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PATRÍCIA BERILLI BATISTA

POTENCIAL ANTIOXIDANTE E ANTI-INFLAMATÓRIO DO CHÁ BRANCO (*Camellia sinensis*) EM RATOS PRATICANTES DE CORRIDA

ANTIOXIDANT AND ANTI-INFLAMMATORY POTENTIAL OF WHITE TEA (C*amellia sinensis*) IN RUNNING TRAINED RATS

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Dissertação apresentada à Faculdade de Engenharia de Alimentos da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Alimentos e Nutrição, na Área de Nutrição Experimental e aplicada à Tecnologia de Alimentos.

Dissertation presented to the Faculty of Food Engineering of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Food and Nutrition, in the area of Experimental Nutrition and applied to Food Technology.

Supervisor/Orientador: Dr. MÁRIO ROBERTO MARÓSTICA JÚNIOR

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ESTE EXEMPLAR CORRESPONDE À VERSÃO FINAL DA DISSERTAÇÃO DEFENDIDA PELA ALUNA PATRÍCIA BERILLI BATISTA, ORIENTADA PELO PROF. DR. MÁRIO ROBERTO MARÓSTICA JÚNIOR E COORIENTADA PELO PROF. DR. GUSTAVO BERNARDES FANARO.

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DEDICATÓRIA

Ao meu amado filho, luz que ilumina os meus olhos e aquece o meu coração.

“Ninguém é suficientemente perfeito, que não possa aprender com o outro e, ninguém é totalmente estruído de valores que não possa ensinar algo ao seu irmão.”

São Francisco de Assis

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RESUMO

A prática regular de exercício físico proporciona diversos benefícios à saúde e maior longevidade. Contudo, exercícios agudos ou exaustivos estão associados com níveis elevados de estresse oxidativo, lesão muscular e inflamação, os quais podem refletir negativamente no rendimento físico e na saúde de seus praticantes. O chá branco (*Camellia sinensis)* é uma bebida abundante em compostos fenólicos, pouco estudada do ponto de vista nutricional, e que desperta interesse quanto as suas propriedades funcionais no organismo. Assim, o objetivo deste trabalho foi avaliar os efeitos da ingestão de chá branco em marcadores de estresse oxidativo e de inflamação de ratos treinados em corrida, após uma sessão aguda de exercício físico exaustivo. Ratos Wistar foram divididos em grupos que receberam: 1) Chá branco (5 g de planta por L de água); 2), Chá branco diluído em água (50:50; v/v); ou 3) Água. As bebidas foram ingeridas, *ad libitum*, por 5 ou 10 semanas, concomitantemente a um treinamento de corrida. Testes de exaustão foram aplicados antes e após os períodos experimentais. Após a eutanásia o soro e o fígado dos animais foram coletados para análise. Como resultado, o programa de treinamento de corrida utilizado foi capaz de melhorar o rendimento dos animais treinados durante o teste de exaustão com relação aos animais sedentários. O chá branco foi bem aceito e não promoveu alteração de peso corporal ou peso dos órgãos dos animais. A ingestão do chá branco por 10 semanas, em ambas concentrações, promoveu maior capacidade antioxidante no soro dos animais apesar de não ter potencializado as defesas antioxidantes endógenas quando comparado à ingestão de água. O chá branco, em ambas concentrações, atenuou eficientemente a peroxidação lipídica no fígado dos animais após 10 semanas de ingestão. Além disso, aqueles animais que receberam o chá branco diluído durante 10 semanas também apresentaram maior atividade das enzimas antioxidantes e conteúdo de glutationa reduzida no fígado comparados aos animais que receberam água, sugerindo um efeito protetor do chá branco contra danos oxidativos neste órgão. Em nível sérico, a concentração de marcadores inflamatórios (interleucina-1β e interleucina-6) pode ser reduzida após a ingestão de chá branco em relação a ingestão de água. Como conclusão, a ingestão de chá branco por longos períodos pode contribuir para a promoção de um estado antioxidante favorável de ratos submetidos a uma sessão de exercício físico exaustivo.

ABSTRACT

A routine of regular physical exercise is related to many health benefits and improves longevity. However, acute or exhaustive exercises are associated with high levels of oxidative stress, muscle injury and inflammation, which could negatively affect performance and health. White tea (*Camellia sinensis*) is a polyphenol-rich beverage, poorly studied from the nutritional point of view, and arouses the interest in its functional properties in the body. Therefore, the aim of this study was to evaluate the effects of white tea intake on the oxidative stress and inflammatory markers of running-trained rats after an acute strenuous bout of exercise. The Wistar rats were divided into groups which received*:* 1) White tea (5 g of plant per L of water); 2) Water diluted white tea (50:50; v/v); or 3) Water. The drinks were consumed, *ad libitum,* for 5 or 10 weeks, concomitantly with the running training. Exhaustion tests were applied before and after the experimental periods. After euthanasia, serum and liver were collected for analysis. The applied running training protocol was able to improve the performance of the trained animals during the exhaustion test in relation to sedentary animals. White tea was well accepted and did not promote changes in body weight or organ weight of the animals. The white tea intake for 10 weeks, in both concentrations, promoted greater serum antioxidant capacity of the animals despite has not enhanced the endogenous antioxidant defenses compared to the water intake. White tea, in both concentrations, effectively attenuated the lipid peroxidation in the liver of the animals after 10 weeks of ingestion. Furthermore, the animals that received diluted white tea for 10 weeks also presented a higher antioxidant enzyme activities and reduced glutathione content in the liver compared to the animals that received water, suggesting a protective effect against oxidative damages in this organ. At serum level, the inflammatory markers contents (interleukin-1β and interleukin-6) could be reduced after the white tea intake in relation to the water intake. In conclusion, a long-term white tea intake could help to promote a favorable antioxidant status of rats subjected to an exhaustive physical exercise session.

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INTRODUÇÃO GERAL E OBJETIVOS

INTRODUÇÃO GERAL

Não há dúvidas de que a prática regular de exercício físico está associada com inúmeros benefícios à saúde. Comparado com indivíduos sedentários, indivíduos fisicamente ativos desfrutam de menor risco de mortalidade por todas as causas, doenças cardiovasculares, distúrbios do metabolismo, alguns tipos de câncer e depressão (WHO, 2010; MILLER *et al.*, 2014; AREM *et al.*, 2015).

Por outro lado, os benefícios resultantes da prática esportiva podem ser limitados sob algumas circunstâncias. Estudos têm demonstrado que exercícios intensos e prolongados, exercícios exaustivos ou ainda uma frequência de treinamento alta com períodos de recuperação inadequados podem resultar em efeitos indesejados. São citados casos de lesões musculares graves, susceptibilidade a infecções, inflamação e estresse oxidativo, os quais podem comprometer a qualidade de vida e a saúde, assim como o rendimento esportivo dos praticantes de exercício (HOHL *et al.*, 2009; TANSKANEN; ATALAY; UUSITALO, 2010; GLEESON *et al.*, 2013; MOHAMED; LAMYA; HAMDA, 2016).

Nas últimas décadas, o estresse oxidativo induzido pelo exercício físico vem ganhando notoriedade na literatura (PEAKE; SUZUKI; COOMBES, 2007; POWERS; JACKSON, 2008). Esta condição biológica é tida como o resultado de um desbalanço entre agentes oxidantes e antioxidantes, a favor dos primeiros, os quais são representados pelas “Espécies Reativas de Oxigênio e Nitrogênio” (ERONs) (SIES; CADENAS, 1985). Durante o exercício físico, vários mecanismos resultam na produção de ERONs, com destaque para o metabolismo aeróbico mitocondrial (DEATON; MARLIN, 2003). Quando associado ao treinamento físico regular, a produção de baixos ou moderados níveis de ERONs parece funcionar como estímulo necessário para que ocorram adaptações fisiológicas benéficas. Em contraste, a presença de ERONs em níveis elevados pode estar associada com danos oxidativos severos à componentes celulares, incluindo lipídios, proteínas e o material genético comprometendo o bom funcionamento do organismo (SIES; CADENAS, 1985; JACKSON, 1999; CRUZAT *et al.*, 2007).

A realização de uma única sessão de exercício de resistência já mostrou ser suficiente para elevar os marcadores de danos oxidativos no sangue (CECI *et al.*, 2014). No entanto, a magnitude dos danos oxidativos em resposta ao esforço físico é influenciada pela interação de diferentes fatores, dentre estes o estado nutricional individual, nível de treino e

magnitude do exercício (BLOOMER; FISHER-WELLMAN, 2008; MOHAMED *et al.*, 2016; ROH; CHO; SO, 2017).

A ativação de inflamação local e sistêmica induzida pelo exercício também tem um forte elo de ligação com o estresse oxidativo. Em resposta ao dano muscular, citocinas pró e anti-inflamatórias recrutam células fagocitárias do sistema imune que produzem ERONs no tecido lesado. As ERONs, por sua vez, estimulam a produção de mais citocinas por meio da ativação de vias redox sensitivas, resultando em um ciclo de retroalimentação (PEDERSEN; TOFT, 2000; SPURWAY *et al.*, 2006; KRZEMIŃSKI *et al.*, 2016).

Nesse contexto, abordagens nutricionais de caráter antioxidante têm sido estudadas no sentido de se amenizar os efeitos indesejados inerentes ao estresse oxidativo e à inflamação, contribuindo para a manutenção da saúde, para maximizar a recuperação pós-exercício e o rendimento nos esportes (CLOSE *et al.*, 2016).

O chá branco é obtido da infusão ou decocção de folhas recém-formadas e brotos não fermentados da *Camellia sinensis* (L.) Kuntze (HILAL; ENGELHARDT, 2007). Dentre os compostos bioativos do chá branco, os compostos fenólicos, especialmente as catequinas, se destacam pelo seu elevado potencial antioxidante (SHARANGI, 2009). Contudo, comparado com os demais chás da *C. sinensis*, como o chá verde, existem poucos relatos de estudos *in vivo* envolvendo as propriedades funcionais do chá branco (DIAS *et al.*, 2013).

Os chás da *C. sinensis* são frequentemente associados com diversos benefícios à saúde, os quais são atribuídos ao seu potencial antioxidante (BASU *et al.*, 2013), anti-inflamatório (CAVET *et al.*, 2011), antiobesogênico (CHEN *et al.*, 2009), antimutagênico (HAJIAGHAALIPOUR *et al.*, 2015), cardioprotetor (GREYLING *et al.*, 2014), entre outros. Considerando que os chás (*Camellia sinensis)* em conjunto assumem a posição de bebida manufaturada mais consumida no mundo, acredita-se que os chás, como o chá branco, sejam um veículo importante de compostos bioativos na alimentação da população mundial (CHANG, 2015).

Partindo do pressuposto de que a ingestão regular de compostos fenólicos é capaz de aumentar o potencial antioxidante do organismo, neste trabalho buscou-se avaliar o efeito da ingestão de chá branco em parâmetros associados ao estresse oxidativo induzido pelo exercício físico agudo extenuante (PANZA *et al.*, 2008; MARTINS; BARROS; FERREIRA, 2016).

OBJETIVOS

Objetivo geral

Avaliar os efeitos da ingestão de chá branco (*Camellia sinensis*) no perfil antioxidante e inflamatório de ratos Wistar treinados, após uma sessão aguda de exercício físico exaustivo.

Objetivos específicos

a) Determinar o conteúdo de compostos fenólicos e a capacidade antioxidante do chá branco *in vitro*;

b) Avaliar os efeitos da ingestão de chá branco em animais saudáveis considerando os seguintes parâmetros:

- Peso corporal e peso dos órgãos;
- Capacidade antioxidante sistêmica;
- Nível de peroxidação lipídica hepática;
- Atividade do sistema de defesa antioxidante endógeno (enzimas antioxidantes e glutationa reduzida) no soro e no fígado;
- Perfil inflamatório no soro e no fígado.

c) Determinar qual a concentração e o tempo de ingestão de chá branco refletem em melhores respostas nos parâmetros analisados *in vivo*.

CAPÍTULO 2

REVISÃO BIBLIOGRÁFICA

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1. O exercício físico como indutor de estresse oxidativo

O primeiro relato associando exercício físico e estresse oxidativo em humanos foi publicado há 40 anos quando Dillard *et al.* (1978) observaram que a concentração de pentano (subproduto da peroxidação lipídica) aumentava no gás expirado após uma sessão de exercício de intensidade moderada e longa duração. No mesmo estudo, os autores atestaram que a suplementação de vitamina E era capaz de reduzir a produção deste marcador de estresse oxidativo (DILLARD *et al.*, 1978). Desde então, muitos estudos têm sido conduzidos nesse sentido (THIRUMALAI *et al.*, 2011).

Radicais livres são moléculas que apresentam um ou mais elétrons não pareados em seu orbital eletrônico mais externo, tornando-as quimicamente muito reativas e de meia vida curta. O termo "espécies reativas de oxigênio e nitrogênio" (ERONs), por sua vez, engloba radicais livres derivados do oxigênio (radical superóxido e hidroxila) e do nitrogênio (óxido nítrico), assim como espécies não radicalares como o peróxido de hidrogênio (H_2O_2), o oxigênio *singlete* e o ácido hipocloroso (FERREIRA; MATSUBARA, 1997; BARBOSA *et al.*, 2010).

Em nível celular, vários componentes são alvo de oxidação das ERONs. A membrana das células, em função do alto teor de ácidos graxos insaturados, é altamente susceptível à peroxidação lipídica, processo que culmina em alterações estruturais e morte celular. Outros danos deletérios podem ocorrer em função da oxidação de lipídeos e ácidos nucléicos e da carbonilação de proteínas mediados pelas ERONs (POWERS; JACKSON, 2008; MADIAN *et al.*, 2011).

O organismo dispõe de um sistema de defesa especializado em combater espécies reativas que envolve antioxidantes enzimáticos e não enzimáticos. As enzimas antioxidantes incluem a catalase, a superóxido dismutase (em duas isoformas: cobre e zinco dependente, e manganês dependente), a glutationa peroxidase e a glutationa redutase. Os antioxidantes não enzimáticos, por sua vez, incluem as vitaminas C e E, a glutationa, os flavonoides, entre outros (AGUILÓ *et al.*, 2005; VALKO *et al.*, 2007). Esses compostos atuam em sinergia para manter a homeostase redox endógena (Figura 1) (BARBOSA *et al.*, 2010). Todavia, quando as defesas antioxidantes são incapazes de eliminar as espécies reativas eficientemente, ocorre um desequilíbrio a favor das segundas, caracterizando assim o estresse oxidativo (VALKO *et al.*, 2007).

Evidências científicas apontam que a cronicidade do estresse oxidativo está intimamente envolvida com o envelhecimento precoce, bem como com o desenvolvimento de vários processos fisiopatológicos como câncer (VALKO *et al.*, 2006), diabetes (REDDY *et al.*, 2009), doenças neurológicas (JIANG; SUN; CHEN, 2016), aterosclerose (LAKKUR *et al.*, 2015) e outras, comprovando que atenção especial deve ser voltada ao desbalanço no estado *redox* do organismo.

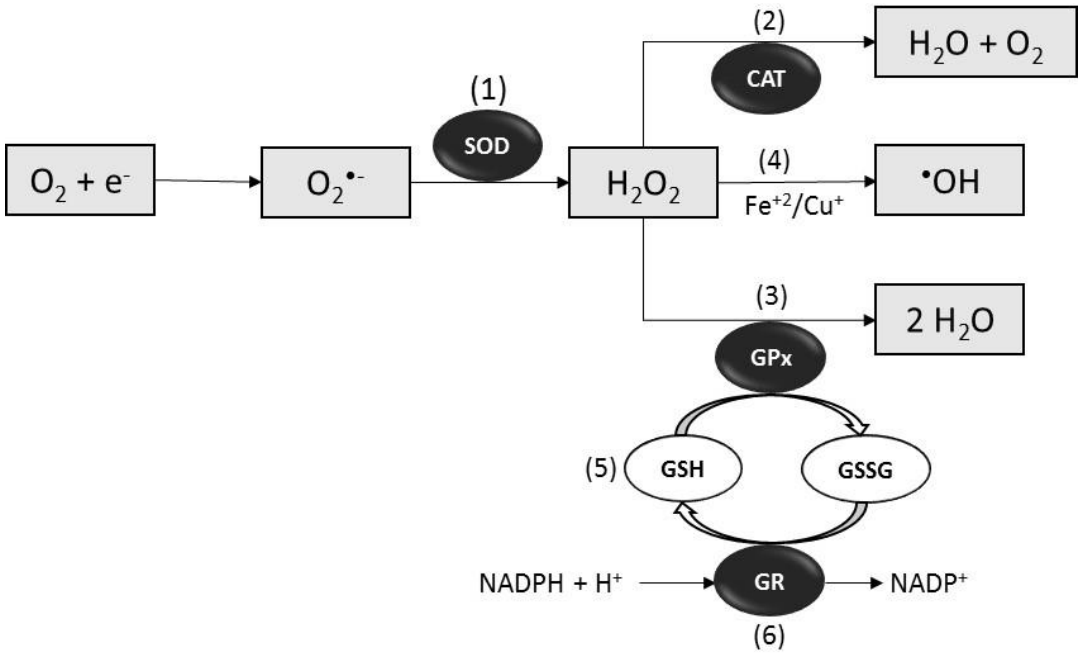

Figura 1. Esquema do funcionamento do sistema de defesa antioxidante enzimático com a participação da glutationa reduzida. (1) A superóxido dismutase (SOD) converte o radical ânion superóxido ($O_2^{\bullet-}$) em H_2O_2; (2 e 3) O H_2O_2, por sua vez, pode sofrer ação da catalase (CAT) ou da glutationa peroxidase (GPx) se convertendo a H_2O, ou, (4) na presença de metais de transição, o H_2O_2 se converte em radical hidroxila ($^{\bullet}OH$); (5) Quando a glutationa reduzida (GSH) é oxidada para garantir a ação da GPx, ocorre uma interligação de duas moléculas de GS por uma ponte dissulfeto, resultando em glutationa oxidada (GSSG); e (6) A glutationa redutase (GR) utiliza nicotinamida adenina dinucleotídeo fosfato (NADPH) para converter GSSG em GSH, permitindo assim a continuidade do ciclo redox da glutationa. Adaptado de Barbosa *et al.* (2010).

Durante e após o exercício físico ocorre um aumento da produção de ERONs como consequência de diversos processos (POWERS; NELSON; HUDSON, 2011). Nos exercícios de resistência, a fosforilação oxidativa mitocondrial é frequentemente reconhecida como a fonte

majoritária de espécies reativas de oxigênio (EROs). O oxigênio molecular (O_2), atuando como receptor de elétrons ao final da cadeira respiratória na mitocôndria, é essencial para a síntese aeróbica de adenosina trifosfato (ATP). No entanto, estima-se que cerca de 2-5% das moléculas de O_2 consumidas não sejam reduzidas completamente a moléculas de água (H_2O), produzindo EROs (H_2O_2 e ânion superóxido) como produtos intermediários. Considerando uma demanda energética e um consumo de O_2 substancialmente aumentados durante a contração muscular, a produção de EROs também aumenta proporcionalmente durante o exercício físico (DAVIES *et al.*, 1982; POWERS; JACKSON, 2008).

Outros mecanismos propostos de geração de espécies reativas em resposta ao exercício físico envolvem a ação da xantina oxidase (HELLSTEN *et al.*, 1997), o processo de isquemia-reperfusão nos tecidos, NADPH oxidases, a oxidação da hemoglobina, reações catalisadas por ferro, a ativação de células fagocitárias em resposta ao dano muscular, entre outros (DEATON; MARLIN, 2003; POWERS *et al.*, 2011).

Portanto, parece paradoxal que, embora o exercício desencadeie o estresse oxidativo, a prática regular do mesmo esteja associada a diversos benefícios à saúde que contribuem para a redução da incidência de doenças cardiovasculares (LIN *et al.*, 2015), câncer (HOJMAN *et al.*, 2017), diabetes mellitus tipo 2 (SANZ; GAUTIER; HANAIRE, 2010) e um menor risco de mortalidade por todas as causas (AREM *et al.*, 2015).

Conforme o princípio da adaptação, a quebra da homeostase é essencial para que ocorram adaptações a um agente estressor, desde que o estímulo seja continuado (HANS, 1936; JI; GOMEZ-CABRERA; VINA, 2006). Dessa forma, a exposição regular a níveis moderados ERONs, obtida por meio do treinamento físico, culmina em adaptações fisiológicas benéficas que em conjunto preparam o corpo para um novo estresse, tais como a melhoria das defesas antioxidantes e o aumento no conteúdo de mitocôndrias (JACKSON, 1999; POLI *et al.*, 2004; MASON *et al.*, 2016).

A homeostase redox sofre influência de diversas variáveis sendo, portanto, complexo demarcar claramente a quantidade de oxidação necessária para invocar respostas biológicas evolutivas ou danos deletérios (POWERS; JACKSON, 2008). Aspectos relacionados ao exercício, como a intensidade, o volume e o período de recuperação, além de aspectos relacionados ao praticante do exercício, como o nível de treino, o gênero e o estado nutricional, parecem exercer importante participação nesse processo (BLOOMER; FISHER-WELLMAN, 2008; MOHAMED *et al.*, 2016; ROH *et al.*, 2017).

O Colégio Americano de Medicina Esportiva (ACSM) recomenda que adultos (18-65 anos) saudáveis estejam engajados em treinamentos de exercícios aeróbicos de intensidade moderada (≥ 30 min/d em ≥ 5 d/sem) ou de intensidade vigorosa (≥ 20 min/d em ≥ 3 d/sem) para promover e manter a saúde. Outra alternativa seria trabalhar com uma combinação de exercícios de intensidade moderada e vigorosa para se atingir um gasto energético total de ≥ 500-1000 do equivalente metabólico (MET) do indivíduo por min/sem (considerando que 1 MET representa o gasto energético de um indivíduo enquanto está em repouso) (GARBER *et al.*, 2011).

Por outro lado, sessões agudas (em indivíduos não treinados) ou exaustivas de exercícios predominantemente aeróbicos ou anaeróbicos, assim como treinamentos intensos sem o devido período de recuperação, têm sido associados com danos oxidativos, além de inflamação e lesão muscular (LOVLIN *et al.*, 1987; NIMMO *et al.*, 2013; MRAKIC-SPOSTA *et al.*, 2015; MOHAMED *et al.*, 2016). No estudo de Turner *et al.* (2011), por exemplo, imediatamente após uma corrida de 233 km os participantes apresentaram níveis elevados de dano oxidativo no DNA de células mononucleares do sangue periférico (PBMC), peroxidação lipídica e carbonilação de proteínas no plasma, se estendendo por horas ou dias.

Além dos prováveis efeitos adversos à saúde como consequência da danificação de biomoléculas pelas ERONs, supõe-se que níveis elevados de estresse oxidativo induzidos pelo exercício também favoreçam a ocorrência fadiga muscular precoce e *overtraining,* comprometendo o rendimento esportivo (REID *et al.*, 1994; POWERS *et al.*, 2011; PINGITORE *et al.*, 2015). Reid *et al.* (1993) propuseram um modelo teórico para explicar a relação entre homeostase redox muscular e produção de força isométrica, conforme apresentado na Figura 2. Segundo os autores, existe um estado redox ótimo onde a produção máxima de força isométrica pode ser alcançada e qualquer desvio desse ponto resulta em prejuízos na produção de força pelo músculo.

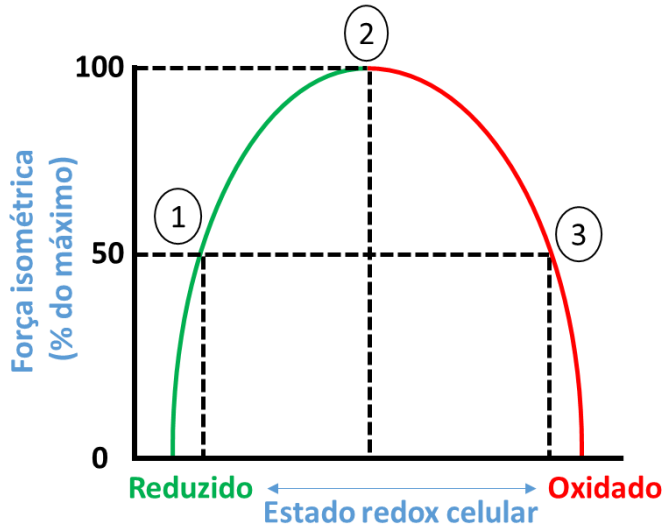

Figura 2. Modelo teórico proposto por Reid *et al.* (1993) e redesenhado por Powers *et al.* (2011), que descreve os efeitos bifásicos das ERONs na produção de força pelo músculo esquelético. 1) Ilustra a força gerada pelo músculo no seu estado basal; 2) ilustra a força produzida pelo músculo não fatigado exposto a baixos/moderados níveis de oxidantes. Este representa o estado redox ideal para a produção de força; e 3) Ilustra os efeitos deletérios das ERONs em excesso na força gerada pelo músculo.

2. A inflamação induzida pelo exercício físico

O exercício físico pode ser considerado um modelo de estresse físico agindo como um indutor agudo de injúrias sobre estruturas biológicas envolvidas com o movimento, como o músculo esquelético e as articulações (PEDERSEN, 2000). Em resposta ao dano muscular ocorre a ativação da inflamação local e sistêmica que tem como objetivo promover o reparo e o remodelamento do tecido lesado. Nesse sentido, a inflamação induzida pelo treinamento sistematizado, é considerada um processo benéfico e necessário para a adaptação a carga do exercício (SMITH *et al.*, 2008).

Citocinas pró e anti-inflamatórias atuam como reguladoras da magnitude e duração dos processos inflamatórios. Inicialmente, são produzidas citocinas pró-inflamatórias, principalmente a Interleucina (IL)-1β e o fator de necrose tumoral (TNF)-α que estimulam a produção de IL-6, seguido pela liberação de citocinas anti-inflamatórias como o receptor agonista de interleucina-1 (IL-1ra), o receptor de TNF-α (TNF-R) e a IL-10. Os neutrófilos, monócitos e linfócitos recrutados para o local da lesão produzem ERONs e

enzimas proteolíticas para limpar e reparar o tecido danificado (PEDERSEN, 2000; PETERSEN; PEDERSEN, 2005; SPURWAY *et al.*, 2006). As ERONs, por sua vez, estimulam a produção de mais citocinas por meio da ativação de fatores de transcrição como o fator nuclear κB (NF-κB), resultando assim em um ciclo vicioso no qual ERONs e citocinas se retroalimentam intensificando o nível de estresse oxidativo instalado (TIDBALL, 2005; MORGAN; LIU, 2011).

A produção de citocinas durante e após o exercício é influenciada por outros fatores além da ruptura de miofibrilas e ação das ERONs, por exemplo, em função do aumento da permeabilidade intestinal, por hormônios do estresse (catecolaminas, hormônio do crescimento, cortisol), pela depleção dos estoques de glicogênio e cálcio muscular ou pelo próprio "fator exercício" (contração muscular) (PEAKE *et al.*, 2007; PEDERSEN; FISCHER, 2007).

Nos últimos anos o músculo esquelético tem sido reconhecido como um órgão endócrino capaz de expressar e secretar citocinas, chamadas de "miocinas" nesse contexto, em resposta a contração muscular. As miocinas, com destaque para a IL-6, parecem influenciar o metabolismo e mediar uma resposta anti-inflamatória sistêmica por efeitos parácrinos e endócrinos, explicando, ao menos em partes, os benefícios a saúde associados a prática regular de exercício físico (PEDERSEN; FISCHER, 2007).

Tipicamente, durante o exercício prolongado ocorre um aumento marcante da IL-6 comparado as demais citocinas no plasma, independente da presença de dano muscular, seguido de uma diminuição no período pós-exercício (Figura 3). Ela é produzida em grande escala no músculo em contração e liberada na circulação resultando em efeitos sistêmicos diversos. A magnitude deste aumento está relacionada especialmente com a intensidade e duração do exercício (PEDERSEN, 2000; PEDERSEN; TOFT, 2000; PETERSEN; PEDERSEN, 2005). Após exercícios de resistência extenuantes, por exemplo uma corrida de 160 km, os níveis plasmáticos de IL-6 podem superar o nível basal na ordem de 100 vezes, assim como observado no estudo de Nieman *et al.* (2005).

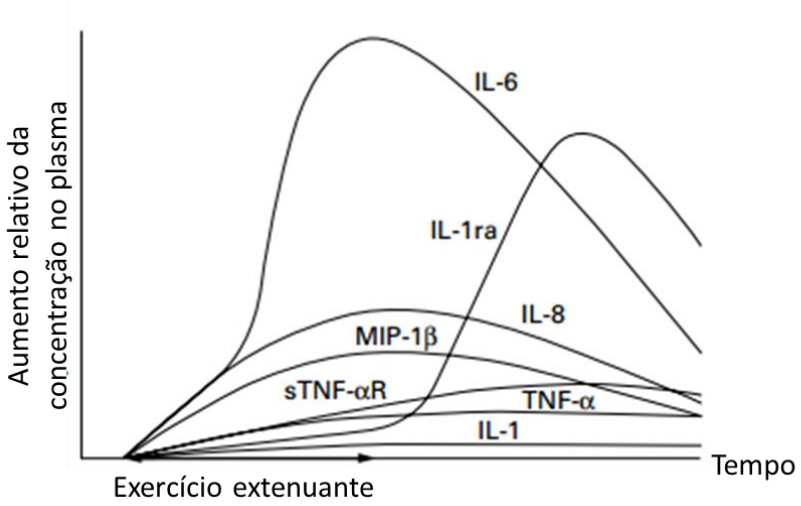

Figura 3. Esquema representando a mudança na concentração das citocinas durante e após uma sessão de exercício extenuante (PEDERSEN, 2000).

Frequentemente a IL-6 é associada a processos danosos e fisiopatológicos (SINDHU *et al.*, 2015). Em estudos de base populacional, os níveis plasmáticos de IL-6 têm se mostrado um preditor de mortalidade cardiovascular e morte por todas as causas (SU *et al.*, 2013; SINGH-MANOUX *et al.*, 2017). Embora a IL-6 seja comumente classificada como uma citocina pró-inflamatória, ela também desempenha propriedades anti-inflamatórias, em especial quando envolve o exercício físico suportável e regular. A IL-6 estimula a produção de citocinas anti-inflamatórias como a IL-10 e o IL-1ra, e inibe a produção do TNF-α. Estimula também a síntese de proteínas de fase aguda no fígado e de cortisol. Estudos têm demonstrado que a IL-6 auxilia na regulação do metabolismo energético assistindo a homeostase da glicose e a lipólise por mecanismos que envolvem a ativação da proteína quinase ativada por AMP (AMPK) (VAN HALL *et al.*, 2003; PEDERSEN, 2005; PEDERSEN; FEBBRAIO, 2005; CAREY *et al.*, 2006; WOLSK *et al.*, 2010).

Por outro lado, a produção de IL-1β e TNF-α parece acontecer independente da contração muscular (PEDERSEN, 2000). A IL-1β e TNF-α são as citocinas pró-inflamatórias mais relevantes em eventos que envolvem traumas sendo consideradas “citocinas-alarme”. Juntas elas compartilham ações como a ativação de células endoteliais de vasos sanguíneos locais, que são estimuladas a produzir citocinas diversas. Elas também atuam de forma sistêmica induzindo a síntese de proteínas de fase aguda no fígado e auxiliando no controle da temperatura corporal por ação direta no hipotálamo. Portanto, são constantemente utilizadas

como marcadores de dano no que diz respeito ao exercício (SMITH, 2000; 2004; ROTH *et al.*, 2017).

De modo semelhante ao considerado para o estresse oxidativo, a magnitude do processo inflamatório em resposta ao exercício físico parece estar relacionada às características inerentes ao exercício, tais como a intensidade, a duração, a frequência e o tipo de ação muscular envolvida. Exercícios extenuantes associados a períodos de descanso insuficientes geralmente induzem danos musculares severos e inflamação que refletem em longos períodos de recuperação - podendo ultrapassar uma semana -, comprometendo a geração de força muscular e a saúde (SMITH, 2000; KASAPIS; THOMPSON, 2005; PAULSEN *et al.*, 2012; KRZEMIŃSKI *et al.*, 2016).

3. Compostos bioativos do chá branco (*Camellia sinensis*)

Na literatura, o termo "chá" refere-se exclusivamente ao produto obtido da infusão ou decocção de espécies do gênero *Camellia* sp., principamente da *Camellia sinensis* (Linnaeus) Kuntze, sendo que para outros tipos de planta usa-se apenas o termo "infusão" (HILAL; ENGELHARDT, 2007). No Brasil, a Agência Nacional de Vigilância Sanitária (ANVISA) aprovou o regulamento técnico para chás e outros produtos, por meio da Resolução de Diretoria Colegiada – RDC nº 277, propondo a seguinte definição (BRASIL, 2005):

"Chá é o produto constituído de uma ou mais partes de espécie(s) vegetal(is) inteira(s), fragmentada(s) ou moída(s), com ou sem fermentação, tostada(s) ou não, constantes de Regulamento Técnico de Espécies Vegetais para o Preparo de Chás."

Neste trabalho, o termo "chá" corresponde a definição da literatura.

A mesma espécie da planta [*Camellia sinensis* (L.) Kuntze] pode dar origem a diversos tipos de chás, dependendo do seu beneficiamento. Os mais comuns são o chá verde (não fermentado), o preto (fermentado) e o oolong (semifermentado), que utilizam folhas e talos da planta como matéria-prima. Vale ressaltar que, embora o termo fermentação seja aceito popularmente, o processo envolvido é a oxidação catalizada por enzimas do tecido vegetal. Em contraste, o chá branco é obtido de folhas recém-formadas e brotos da planta, não enrolados ou comprimidos, levemente cozidos no vapor e secos imediatamente após a colheita a fim de se evitar a oxidação (HILAL; ENGELHARDT, 2007; RUSAK *et al.*, 2008; CHATURVEDULA; PRAKASH, 2011).

Os chás obtidos da *Camellia sinensis* em conjunto assumem o posto de bebida manufaturada mais consumida no mundo sendo de grande importância socioeconômica e cultural, sobretudo para os países orientais (CHANG, 2015). De forma especial, o chá branco e o chá verde vêm despertando crescente interesse da população e da indústria quanto às suas propriedades biológicas benéficas (DIAS *et al.*, 2013).

Quimicamente, a composição dos chás é complexa e inclui principalmente proteínas, aminoácidos livres, carboidratos, ácidos graxos, vitaminas, minerais, alcaloides (cafeína, teobromina), policosanóis, compostos fenólicos, pigmentos (clorofila e carotenoides) e inúmeros compostos voláteis (LE GALL; COLQUHOUN; DEFERNEZ, 2004; RETO *et al.*, 2007; ZHAO *et al.*, 2011; SHEN *et al.*, 2015; CHOI *et al.*, 2016; MILANI; MORGANO; CADORE, 2016). Dentre todos, o elevado conteúdo de compostos fenólicos merece destaque (SHARANGI, 2009).

Entre os compostos fenólicos presentes no chá branco, os mais abundantes são as catequinas, da classe dos flavanóis, especialmente os quatro tipos: epigalocatequina (EGC), epigalocatequina galato (EGCG), epicatequina (EC) e epicatequina galato (ECG) (Figura 4) (ZHAO *et al.*, 2011).

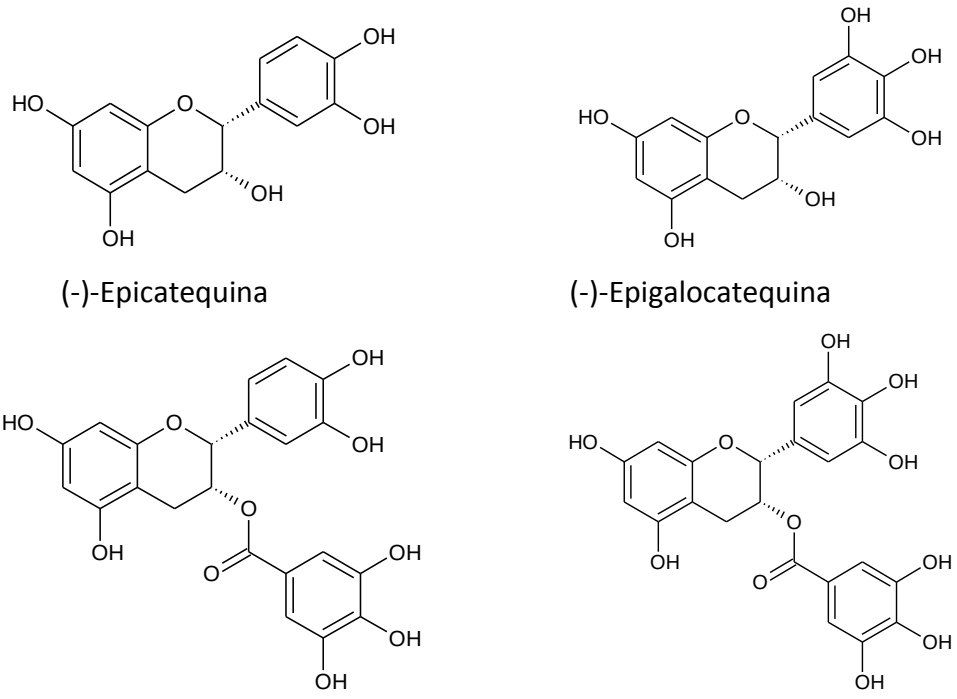

Figura 4. Estrutura química dos polifenóis majoritários nos chás (*C. sinensis*).

Os compostos fenólicos são caracterizados por conter um ou mais anéis aromáticos com graus variados de hidroxilação. Os grupos hidroxilas representam importantes fontes de elétrons que atuam neutralizando espécies reativas no organismo, contendo o estresse oxidativo (UPADHYAY; DIXIT, 2015). Como mostrado em alguns estudos, os compostos fenólicos também influenciam diretamente diversas vias de sinalização moleculares, como as que envolvem a cascata de inflamação, proliferação celular, enzimas antioxidantes e enzimas detoxificantes de fase 2 (FENG *et al.*, 2005; NITURE; KHATRI; JAISWAL, 2014; UPADHYAY; DIXIT, 2015).

Nesse sentido, o consumo de chás tem sido associado não só a efeitos antioxidantes (BASU *et al.*, 2013), mas também a efeitos anti-inflamatório (CAVET *et al.*, 2011), anti-obesogênico e antidiabético (CHEN *et al.*, 2009), antimutagênico (HAJIAGHAALIPOUR *et al.*, 2015), neuroprotetor (FENG *et al.*, 2012) e cardioprotetor (GREYLING *et al.*, 2014).

De maneira geral, o chá verde e o chá branco apresentam capacidade antioxidante, teor de fenóis totais, flavonoides e conteúdo de aminoácidos superiores aos demais chás da *C. sinensis* (ALCÁZAR *et al.*, 2007; ALMAJANO *et al.*, 2008; ZHAO *et al.*, 2011). O conteúdo de catequinas totais parece ser semelhante entre o chá branco e o chá verde, no entanto, o teor de EGCG é maior no primeiro e os teores de EGC, EC e ECG são maiores no segundo (ZHAO *et al.*, 2011). Além disso, maiores teores de cafeína e zinco estão presentes no chá branco comparado aos demais, inclusive o chá verde (ZHAO *et al.*, 2011; MILANI *et al.*, 2016). Todavia, é importante considerar que a composição dos chás está sujeita a variações em função de fatores externos tais como a localização geográfica da planta e as condições de preparo do chá (RAMALHO *et al.*, 2013; YE *et al.*, 2016).

Algumas evidências apontam que o chá branco pode ter atividade antioxidante e antimutagênica superiores ao chá verde, devido a maiores concentrações de alguns compostos antioxidantes (SANTANA-RIOS *et al.*, 2001; DIAS *et al.*, 2014). No entanto, poucos trabalhos foram conduzidos com o chá branco em comparação com os inúmeros realizados com o chá verde.

4. Antioxidantes no contexto do exercício físico

O uso de suplementos dietéticos faz parte da rotina alimentar de muitos atletas, podendo chegar a mais de 90% dependendo do esporte e da definição de suplemento

empregado na pesquisa (KNAPIK *et al.*, 2016; SOUSA *et al.*, 2016). De modo geral, a busca por suplementos esportivos visa a uma melhora do sistema imune, a ganhos adicionais de desempenho e a manutenção da saúde por parte dos praticantes de exercício físico (NIEPER, 2005). No que concerne a suplementação de antioxidantes, o principal mecanismo de ação proposto se baseia na capacidade de compostos variados atenuarem os danos oxidativos às estruturas celulares induzidos pelas ERONs, reduzindo assim a fadiga, inflamação e dor muscular (PETERNELJ; COOMBES, 2011; MERRY; RISTOW, 2016).

Embora existam algumas evidências científicas de efeitos positivos resultantes da utilização de antioxidantes associada ao exercício físico, a interpretação dos dados existentes é confusa por questões de design do estudo incluindo a variabilidade das características dos sujeitos (nível de treino e estado nutricional), das características do exercício (modalidade, protocolos de treinamento), assim como a variabilidade das doses e combinações de antioxidantes utilizados (EICHENBERGER; COLOMBANI; METTLER, 2009; PETERNELJ; COOMBES, 2011; JÓWKO *et al.*, 2014; PANZA *et al.*, 2016). Em suma, parece que o uso controlado de antioxidantes beneficia especialmente indivíduos submetidos a dietas restritivas ou com alguma deficiência nutricional, bem como atletas envolvidos com competições sucessivas separadas por tempos de recuperação limitados (PASCHALIS *et al.*, 2016; RANCHORDAS; DAWSON; RUSSELL, 2017).

Por outro lado, alguns estudos sugerem que, quando ingeridas altas doses de antioxidantes, as adaptações fisiológicas benéficas induzidas pelo estresse oxidativo em resposta ao exercício, poderiam ser prejudicadas com o bloqueio da sinalização das ERONs, comprometendo assim o desempenho físico (GOMEZ-CABRERA *et al.*, 2008; MORRISON *et al.*, 2015; MERRY; RISTOW, 2016). Por conseguinte, não existe um consenso a respeito da necessidade de suplementação dietética de antioxidantes no esporte. A estratégia mais segura e eficaz, de acordo com a posição da Academia de Nutrição e Dietética (AND), Dietistas do Canadá (DC) e do ACSM, se mantém a de consumir uma dieta equilibrada contendo alimentos ricos em compostos antioxidantes (THOMAS; ERDMAN; BURKE, 2016).

Outro aspecto relevante diz respeito à presença substâncias proibidas em suplementos dietéticos que, segundo dados disponíveis, gira em torno de 10 e 15% (OUTRAM; STEWART, 2015). Frente ao risco de contaminação e reprovação em testes antidrogas, observa-se uma tendência de que os suplementos esportivos sejam baseados em produtos

dispensáveis de testes antidrogas e sejam prescritos com mais cautela (OUTRAM; STEWART, 2015; CLOSE *et al.*, 2016).

Nesse sentido, o presente trabalho buscou avaliar o efeito do consumo do chá branco, como uma bebida rica em compostos fenólicos, nos marcadores de estresse oxidativo e inflamação associados ao exercício de resistência agudo exaustivo em animais treinados. Uma representação das interações esperadas entre a ingestão de chá branco e as respostas biológicas induzidas pelo exercício exaustivo agudo é mostrada na Figura 5.

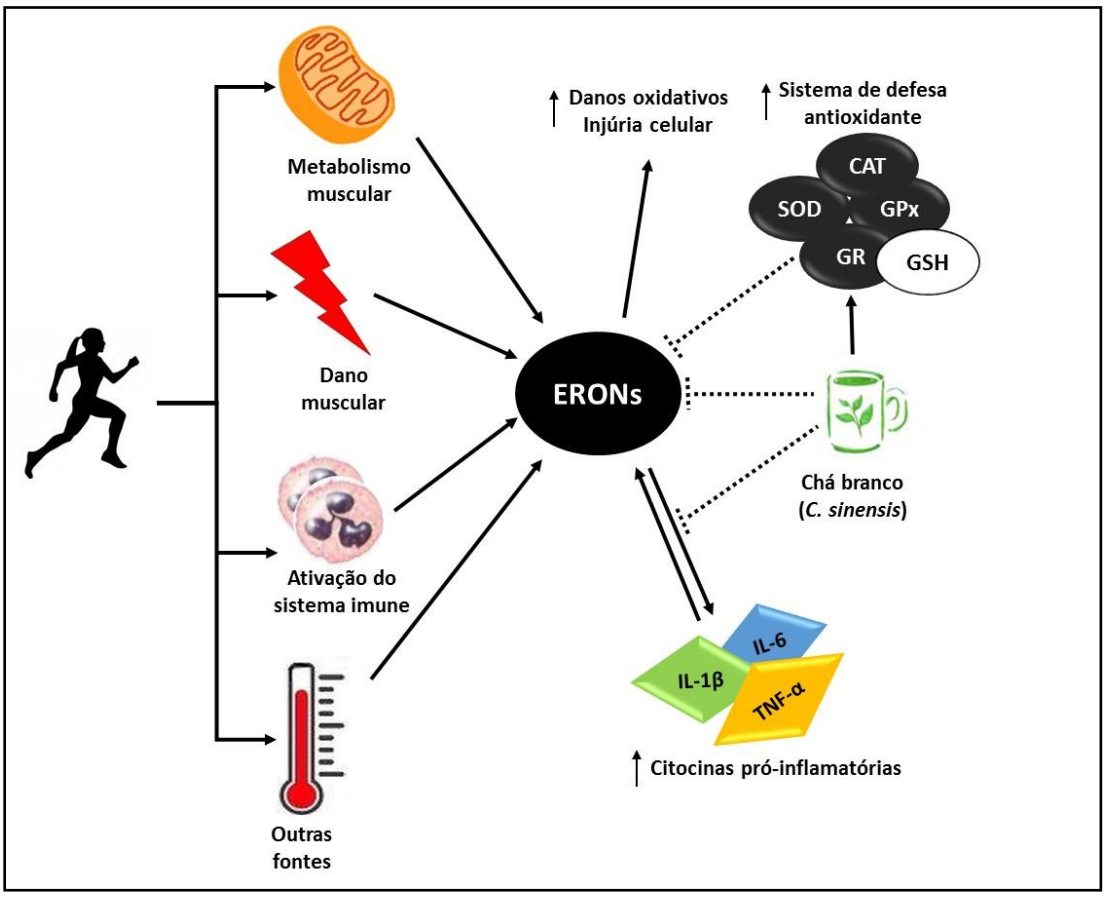

Figura 5. Esquema indicando possíveis interações entre exercício, ERONs, antioxidantes do chá branco (*C. sinensis*) e citocinas inflamatórias. As linhas sólidas representam estímulo; e as linhas tracejadas representam inibição parcial (Esquema elaborado pelos autores).

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CAPÍTULO 3

ARTIGO ORIGINAL

*Research article**

White tea modulates antioxidant defense of endurance-trained rats

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Abstract

The interest in nutritional strategies that may counteract the biologic deleterious effects induced by oxidative stress, such as observed in exhaustive exercises sessions, is remarkable. White tea (*Camellia sinensis*) (WT) has been considered as a functional food due to high polyphenol concentrations. The aim of this study was to investigated the influence of the WT intake on biomarkers of antioxidant and inflammatory status of endurance-trained rats submitted to an acute exhaustive exercise. The Wistar rats were divided into groups which received: 1) White tea (5 g of plant per L of water); 2) Water diluted white tea (50:50; v/v); or 3) Water. The drinks were consumed, *ad libitum*, for 5 or 10 weeks, concomitantly with the running training. Exhaustion tests were applied before and after the experimental periods. The serum and liver were collected immediately after an exhaustion test. Compared to water, the intake of both WT resulted in a higher serum antioxidant potential by the ORAC assay, despite it was not followed by an improvement in endogenous antioxidant defenses. The ingestion of both WT for 10 weeks attenuated lipid peroxidation in the liver. This was

paralleled by increased activities of superoxide dismutase, glutathione peroxidase, glutathione reductase and glutathione content in rat livers that received the diluted WT. The level of some cytokines in serum (IL-1β and IL-6) could be downregulated by the tea intake compared to the water intake. These findings contributed to comprehend that natural source of antioxidants, such as white tea, must be used as adjuvant to exercise-induced oxidative stress management.

Keywords: Polyphenols; *Camellia sinensis*; oxidative stress; exhaustive exercise.

1. Introduction

Regular moderate- or vigorous-intensity physical exercises are associated with nearly the maximum longevity benefit (Arem et al., 2015). Some mechanisms involved in the process of physiological adaptation to exercise training are the same one that may impair physical performance and health if they are not well controlled. Sedentary individuals submitted to acute exercise, or trained individuals submitted to exhaustive exercise sessions, or even to intense training load allied to insufficient recovery period, could be conditions that led to non-negligible mechanical stress, inflammation process and oxidative stress (Fatouros et al., 2010; Videbaek, Bueno, Nielsen, & Rasmussen, 2015).

A number of factors like aerobic mitochondrial metabolism, muscular damage, xanthine oxidase reactions, NADPH oxidase enzymes and cytokines are responsible for reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation during and after endurance exercise (Mason, Morrison, McConell, & Wadley, 2016; Peake, Suzuki, & Coombes, 2007). The cytokine production may be also influenced by ROS and RNS by the activation of the redox-sensitive signal transduction pathways, showing one of which can be easily induced by another (Morgan & Liu, 2011). The ROS and RNS play a central role in oxidative damage to cell membranes and biomolecules like proteins, lipids and DNA. In the sports' scenario, oxidative stress has been observed in events such as delayed fatigue, infections and overtraining syndrome (Fatouros et al., 2010; Tanskanen, Atalay, & Uusitalo, 2010).

In order to protect the body from the damage caused by reactive species, the organisms developed a series of defense mechanisms. The antioxidant defenses include enzymatic (superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase) and non-enzymatic (vitamin C, vitamin E, carotenoids, glutathione, uric acid and polyphenols) constituents (Peternelj & Coombes, 2011). The effects of dietary bioactive compounds from teas, spices and fruits on antioxidant status have been extensively studied, especially with regard to the ROS or RNS suppression and the ability to up-regulate endogenous antioxidant defenses (Batista et al., 2014; da Silva et al., 2017; Ene-Obong, Onuoha, Aburime, & Mbah, 2018; Panza et al., 2016).

Despite the popular use of antioxidant supplements, more literature evidences are still needed (Close, Hamilton, Philp, Burke, & Morton, 2016). Accordingly, the Academy of Nutrition and Dietetics, Dietitians of Canada, and the American College of Sports recommend

for physically active individuals a diet rich in antioxidant foods (Thomas, Erdman, & Burke, 2016).

Tea (*Camellia sinensis*) is the most widely consumed drink in the world, excluding water (Chang, 2015). White tea (WT), obtained from young leaves and buds of the plant, undergoes minimal processing and is one of the less studied variety of tea (Alcázar et al., 2007). Several biological properties of WT are attributed to its high content of phenolic compounds, especially catechins and its derivatives. Furthermore, concerning catechin and total phenol levels or total antioxidant activity, WT is comparable to green tea accordingly to some studies (Almajano, Carbó, Jiménez, & Gordon, 2008; Karori, Wachira, Wanyoko, & Ngure, 2007; Rusak, Komes, Likić, Horžić, & Kovač, 2008; Unachukwu, Ahmed, Kavalier, Lyles, & Kennelly, 2010).

WT is greatly appreciated for its flavor, proving to be an interesting nutritional strategy for people all over the World motivated to consuming bioactive compounds for health reasons (Hilal & Engelhardt, 2007). WT has been associated with antioxidant, anti-inflammatory, anti-viral, anti-carcinogenic activities and reduction of DNA oxidative damage (Dias et al., 2013; Hajiaghaalipour, Kanthimathi, Sanusi, & Rajarajeswaran, 2015; Pastoriza, Mesías, Cabrera, & Rufián-Henares, 2017). Therefore, the aim of the present study was to evaluate the influence of the white tea intake on antioxidant and inflammatory parameters associated with an acute exhaustive exercise in endurance-trained rats.

2. Material and methods

2.1. *Camellia sinensis* sample and aqueous extract – White Tea (WT)

C. sinensis sample (young leaves and buds) was purchased in a São Paulo market, Brazil, in 2015. The white tea was produced in two concentrations labeled White tea 1 (WT1) and White tea 2 (WT2). Firstly, the WT2 was prepared though the infusion of 5 g of plant sample in 1 L of previously boiled water at 95-100 °C, and submitted to homogenization for 15 min (Ramalho et al., 2013) using a magnetic stirrer. The resulting infusion was vacuum-filtered through qualitative filter paper (Cat. no. 516–0819, VWR, Leuven, France). In order to obtain WT1, the WT2 was diluted in water (50:50; v/v). Teas were immediately cooled by immersion in ice bath until it reaches 22 ± 2 ºC to offer to the animals. The teas were prepared every Monday, Wednesday and Friday.

2.2. White tea characterization

The moisture content of plant samples was determined using a standard methodology (AOAC, 2002). WT2 was characterized and it was assumed that WT1 presented proportionally half of the values found to the WT2. All the analyses were performed using a spectrophotometer (Sinergy HT, Biotek, Winooski, VT, USA) and Gen5TM 2.0 data analysis software.

2.2.1. Total phenols content

The total phenolic constituents were determined using the Folin-Ciocalteau method as described by Swain and Hillis (1959), with adaptations. The absorbance was measured at 725 nm and results are expressed in terms of the used standard - gallic acid equivalents (mg GAE/L).

2.2.2. *In vitro* antioxidant potential

2.2.2.1. The oxygen radical absorbance capacity (ORAC) assay

The oxygen radical absorbance capacity (ORAC) assay (Ou, Chang, Huang, & Prior, 2013) was carried out adding WT2 or standard solutions, fluorescein (3',6'-dihidroxi(isobenzofurano-1(3H), 9'(9H)-xanten)-3-ona) solution and AAPH (2,20-azobis (2-methylpropionamidine) dihydrochloride) to black microplates, in the dark. Phosphate buffer (pH 7.4) was used as diluent and Trolox ((±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) was used as standard. The readings were done in the following fluorescent filters: excitation wavelength at 485 nm and emission wavelength at 520 nm; for 80 min every 1 min, at 37 °C. The results are expressed as µmol Trolox equivalent (TE)/L.

2.2.2.2. The ferric reducing antioxidant power (FRAP) assay

The ferric reducing antioxidant power (FRAP) assay was performed according with Benzie and Strain (1996). In brief, working FRAP reagent [acetate buffer, TPTZ (2,4,6-tris(2-pyridyl)-S-triazine) in a HCl solution, and $FeCl_3$) was mixed with water diluted WT2 or standard solutions (Trolox) in a microplate, incubated in the dark for 30 min at 37 °C, cooled to room temperature (22 ± 2 ºC) and then absorbance was read at 595 nm. The results are expressed as µmol Trolox equivalent (TE)/L.

2.3. *In vivo* experiment

2.3.1. Animals and diet

The experiment was previously approved by the Ethics Committee on Animal Experiments (CEUA/UNICAMP), protocol number 3595-1/14 and followed the institutional ethical guidelines. Sixty-three male Wistar rats (Rattus norvegicus, 3-weeks old) obtained from the Multidisciplinary Center for Biological Research at Unicamp (CEMIB) were maintained under controlled conditions of temperature (22 °C ± 2), humidity (60-70%), and a standard dark cycle (7:00 a.m. until 7:00 p.m.), in individual cages. Food (commercial diet - Nuvilab®) and drink (water and teas) were supplied under free access throughout the experimental period. The food and drink intake were monitored three times a week and the weight gain once a week.

2.3.2. Treadmill training and exhaustive test protocols

A motorized treadmill without inclination containing 12 individual lanes was used in a dark room with minimum light. A shock grid at the back of the treadmill provided a mild shock (1.5 mA) when the pace of the rats went below the treadmill rate. The exercise protocols used were adapted from Hohl et al. (2009). After a growth period of 3 weeks, all rats were submitted to walking on a treadmill for 2 weeks to acclimation before the beginning of the experiments. The animals that refused to run were excluded from the study. In addition, we eliminated the animals that started running but refused to run during the experiment. The animals were subjected to 10 experimental weeks of running training on the treadmill, divided into two phases of 5 weeks each, as shown in Table 1. Phase 1 consisted of an acquisition period to improve fitness, characterized by progressive increase of speed and running time, while in phase 2 the running parameters remain constant. Thus, we distinguish three groups of experiments based on the training time: T0, T5 and T10. The T0 represent the beginning control, while the T5 and T10 experiments represent Phase 1 concluded, and Phase 1 + Phase 2 concluded, respectively. All animals ran on treadmill on the same day, at a time between 1:00 p.m. and 5:00 p.m.

Exhaustive running tests were applied at the end of each experiment (T0, T5 and T10), always 72 h after the last training session. The test started at an initial speed of 12 m/min and it was increased by 1 m/min every 2 min, until it reached 20 m/min. After that, the speed was increased by 2 m/min every 3 min, until the rats reached exhaustion, defined as the

moment the animals were unable to sustain the exercise on all four legs and then it was rescued. Time to reach exhaustion was recorded.

Table 1. Exercise training protocol.

Experimental weeks	Exercise training phases	Running speed (m/min)	Running time (min)	Number of daily sessions	Number of weekly sessions
0	Acclimation	12.0	10	1	2
1	1	14.0	20	1	3
2	1	15.5	30	1	3
3	1	17.0	40	1	3
4	1	18.5	50	1	3
5	1	20.0	60	1	3
6 - 10	2	20.0	60	1	3

2.3.3. Experimental groups

After acclimation period on the treadmill, the rats (8-weeks old) were randomly distributed into four groups: a) Sedentary control (SC) (n = 21), subdivided into three subgroups (n = 7 each) sacrificed at T0, T5 and T10, respectively; b) Exercise training control (EC) (n = 14), subdivided into two subgroups (n = 7 each) sacrificed at T5 and T10, respectively; c) Exercise training plus White tea 1 (WT1) (n = 14), subdivided into two subgroups (n = 7 each) sacrificed at T5 and T10, respectively; and d) Exercise training plus White tea 2 (WT2) (n = 14), subdivided into two subgroups (n = 7 each) sacrificed at T5 and T10, respectively. The WT1 and WT2 groups had water replaced by white tea throughout the experimental period. All groups performed the exhaustive running test immediately before euthanasia. The overview of the experimental design is presented in Figure 1.

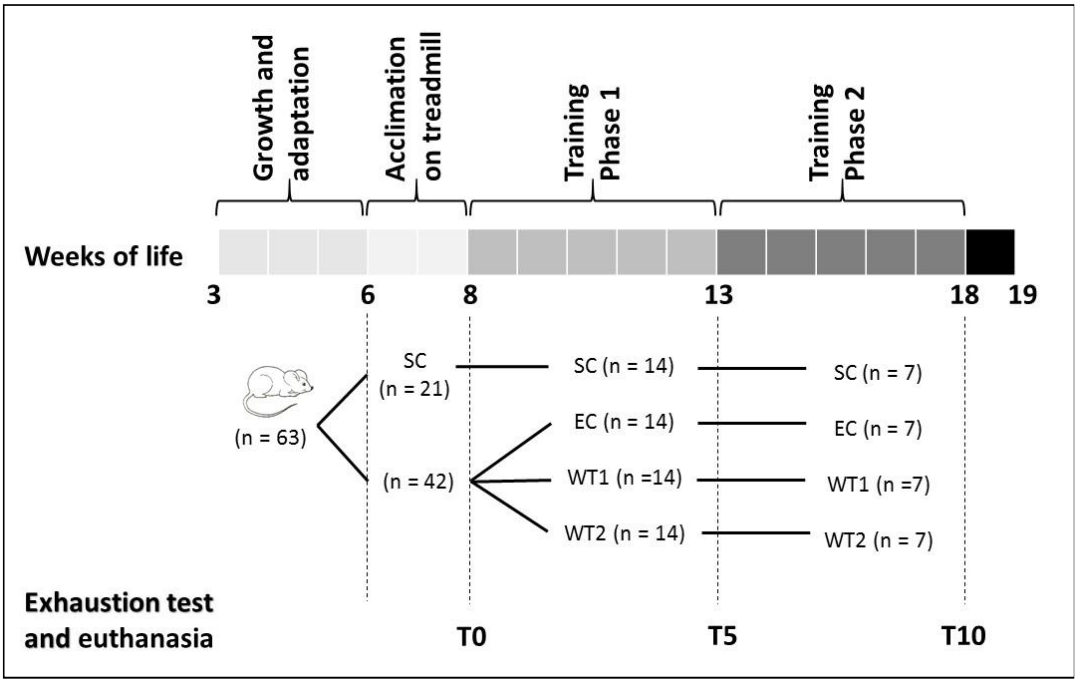

Figure 1. Overview of the experimental design. The T0 experiment consist in one subgroup (n = 7): SC; The T5 experiment consisted in four subgroups (n = 7 each): SC, EC, WT1 and WT2; and the T10 experiment consisted in four subgroups (n = 7 each): SC, EC, WT1 and WT2. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise training + White tea 1 groups; WT2: Exercise training + White tea 2 groups.

2.3.4. Biologic Sampling

At the end of the respective experiments, the animals were anaesthetized with ketamine (Dopalen®) and xylazine (Anasedan®), and euthanized by exsanguination through cardiac puncture. The blood samples were collected in tubes lacking ETDA and centrifuged at 3,000 g for 15 min to obtain serum. The whole liver, heart, gastrocnemius and soleus muscles were quickly removed, cleaned with saline solution and weighed. The serum and liver were stored at - 80 °C until analysis. The liver homogenate was prepared at a ratio of about 100 mg wet tissue per 1 mL of 50 mmol/L phosphate buffer (pH 7.4) solution using a manual homogenizer (MA102/Mini, Marconi, Piracicaba, SP, Brazil). The homogenate protein concentrations were determined using the Bradford method (Bradford, 1976).

2.4. Antioxidant status in serum and liver

All the analyses were performed using a spectrophotometer (Sinergy HT, Biotek, Winooski, VT, USA) and the Gen5TM 2.0 data analysis software.

2.4.1. Total antioxidant potential in serum

The serum was deproteinized using ethanol: ultrapure water (2:1, v/v) and 0.75 mol/L metaphosphoric acid (Leite et al., 2011). After that, the ORAC assay was performed as previously described to the white tea (see 2.2.2.1. session) (Ou et al., 2013). The values are expressed in µmol trolox equivalent (TE)/L serum.

2.4.2. Enzymatic endogenous antioxidant systems in serum and homogenate liver

The cytosolic superoxide dismutase (SOD) activity was quantified using the methodology described by Winterbourn, Hawkins, Brian, and Carrell (1975). The samples and working solution (0.1 mmol hypoxanthine, 0.07 U xanthine oxidase, and 0.6 mmol NTB in PB at 1:1:1 proportions) were added in a microplate and the kinetic reaction was monitored at 560 nm for 10 min. The SOD activity is expressed as U/mL or U/mg protein for serum and liver, respectively.

The glutathione reductase (GR) activity was measured by monitoring the decrease in absorbance at 340 nm for 10 min after induction by oxidized glutathione (1 mmol/L), in the presence of NADPH (0.1 mmol/L), according to Carlberg and Mannervik (1985).

The glutathione peroxidase (GPx) activity was determined as described by Flohe and Gunzler (1984). Samples were mixed with reduced glutathione (10 mmol/L), NADPH (4 mmol/L) and GR (1 U) in a microplate. The decrease in absorbance after induction by H_2O_2 (0.25 mmol/L) was monitored, at 365 nm for 10 min.

The results of GR and GPx activities are presented as nmol NADPH consumed/min/mL or nmol NADPH consumed/min/mg protein for serum and liver, respectively.

2.4.3. Non-enzymatic endogenous antioxidant systems in serum and liver

The reduced thiol (GSH) content was determined in serum and liver homogenate protein free using DTNB (5,5'- dithiobis-(2-nitrobenzoic acid)), the Ellman's reagent (Ellman, 1959). The GSH was used as the external standard and colors' samples were read at 412 nm.

The GSH content is expressed as nmol GSH/mL and nmol GSH/mg protein from serum and liver, respectively.

2.4.4. Lipid peroxidation in liver

The thiobarbituric acid reactive substances (TBARS) levels in liver were measured according to the method described by Ohkawa, Ohishi, and Yagi (1979), with modifications. The homogenate was mixed with 8.1% sodium dodecyl sulphate (SDS) and working reagent (TBA, 20% acetic acid, and 5% sodium hydroxide) using a vortex. After 60 min of heating (95 °C), samples were kept in an ice bath for 10 min and then centrifuged at 10,000 g for 10 min (4 °C). The absorbance of supernatant was determined at 532 nm in a clear microplate using a TEP (1,1,3,3-tetramethoxypropane, Sigma-Aldrich, St Louis MO, USA) as standard. The results are expressed as nmol malondialdehyde (MDA)/mg protein.

2.5. Anti-inflammatory potential in serum and liver

The cytokine levels in serum (interleukin (IL)-1β and IL-6) and liver homogenate [IL-1β, IL-6 and tumour necrosis factor (TNF)-α) were measured using commercial Elisa kits (Peprotech, Ribeirão Preto, SP, Brazil), according to the manufacturer's instructions. The results are expressed as nmol/mL for serum or nmol/mg protein from liver.

2.6. Statistical analysis

Student's t-test was performed to compare averages among two groups, and One-way analysis of variance (ANOVA) followed by a Tukey test to compare more than two groups. The data are expressed as the means ± SEM and the difference was considered to be statistically significant when $P \leq 0.05$. The statistical analyses were carried out using GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, CA, USA) software.

3. Results

3.1. White tea characterization

The moisture content of the *C. sinensis* plant samples was 8.4 ± 0.2 g/100 g. The total phenolic compounds by the Folin assay in WT2 was 92.78 ± 1.34 mg GAE/L, and the antioxidant activity according to the ORAC and FRAP assays were 1758.04 ± 94.41 µmol TE/L and 2024.21 ± 15.95 µmol TE/L, respectively.

3.2. Food and drink intake, body and tissue weight

The WT intake and exercise training did not influence food and drink intake in T5 or T10 experiment (see Figure 1 in Complementary Material) pointing out that the results are not attributed to the quantitative differences in the diet or drink intake. Considering that the animals of WT1 and WT2 groups had a median daily tea intake of 39.92 ± 3.24 mL and 42.56 ± 3.89 mL, respectively, the mean intake of the antioxidant compounds were 1.85 mg/d to WT1 group and 3.95 mg/d to WT2 group at the days of tea preparation, based on the Folin assay.

There was no difference in the body weight of the animals from the T5 or T10 groups throughout the experimental weeks (Figure 2). The liver, soleus and gastrocnemius muscles weights were also similar in the T5 or T10 groups (see Figure 2 in complementary material). However, a significant increase in the heart weight were observed in all trained groups compared to the sedentary control group in T10.

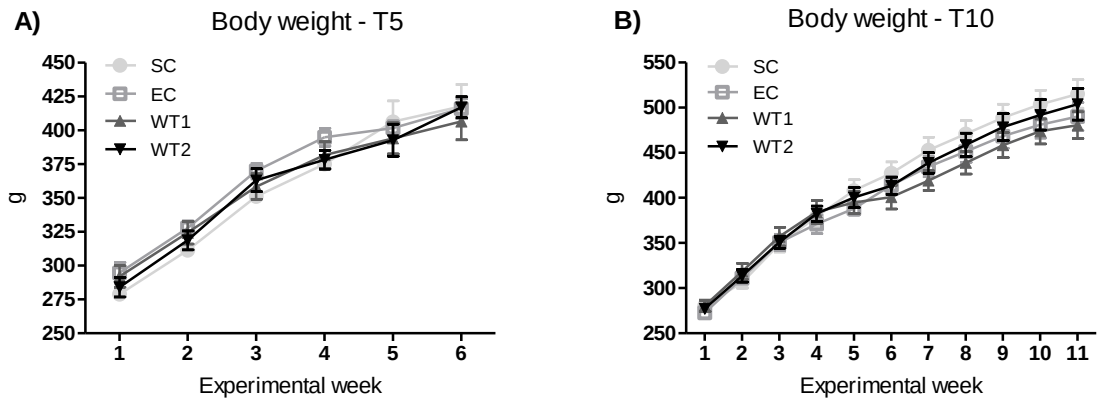

Figure 2. Curve of body weight throughout the experimental weeks. (A) T5 experiment; (B) T10 experiment. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise + White tea 1 groups; WT2: Exercise + White tea 2 groups. Values expressed as mean ± SEM. No statistic differences were observed between groups (n = 5-7) at the same experimental week by one-way ANOVA followed by a Tukey test, $P > 0.05$.

3.3. Time to exhaustion on treadmill running test

As shown in Figure 3, the time to exhaustion of the sedentary groups was lower than the trained groups at both experiments (T5 and T10), meaning that the rats were

submitted to different workloads and exposured to different levels of ROS/RNS in the exhaustion test (Gargallo et al., 2018). As expected, the EC groups improved running time compared to their corresponding sedentary control groups, in 1.53 and 3.05 times at T5 and T10, respectively, showing that the training protocol was efficient to improve endurance capacity of the rats. The white tea intake did not promote additional gain on endurance capacity. Despite the WT1 group at T5 experiment showed a lower exhaustion time compared with the EC group, after 5 weeks maintenance of the exercise workload, the WT1 group exhibited a tend to perform a higher exhaustion time than the EC group in T10.

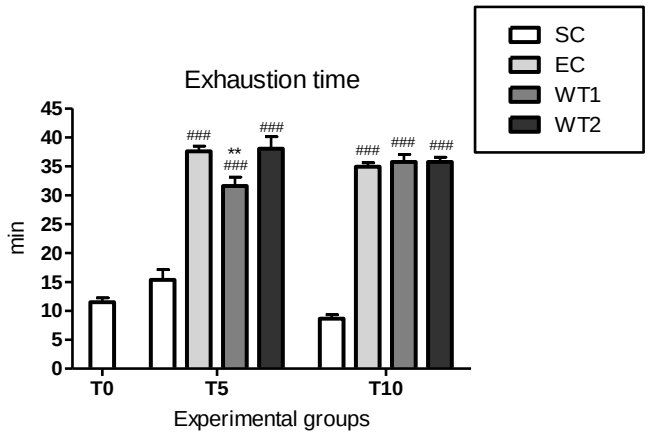

Figure 3. Results from the exhaustion test. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise training + White tea 1 groups; WT2: Exercise training + White tea 2 groups. Values expressed as mean ± SEM. The subgroups (n = 5-7) were compared at the same experimental group (T5 or T10). #Indicates significant differences from the SC group and *indicates significant differences from the EC group according to Student's t-test (1 sign = $P < 0.05$; 2 sign = $P < 0.01$; and 3 sign = $P < 0.001$).

3.4. Serum antioxidant parameters

According to the ORAC assay, the animals that received WT2 presented a greater serum antioxidant potential compared to the control groups, independent of the duration of the white tea intake (5 or 10 weeks) (Figure 4.A). The WT1 showed similar effect when ingested for 10 weeks. In addition, a positive correlation ($R^2 = 0.79$) should be established between the dose of tea and the serum antioxidant potential of the T10 trained groups.

In the T5 experiment, the antioxidant enzymes activities (SOD, GPx and GR) were statistically similar among WT groups and EC group (Figure 4.B, C and D); however, in the T10 experiment the WT1 group presented significantly lower activities of these three enzymes

than the EC group. Regarding the thiol group content, the WT2 group showed a higher GSH level in serum compared to the trained and sedentary control groups in the T5 experiment, at 17.0% and 23.7% range, respectively (Figure 4.E), but in T10 was not difference among the groups.

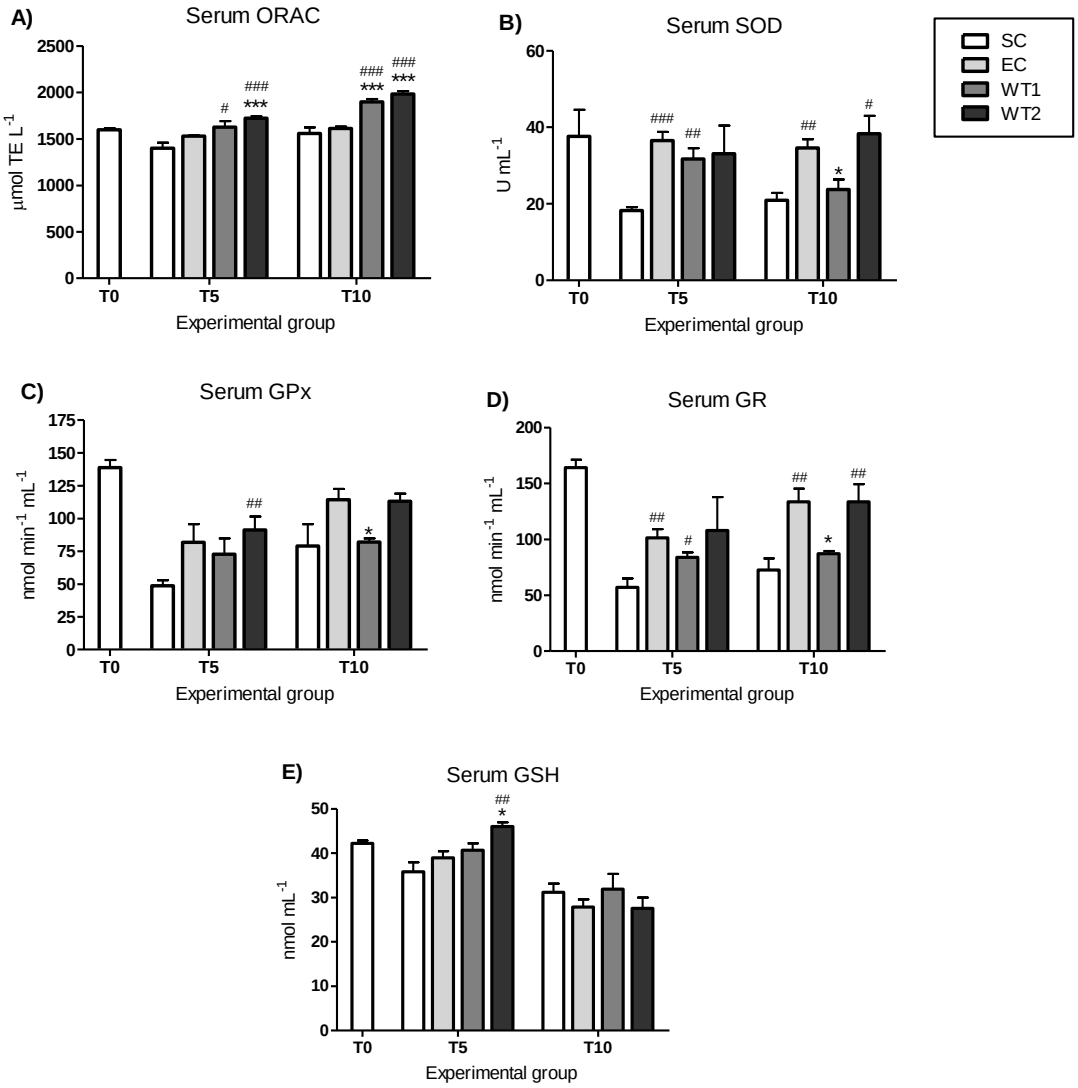

Figure 4. Serum antioxidant status and antioxidant defense system. (A) ORAC; (B) SOD activity; (C) GPx activity; (D) GR activity; and (E) GSH content. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise training + White tea 1 groups; WT2: Exercise training + White tea 2 groups. Values expressed as mean ± SEM. The subgroups (n = 4-7) were compared at the same experimental group (T5 or T10). #Indicates significant differences from the SC group and *indicates significant differences from the EC group according to Student's t-test (1 sign = $P < 0.05$; 2 sign = $P < 0.01$; and 3 sign = $P < 0.001$).

3.5. Liver antioxidant parameters and lipid peroxidation

A long-term white tea intake reduced lipid peroxidation in the rat livers. In the T10 experiment, the animals that received white tea showed lower levels of liver MDA (39.0% for WT1 group and 22.1% for WT2 group) relative to the animals from EC group (Figure 5.A). Interestingly, the liver MDA values of both WT groups did not differ from the sedentary group even though which one was submitted at a higher workload (volume and intensity) in the exhaustion test.

In the T5 experiment, the white tea intake did not cause a significant impact on the SOD activity and GSH contents in liver (Figure 5.B and C). However, the liver GPx activity was increased in the WT1 (29.6%) and WT2 (44.5%) groups in comparison to the EC group (Figure 5.D). Additionally, the liver GR activity was 1.7 times higher in the animals from the WT2 group (Figure 5.E) compared to the trained control group.

In the T10 experiment, despite the GPx activity exhibited a dependent dose response pattern to the white tea intake, the WT1 seemed to be most efficient dose to improve the liver antioxidant defenses. The WT1 group, but not WT2 group, had improved SOD, GPx and GR activities (Figure 5.B, D, and E) and GSH content (Figure 5.C) compared to the EC group.

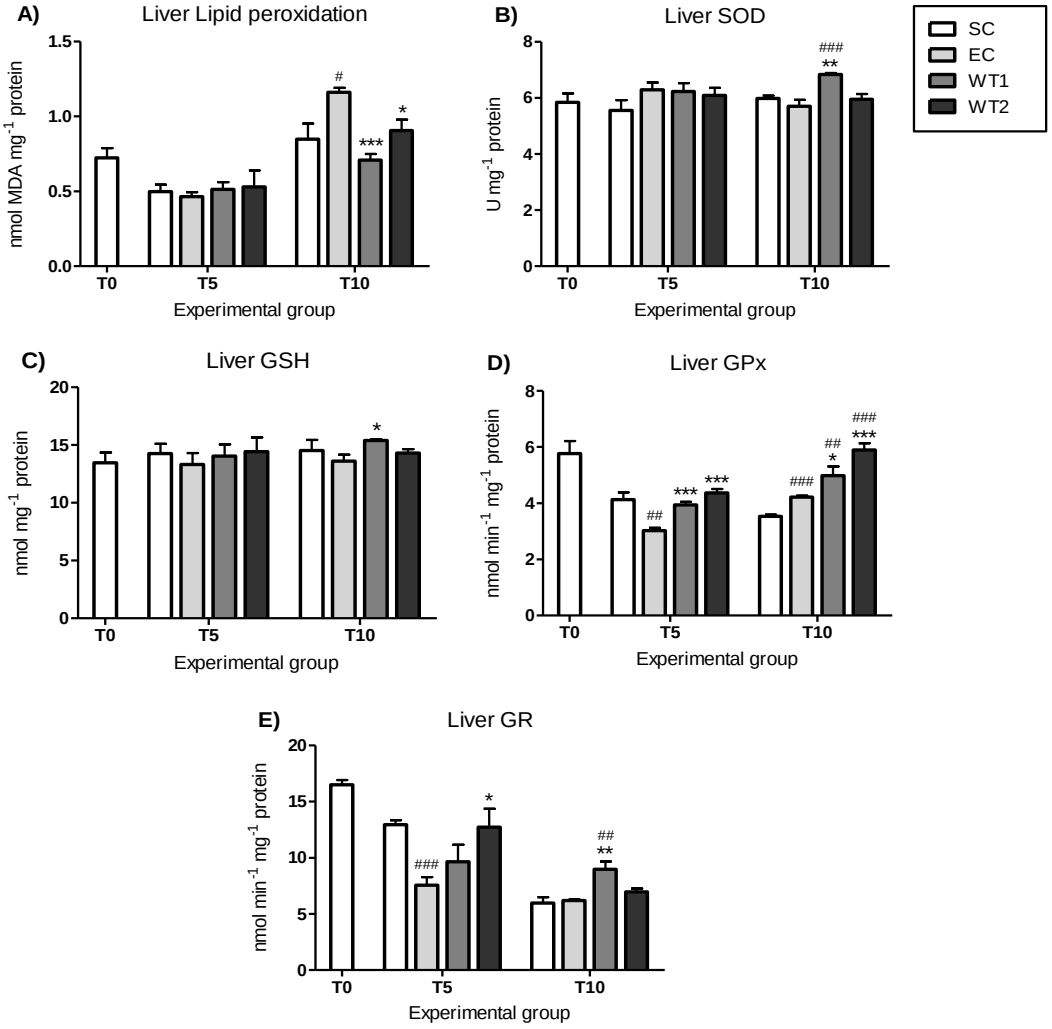

Figure 5. Liver lipid peroxidation and antioxidant defense system. (A) TBARS; (B) SOD activity; (C) GSH content; (D) GPx activity; and (E) GR activity. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise training + White tea 1 groups; WT2: Exercise training + White tea 2 groups. Values expressed as mean ± SEM. The subgroups (n = 3-7) were compared at the same experimental group (T5 or T10). #Indicates significant differences from the SC group and *indicates significant differences from the EC group according to Student's t-test (1 sign = $P < 0.05$; 2 sign = $P < 0.01$; and 3 sign = $P < 0.001$).

3.6. Serum and liver inflammatory biomarkers

As shown in Figure 6.A, the trained control groups presented a higher IL-1β levels (16.6% in T5 and 38.4% in T10) in serum than the sedentary control groups. Possibly, a higher workload sustained in exhaustion test was related to a higher muscular damage (Koch, Pereira, & Machado, 2014) and subsequent higher inflammatory response in the EC groups compared to the SC groups. The white tea intake attenuated this increase by 20.1% and 17.3% in the WT1 and WT2 groups at T5, respectively, and by 7.6% in the WT1 at T10. Nevertheless, the serum IL-6 level (Figure 6.B) was statistically similar among EC and SC groups, in both experiments. While the WT1 group (T5) had a higher serum IL-6 level than the EC and SC groups, the WT2 group (T10) had a lower IL-6 level than their respective controls.

In liver, the IL-1β and IL-6 values (Figure 6.C and D) did not differ among trained groups in the T5 experiment. However, the WT2 group presented a higher TNF-α content (Figure 6.E) than the EC at the same experiment. On the other hand, in the T10 experiment, the TNF-α levels did not differ between the trained groups, but the WT1 and WT2 groups presented a higher IL-6 levels, and the WT2 group showed a higher IL-1β level compared with the trained control group. Curiously, the IL-1β (in T10) and IL-6 (in T10) values showed a dose dependent response concerning to the white tea concentration (Figure 6.C and D).

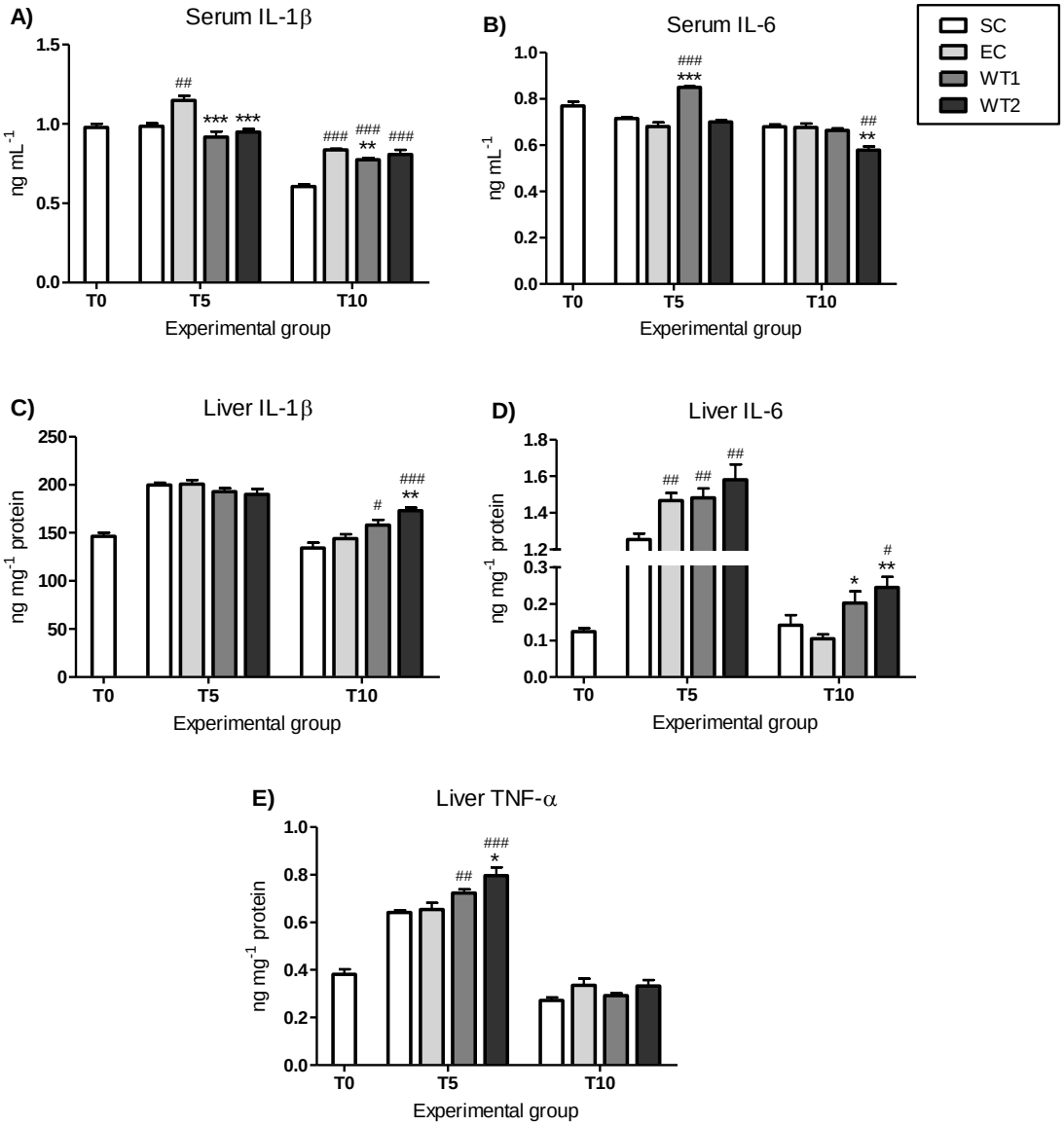

Figure 6. Inflammatory cytokine levels in serum and liver. (A) Serum IL-1β; (B) Serum IL-6; (C) Liver IL-1β; (D) Liver IL-6; and (E) Liver TNF-α. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise training + White tea 1 groups; WT2: Exercise training + White tea 2 groups. Values expressed as mean ± SEM. The subgroups (n = 3-7) were compared at the same experimental group (T5 or T10). #Indicates significant differences from the SC group and *indicates significant differences from the EC group according to Student's t-test (1 sign = $P < 0.05$; 2 sign = $P < 0.01$; and 3 sign = $P < 0.001$).

4. Discussion

The regular consumption of foods containing phenolic compounds have promising notable health effects including cardioprotective, chemopreventive and anti-inflammatory actions (Rehman et al., 2013; J. Wang, Li, & Zhang, 2016; Zhao et al., 2017). Black and green tea from *Camellia sinensis* are included in the top richest dietary sources for total polyphenols in Phenol-Explorer database, based on the comparison among 452 foods (Pérez-Jiménez, Neveu, Vos, & Scalbert, 2010). Catechins, from flavanol family, are the major class of polyphenols in these teas, which are attributed to a great antioxidant capacity. Although present similarities of phenolic compounds, WT has been poor explored in the literature compared to black and green tea (Carloni et al., 2013). Thus, we decided to investigate the effect of a long-term WT - a polyphenol-rich beverage - intake on antioxidant and inflammatory responses after an exhaustive exercise in healthy trained animals.

Our first interesting finding was related to heart: endurance training for 10 weeks increased myocardial mass. Cardiac hypertrophy may reflect an pathological condition when progresses to heart failure (B. Wang et al., 2017). Studies suggest that long-term exercise encourages adaptive physiological remodeling of the heart which differs from the elicited by pathological stimuli, such as hypertension. Therefore, cardiac enlargement observed in response to regular endurance exercise is typically associated with enhanced cardiac function and cardioprotective effect (Bernardo & McMullen, 2016; Platt, Houstis, & Rosenzweig, 2015; Vega, Konhilas, Kelly, & Leinwand, 2017).

It is clear that regular exercise training results in total antioxidant capacity improvement (Carlsohn et al., 2008; de Sousa et al., 2017). In current study, the trained animals that received WT exhibited a higher serum antioxidant potential, in a dose dependent manner, than the trained control. This result might be attributable to the association between a great antioxidant status pre-exercise and a controlled oxidative stress levels during an intense exercise (Jówko, Długołęcka, Makaruk, & Cieśliński, 2014). A previous study reported that flavanol and its metabolites can be found in plasma until 8 hours following the ingestion of 500 mL of green tea (containing 648 µmol of flavan-3-ols) (Stalmach, Troufflard, Serafini, & Crozier, 2009). Hence, circulating WT polyphenols and derivatives may have acted directly as ROS/RNS scavenger or as an electron donator contributing, at least partially, to the greater serum antioxidant status in response to the WT intake.

Antioxidant enzymes are important adjuvants in oxidative balance control of the body (Kurutas, 2016). In the present study, the antioxidant enzymes activities (SOD, GR and GPx) in serum were not correlated with the total antioxidant capacity. In the literature, reports on systemic enzymatic antioxidant defenses in endurance exercise context are conflicting possibly due to the use of different methodologies and biological samples (serum, plasma or erythrocytes) as well as the diverse exercise protocols applied (Oztasan et al., 2004).

According to the hormesis theory, disruption of body redox homeostasis by ROS/RNS generation is essential to regulate endogenous defense adaptations in response to repeated activation. In contrast to a moderate intensity exercise training, exhaustive exercise is not normally a regular stimuli and, therefore, it could induce deleterious physiological events which negatively affect health and performance (Pingitore et al., 2015; Powers, Nelson, & Hudson, 2011). The excessive oxidative stress have been related with alterations in cell membrane permeability and secondary damage tissues. Indirect indicators of cell damage include the presence of cytosolic and mitochondrial enzymes in body fluids, e.g. creatine phosphokinase, lactate dehydrogenase, myoglobin, aspartate aminotransferase and alanine aminotransferase (Haramizu, Ota, Hase, & Murase, 2013; Mohamed, Lamya, & Hamda, 2016). In this sense, we suggest that the WT1 intake for 10 weeks possibly contributes to maintenance of the cell integrity during an acute exhaustive exercise since resulted in lower serum SOD, GR and GPx (which are intracellular enzymes) activities compared to the water intake; however, additional biomarkers of cell damage should be performed to prove this hypothesis.

White tea could efficiently up-regulate the activity of the endogenous antioxidant defense system in the hepatic tissue when it was ingested for 5 weeks (GPx and GR) or 10 weeks (SOD, GPx, GR and GSH). Evidence suggests that natural antioxidants, e.g. catechins, can activate the transcription factor Nrf2 (nuclear factor - erythroid 2 - related factor 2), the master regulator of the antioxidant enzymes expression, which could explain these findings (Upadhyay & Dixit, 2015; D. Wang, Wang, Wan, Yang, & Zhang, 2015).

In addition, GPx, whose activity was higher in the WT1 and WT2 groups compared to the EC groups, is particularly engaged in reducing hydrogen peroxide (H2O2) and organic peroxides (LOOH) (Lushchak, 2012). Therefore, the protection against liver lipid peroxidation observed after a long-term WT intake, accessed by the TBARS assay, may be attributed, at

least in part, to an improvement in the antioxidant enzymes activities, especially by the GPx activity.

GSH is directly involved with the balance of the enzymatic antioxidant defense system: the GSH act as substrate for GPx being oxidized to GSSG, which is reduced by GR at the presence of the NADPH. Furthermore, together with the other non-enzymatic antioxidant components, the GSH is responsible for reducing ROS and other antioxidants in oxidized form, complexing metal ions, as well as, act as coadjuvant in repair processes of damaged cells. Besides synthesized exclusively in the cytosol, the GSH can be transported across the plasma membrane to supply other cells and organs (Lushchak, 2012; Makarov, Kropf, Wiswedel, Augustin, & Schild, 2006). Maintain or improve the serum GSH levels should be especially important in the aerobic exhaustive exercise due to an increase in ROS production and the provision of ATP and NADPH, which are limiting factors for the GSH pathway, compete for other metabolic demands (Vezzoli et al., 2016).

The exhaustive exercise can induce muscle damage and a high ROS/RNS production, which together trigger a series of inflammatory responses (Mohamed et al., 2016). Importantly, the dietary biocompounds have shown the ability to modulate cytokine production and downregulate inflammatory pathways activated by them (Lin et al., 2014). In our study, the WT intake counteracted the augment of IL-1β in serum, which is one of the main mediators in inflammatory process. Recent studies have explored the potential therapeutic effect of IL-1 family blockade in diseases with inflammatory component, such as many heart diseases, showing initial relevant evidences (Szekely & Arbel, 2018). Regarding IL-6, we found WT2 intake reduced the serum IL-6 level only after 10 weeks. Haramizu et al. (2013) suggested that the catechins can prevent release of inflammatory cytokines via nuclear factor-κB (NF-κB) pathway inactivation and decreasing neutrophil and macrophage infiltration. However, the influence of antioxidant compounds on exercise-induced inflammatory response are highly variable in the literature. The magnitude of exercise, training level of individuals and supplementation regime are some factors to be considered (Peake et al., 2007).

The exercise training modulates benefic physiologic changes in liver metabolism (Venditti, Napolitano, Barone, & Di Meo, 2014). However, accumulated urea, inflammation, and hepatic damage markers have been reported following an exhaustive exercise (Huang, Lin, Hsu, Tsai, & Hou, 2010). In the current study, inflammatory cytokines (IL-1β, IL-6 and TNF-

α) were similar or higher in the liver of the animals from WT groups in comparison with the control groups (Figure 6). We suggest more detailed investigations should be made to explain the observed results. Polyphenols, after absorption, are metabolized in liver, where they are in large amounts. The green tea infusion is generally safe to consumption nevertheless, there are some evidences that green tea extract are hepatotoxic (García-Cortés, Robles-Díaz, Ortega-Alonso, Medina-Caliz, & Andrade, 2016). Signs of green tea epigallocatechin-3-gallate toxicity in mice include: increased plasma ALT level, lipid peroxidation and suppression of antioxidant enzymes in liver, and mortality (Lambert et al., 2010; D. Wang et al., 2015). In contrast, the animals that received WT for 10 weeks presented a lower MDA levels and a higher antioxidant enzymes activities compared to the trained control. These data indicate that WT has the potential to reducing oxidative damage in liver. In agreement, many studies have reported benefic effects of foods rich in phenolic compounds on lipid peroxidation during or after exercise sessions (Jówko et al., 2014; Tang et al., 2016).

5. Conclusion

In summary, the present study reveals that a long-term white tea intake may play role on supporting a favorable antioxidant status of endurance-trained rats after an acute exhaustive exercise. In hepatic tissue, especially, the white tea intake was effective in counteract lipid peroxidation and enhance endogenous antioxidant defenses, suggesting a protective effect on oxidative damages. Some circulating inflammatory markers could be reduced after the white tea intake, however, the inflammatory response to exercise associated with the white tea intake should be better explored in future research. Furthermore, we suggest new studies should focus on the efficiency of teas, as a natural source of phenolic compounds, to maintenance of the cell integrity and to reduce secondary tissue damage in order to preserve the health of physically active individuals.

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Complementary material

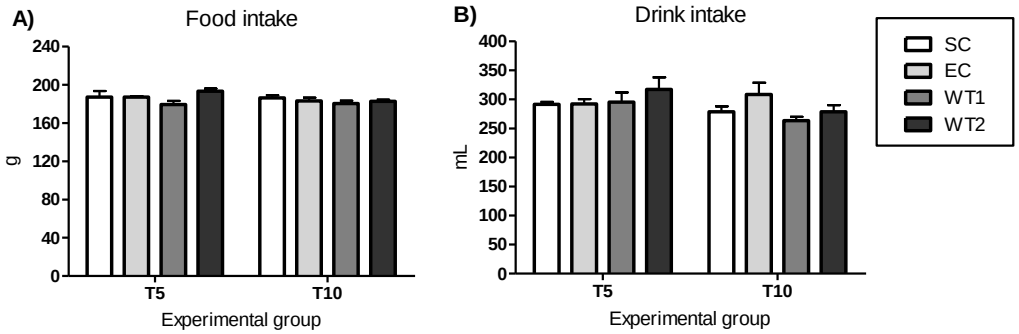

Figure 1. Weekly food and drink intake during the experimental period. (A) Food intake; and (B) Drink intake. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise training + White tea 1 groups; WT2: Exercise training + White tea 2 groups. Values expressed as mean ± SEM. The subgroups (n = 5-7) were compared at the same experimental group (T5 or T10). #Indicates significant differences from the SC group and *indicates significant differences from the EC group according to Student's t-test (1 sign = $P < 0.05$; 2 sign = $P < 0.01$; and 3 sign = $P < 0.001$).

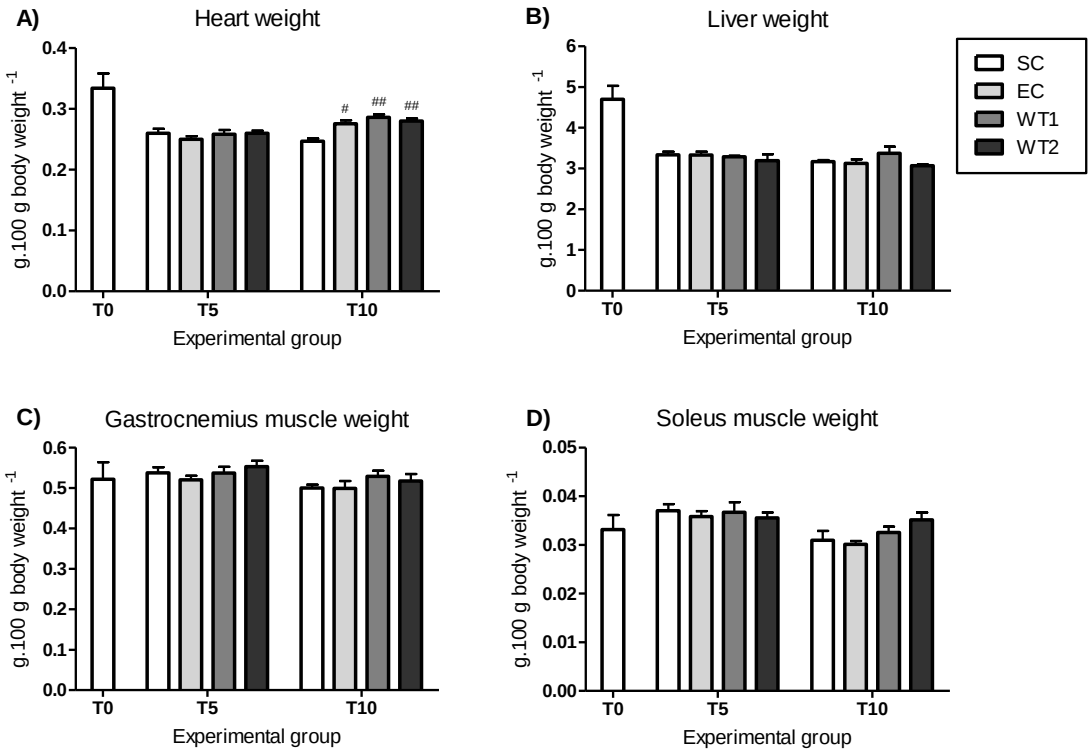

Figure 2. Percentual tissue ratio of the body weight. (A) Heart weight; (B) Liver weight; (C) Gastrocnemius muscle weight; and (D) Soleus muscle weight. SC: Sedentary control groups; EC: Exercise control groups; WT1: Exercise training + White tea 1 groups; WT2: Exercise training + White tea 2 groups. Values expressed as mean ± SEM. The subgroups (n = 5-7) were compared at the same experimental group (T5 or T10). #Indicates significant differences from the SC group and *indicates significant differences from the EC group according to Student's t-test (1 sign = $P < 0.05$; 2 sign = $P < 0.01$; and 3 sign = $P < 0.001$).

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CAPÍTULO 4

CONCLUSÃO GERAL

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O chá branco (*Camellia sinensis*), obtido por meio de infusão aquosa, representa uma fonte alimentar de compostos fenólicos com alto potencial antioxidante associado. Neste trabalho, a sua eficiência como alimento funcional foi testada *in vivo* utilizando um modelo experimental que envolve o exercício físico. O ensaio biológico realizado com ratos Wistar saudáveis demonstrou que o treinamento de corrida, por si só, foi capaz de induzir adaptações fisiológicas que culminaram em hipertrofia cardíaca e melhora da capacidade aeróbica. A ingestão regular e crônica de chá branco, concomitante ao treinamento físico, proporcionou ganhos adicionais aos animais que puderam ser observados após uma sessão de exercício exaustivo. O chá branco demonstrou eficiência em otimizar a capacidade antioxidante sistêmica, mesmo não favorecendo a atividade das enzimas antioxidantes em nível sérico. Em nível hepático, a ingestão do chá branco contribuiu para melhor atividade do sistema de defesa antioxidante endógeno, bem como para a proteção contra danos oxidativos. E, embora não tenha favorecido um perfil anti-inflamatório no fígado, a ingestão de chá branco proporcionou a redução de marcadores inflamatórios em nível sérico.

Com relação as concentrações e ao tempo de ingestão dos chás, em geral, o chá preparado na menor concentração, consumido por períodos prolongados (10 semanas) e associado ao treinamento de resistência, parece refletir em efeitos benéficos mais pronunciados quanto aos parâmetros analisados.

Em resumo, o chá branco pode ser considerado uma bebida fonte de compostos bioativos que auxilia na modulação da resposta antioxidante durante a execução de exercícios físicos agudos e exaustivos. Assim, os resultados obtidos neste trabalho despertam o interesse para investigações futuras sobre o impacto de uma dieta rica em alimentos com propriedades funcionais na saúde de praticantes de exercício físico.

CAPÍTULO 5

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ANEXO

ANEXO 1

Anexo 1. Certificado de aprovação da Comissão de ética no uso de animais da Unicamp.

UNICAMP

CEUA/Unicamp

Comissão de Ética no Uso de Animais
CEUA/Unicamp

CERTIFICADO

Certificamos que o projeto "**Efeito da suplementação de extrato de diferentes chás da planta Camellia sinensis na prática de atividade física em ratos Wistar**" (protocolo nº **3595-1**), sob a responsabilidade de **Mário Roberto Maróstica Junior / Gustavo Fanaro**, está de acordo com os **Princípios Éticos na Experimentação Animal** adotados pela **Sociedade Brasileira de Ciência em Animais de Laboratório (SBCAL)** e com a legislação vigente, **LEI Nº 11.794, DE 8 DE OUTUBRO DE 2008**, que estabelece procedimentos para o uso científico de animais, e o **DECRETO Nº 6.899, DE 15 DE JULHO DE 2009**.

A aprovação pela CEUA/UNICAMP não dispensa autorização prévia junto ao **IBAMA**, **SISBIO** ou **CIBio**.

O projeto foi aprovado pela Comissão de Ética no Uso de Animais da Universidade Estadual de Campinas - CEUA/UNICAMP - em **06 de outubro de 2014**.

Campinas, 06 de outubro de 2014.

Prof. Dr. Alexandre Leite Rodrigues de Oliveira
Presidente

Fátima Alonso
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