). https://doi.org/10.1016/S0168-0102(99)00051-6

Xu, L., Long, J., Su, Z., Xu, B., Lin, M., Chen, Y., & Long, D. (2019). Restored presynaptic synaptophysin and cholinergic inputs contribute to the protective effects of physical running on spatial memory in aged mice. *Neurobiology of Disease*, *132*. https://doi.org/10.1016/j.nbd.2019.104586

Yao, J., Peng, S., Xu, J., & Fang, J. (2019). Reversing ROS-mediated neurotoxicity by chlorogenic acid involves its direct antioxidant activity and activation of Nrf2-ARE signaling pathway. *BioFactors*, *45*(4). https://doi.org/10.1002/biof.1507

Zhao, S., Yang, T., Hou, X., Zhang, H., Zhao, Y., Wang, H., Sun, N., Tan, H., Zhang, J., & Fan, H. (2022). Chlorogenic acid ameliorates chronic stress-induced prefrontal cortex injury through activating the 5-HT/BDNF signaling pathway in rats. *Food Bioscience*, *50*, 102179. https://doi.org/10.1016/J.FBIO.2022.102179

Zuccato, C., & Cattaneo, E. (2009). Brain-derived neurotrophic factor in neurodegenerative diseases. In *Nature Reviews Neurology* (Vol. 5, Issue 6). https://doi.org/10.1038/nrneurol.2009.54

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