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PROGRAMA DE PÓS-GRADUAÇÃO EM NUTRIÇÃO, ATIVIDADE FÍSICA E PLASTICIDADE FENOTÍPICA – PPGNAFPF

WIDEMAR FERRAZ DA SILVA

EFEITOS DO ENXÁGUE BUCAL COM CAFEÍNA SOBRE O DESEMPENHO FÍSICO E COGNITIVO: UMA REVISÃO SISTEMÁTICA

VITÓRIA DE SANTO ANTÃO

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Dissertação apresentada ao Programa de Pós-Graduação em Nutrição, Atividade Física e Plasticidade Fenotípica do Centro Acadêmico de Vitória da Universidade Federal de Pernambuco, como requisito para a obtenção do título de Mestre

Área de Concentração: Fatores Ambientais Moduladores da Plasticidade Fenotípica

Orientador: Prof. Dr. Marcos David da Silva Cavalcante

Coorientadores: Prof. Dr. Guilherme Assunção Ferreira

Prof. Dr. Leandro José Camati Felippe

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Aprovado em 26/02/2021

BANCA EXAMINADORA

____

Prof° Dr. João Paulo Lopes da Silva (Examinador Externo)

Centro Universitário CESMAC

____

Prof° Dra. Carol Virgínia Góis Leandro (Examinadora Interna)

Universidade Federal de Pernambuco

____

Prof° Dr. Kleiner Márcio de Andrade Nemézio (Examinador Externo)

UNINASSAU Maceió

Dedico este trabalho aos meus pais Maria Iranilda Mano e Ademário Ferraz da Silva (*in memorian*) por sempre acreditarem em mim.

Amo vocês!

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RESUMO

A ingestão de cafeína é um dos recursos ergogênicos mais utilizados para melhorar o desempenho atlético e cognitivo. Além disso, o uso de formas alternativas de administração de cafeína foi recentemente proposto como forma de mitigar possíveis efeitos colaterais da ingestão. Realizar uma revisão sistemática dos estudos que examinaram os efeitos do enxágue bucal com cafeína no desempenho físico e cognitivo. Usando as diretrizes PRISMA, identificamos 1.790 estudos em quatro bancos de dados eletrônicos (Cochrane, Pubmed, Science Direct e Web of Science). Destes, 17 artigos atenderam aos critérios de inclusão (14 para desempenho físico e 3 para desempenho cognitivo). Quatro estudos detectaram efeitos positivos do enxágue bucal com cafeína no desempenho físico quando o enxágue bucal repetido foi realizado durante o exercício, enquanto um estudo detectou um efeito positivo do enxágue bucal com cafeína com um único enxágue bucal antes do exercício, mas apenas em jejum. Em contraste, todos os estudos selecionados encontraram uma melhora no desempenho cognitivo com enxágue bucal com cafeína. Os efeitos do enxágue bucal com cafeína sobre desempenho físico são incertos. No entanto, um potencial efeito ergogênico do enxágue bucal com cafeína pode estar presente quando o exercício é realizado em jejum e/ou quando o enxágue bucal com cafeína é repetido durante o exercício. Em relação ao desempenho cognitivo, o enxágue bucal com cafeína parece ser uma estratégia benéfica

Palavras-chave: Cafeína. Enxágue bucal. Recursos ergogênicos. Nutrição esportiva.

ABSTRACT

Caffeine ingestion is one of the most used ergogenic aid for improving athletic and cognition performance. Moreover, the use of alternative forms of caffeine administration has recently been proposed as a form to mitigate possible side effects of ingestion. To conduct a systematic review of the studies examining the effects of caffeine mouth rinsing on physical and cognitive performance. Using the PRISMA guidelines, we identified 1790 studies on four electronics databases (Cochrane, Pubmed, Science Direct and Web of Science). From these, 17 articles fulfilled the inclusion criteria (14 for physical performance and 3 for cognitive performance). Four studies detected positive effects of caffeine on physical performance when repeated mouth rinse was performed during exercise, while one study detected a positive effect of caffeine mouth rinsing with a single mouth rinse before exercise but only in a fasted state. In contrast, all selected studies found an improvement in cognitive performance with caffeine mouth rinsing. The effects of caffeine mouth rinsing on physical performance is uncertain. A potential ergogenic effect of caffeine mouth rinse might be present when exercise is performed in a fasted state and/or caffeine mouth rinse is repeated many times during exercise. In relation to cognitive performance, caffeine mouth rinsing seems to be a beneficial strategy.

Keywords: Caffeine. Mouth rinse. Ergogenic aids. Sports nutrition.

LISTA DE FIGURAS

Artigo de Revisão Sistemática

LISTA DE ABREVIAÇÕES

CAF - Caffeine

DB - Double-blinded

ES - Effect size

M - Males

MR - Mouth rinse

MD - Maltodextrin

NR - Not reported

RM - Repetition maximum

PLA - Placebo

PT - Peak torque

RPE - Rated perceived exertion

SB - Single blinded

SD - Standard deviation

TE - Time exhaustion

TT - Time trial

LISTA DE TABELAS

SUMÁRIO

1 INTRODUÇÃO

A cafeína é um dos recursos ergogênicos mais utilizados por atletas (AGUILAR-NAVARRO *et al.*, 2019). Isso se deve pelo crescente número de estudos demonstrando melhora do desempenho após a sua utilização (SANTOS *et al.*, 2013; FELIPPE *et al.*, 2018; SILVA-CAVALCANTE *et al.*, 2013). A cafeína tem como principal característica a sua ação antagonista aos receptores de adenosina (FREDHOLM *et al.*, 1999). Devido os receptores de adenosina estarem presentes em diversos órgãos, a ingestão de cafeína promove alterações fisiológicas tanto no sistema nervoso central quanto no músculo esquelético (GUEST *et al.*, 2021). De fato, tem sido demonstrado um aumento da excitabilidade cortical (supraespinhal) e espinhal com a ingestão de cafeína (KALMAR, 2005). Quanto à sua ação periférica, embora controversa, concentrações fisiológicas de cafeína podem aumentar a liberação de cálcio do retículo sarcoplasmático e potencializar a atividade da bomba de sódio/potássio, promovendo o aumento da força contrátil do músculo esquelético (MOHR; NIELSEN; BANGSBO, 2011; TALLIS *et al.*, 2012; TARNOPOLSKY; CUPIDO, 2000).

As formas mais utilizadas de cafeína são as cápsulas ou café, porém, nos últimos anos, diversas formas alternativas de utilização de cafeína tem sido estudadas, como as bebidas energéticas, géis, barras e gomas de mascar (WICKHAM; SPRIET, 2018a). Além destas formas anteriormente citadas, um novo método de administração que vem sendo proposto é o enxágue bucal com cafeína, que também parece ser uma alternativa segura e efetiva no aumento do desempenho físico e cognitivo (WICKHAM; SPRIET, 2018a). Ao contrário das demais estratégias, o enxágue bucal vem emergindo como uma forma de administração de cafeína ausente de efeitos colaterais, que são geralmente associados as suas formas ingeríveis (ansiedade, enxaqueca e distúrbios gastrointestinal) (MCLELLAN; CALDWELL; LIEBERMAN, 2016; WILSON, 2016). Isso porque o enxágue bucal com cafeína não promove aumento nas concentrações plasmáticas de cafeína, frequentemente associados com os seus efeitos adversos (DOERING *et al.*, 2014). Adicionalmente, além da ausência de efeito colaterais, o possível efeito imediato do enxágue bucal de cafeína sobre o desempenho torna este método superior aos demais citados.

Os mecanismos de ação associados aos efeitos ergogênicos do enxágue bucal com cafeína ainda não foram completamente elucidados, mas, dois principais mecanismos têm sido especulados na literatura. O primeiro deles diz respeito a ligação da cafeína aos receptores de adenosina localizados na cavidade oral, promovendo o aumento da liberação de neurotransmissores e aumento da taxa de disparo neuromuscular (KAMIMORI *et al.*, 2002). Enquanto o segundo é relacionado aos receptores de gosto amargo localizados na boca, que possuem conexão direta com regiões do cérebro associadas ao processamento de informações e recompensa (GAM; GUELFI; FOURNIER, 2014; ZALD; HAGEN; PARDO, 2002). Em conjunto, estes mecanismos sugerem que soluções de sabor amargo como a cafeína, podem ativar áreas emocionais e motoras do cérebro, o que implica diretamente no desempenho físico e cognitivo.

Enquanto os efeitos da ingestão de cafeína sob o desempenho físico (ASTORINO; ROBERSON, 2010; GRGIC; TREXLER; LAZINICA; PEDISIC, 2018; SALINERO; LARA; DEL COSO, 2019) e cognitivo (CRAWFORD *et al.*, 2017) tem sido amplamente investigado, os métodos alternativos de administração (goma de mascar, spray nasal, enxágue bucal) seguem até então pouco explorados. Logo, o objetivo da presente dissertação foi realizar uma revisão sistemática, sumarizando os estudos que avaliaram os efeitos do enxágue bucal de cafeína sobre o desempenho físico e cognitivo.

2 REVISÃO DA LITERATURA

2.1 Cafeína

2.1.1 Cafeína e Desempenho físico e cognitivo

A cafeína é um dos recursos ergogênicos mais utilizados por atletas, principalmente após sua remoção da lista de substâncias proibidas pela World Anti-Doping Agency (WADA). Estima-se que aproximadamente ~76% dos atletas profissionais façam utilização de cafeína (CHESTER; WOJEK, 2008). Isso se deve pelo crescente número de estudos demonstrando melhora do desempenho após a sua utilização (SANTOS *et al.*, 2013; FELIPPE *et al.*, 2018; SILVA-CAVALCANTE *et al.*, 2013). Felippe *et al.* (2018) verificaram um aumento do desempenho, potência e recrutamento muscular durante uma prova de contrarrelógio de 4 km em ciclistas após ingestão de 5mg/Kg de cafeína. Bowtell *et al.* (2018) mostraram que a ingestão de 6mg/kg em homens fisicamente ativos prolongou o tempo (17,9%) de realização de um exercício isolado (extensão de joelhos) e aumentou a ativação voluntária cortical. Bazzucchi *et al.* (2011) também obtiveram êxito utilizando dosagens de cafeína semelhantes em homens moderadamente ativos, verificando aumento da taxa de desenvolvimento de torque e amplitude do sinal eletromiográfico. Além desses resultados, outros estudos também encontraram melhora no desempenho em diferentes modalidades como corrida (WHALLEY; DEARING; PATON, 2020), ciclismo (VIANA *et al.*, 2020), treinamento de força (GRGIC; TREXLER; LAZINICA; PEDISIC, 2018) e judô (DURKALEC-MICHALSKI *et al.*, 2019). Em conjunto, esses achados demonstram que a cafeína é uma substância que apresenta um efeito ergogênico bem estabelecido na literatura.

Além do já conhecido efeito da cafeína sobre o desempenho físico, a cafeína também vem sendo estudada em atletas e grupos que requerem uma maior demanda cognitiva e estado de alerta em sua rotina. Em especial, os efeitos cognitivos da cafeína têm sido extensivamente estudados no público militar em situações de campo (CRAWFORD *et al.*, 2017). Em condições de restrição do sono (72h), a suplementação de cafeína (200-300mg) reduziu a percepção de fadiga e sonolência, além de melhorar o estado de alerta, vigilância e tempo de reação em militares da U.S Navy Seals (LIEBERMAN *et al.*, 2002).

2.1.2 Cafeína e mecanismos de ação

O cálcio tem sido sugerido como um dos fatores envolvidos na etiologia da fadiga (GRAHAM; RUSH; SOEREN, 1994), uma vez que a redução de seus níveis e/ou queda na sensibilidade dos componentes ligados ao processo de contração tem sido associada à diminuição da produção de força (ALLEN; LAMB; WESTERBLAD, 2008). Westerblad e Allen (1991) investigaram os efeitos *in situ* de impulsos elétricos combinados a presença de cafeína (10mM) sobre o músculo flexor da pata de ratos e observaram um aumento da liberação de cálcio quando comparado a solução controle com ausência de cafeína. De forma semelhante, a exposição do músculo flexor de ratos a uma solução de cafeína (5µM) combinadas a impulsos elétricos (100Hz) também promoveu o aumento da liberação de cálcio (MACINTOSH; GARDINER, 1987). Entretanto, todos estes estudos que demonstram aumento da liberação de cálcio utilizaram doses suprafisiológicas (>70µM), tóxicas para seres humanos. Ainda assim, alguns estudos têm sugerido que a utilização de doses fisiológicas de cafeína podem promover alterações periféricas capazes de otimizar a força muscular (TALLIS *et al.*, 2012; TARNOPOLSKY; CUPIDO, 2000).

Além da ação sobre a liberação de cálcio, a ingestão de cafeína também é capaz de promover outros efeitos a nível periférico. Davis e Green (2009) mostraram em estudo de revisão que entre estes efeitos, destacam-se o aumento da liberação de catecolaminas e glicose, maior ativação do complexo de contração/excitação através da ação do potássio no músculo, facilitando a atividade da bomba de sódio/potássio, inibição da enzima fosfodiesterase e maior contribuição anaeróbia durante o exercício. Apesar da cafeína atuar em diversas áreas do corpo, a literatura vem mostrando o sistema nervoso central como o seu principal alvo de ação, com mecanismos amplamente aceitos para justificar as alterações observadas no desempenho físico e cognitivo.

A cafeína estimula o sistema nervoso central, promovendo redução da percepção de esforço (RPE), aumento da atividade simpática e o recrutamento de unidades motoras (ASTORINO; ROBERSON, 2010). Lopes-Silva *et al.* (2014) observaram uma redução da RPE (14,6%) em judocas após ingestão de cafeína (6mg/Kg) durante um protocolo de Special Judo Fitness Test. Esse resultado está de acordo com uma meta-análise envolvendo 21 estudos que observou que a ingestão de cafeína é capaz de reduzir a RPE em ~5,6% (DOHERTY; SMITH, 2005). Essa ação central se deve principalmente ao bloqueio dos receptores de adenosina, impedindo que este neurotransmissor promova o surgimento de sintomas como cansaço, dor e sonolência (FREDHOLM *et al.*, 1999).

2.2 Métodos alternativos de administração

Apesar das cápsulas serem a forma mais comumente utilizada, um crescente corpo de evidências tem avaliado o uso de formas alternativas de administração para cafeína, como bebidas energéticas, géis, barras, spray nasal e gomas de mascar. Cooper *et al.* (2014) verificaram redução do índice de fadiga em indivíduos ativos após consumo de um gel cafeínado [carboidratos (25g) e cafeína (100 mg)] durante sprints intermitentes (4 blocos envolvendo 11 ciclos) quando comparado ao grupo que fez uso do gel com carboidrato isolado. Ryan *et al.* (2013) também observaram melhora do desempenho com a utilização da goma de mascar cafeínada (300 mg) em ciclistas treinados quando consumida 5 minutos antes de uma prova de contrarrelógio (7 kJ/kg de peso corporal). Por outro lado, as bebidas energéticas não têm exibido resultados satisfatórios no desempenho físico (ECKERSON *et al.*, 2013; KAMMERER *et al.*, 2014). De forma semelhante, outras formas alternativas de administração de cafeína como o spray nasal também tem sido empregadas, porém, sem encontrar resultados positivos sobre o desempenho físico (DE PAUW *et al.*, 2017).

Apesar das formas de administração mais comumente utilizadas envolverem a ingestão da cafeína (FREDHOLM *et al.*, 1999) e promoverem efeitos positivos no desempenho físico e cognitivo (BOTTOMS *et al.*, 2014; VAN CUTSEM *et al.*, 2018), alguns efeitos colaterais indesejáveis são frequentemente relatados, como ansiedade, enxaqueca e desconforto gastrointestinal (MCLELLAN; CALDWELL; LIEBERMAN, 2016). Logo, novas formas de utilização da cafeína que reduzam a incidência destes efeitos deletérios e promovam a melhora do desempenho físico e cognitivo são de grande interesse.

2.3 Enxágue bucal com cafeína e desempenho

O enxágue bucal com cafeína tem emergido como uma alternativa promissora nos últimos anos. Essa estratégia envolve o enxágue bucal com cafeína por alguns segundos (5-20 s) sem a sua ingestão (VAN CUTSEM *et al.*, 2018). Carter, Jeukendrup e Jones (2004) foram os pioneiros com esta técnica, ao mostrar pela primeira vez que o enxágue bucal com carboidratos era capaz de promover uma melhora no desempenho físico por meio da estimulação de receptores da cavidade oral associados aos centros de recompensa e/ou prazer no cérebro. Após esse achado, vários outros estudos continuaram a investigar os efeitos ergogênicos do enxágue bucal com carboidratos (BAZZUCCHI *et al.*, 2017; CLARKE *et al.* 2017; LANE *et al.*, 2012; LUDEN *et al.*, 2016). A partir disto, surgiu o interesse em avaliar os efeitos de outros compostos que pudessem ser usados durante o enxágue bucal, melhorando o desempenho físico e cognitivo.

Beaven *et al.* (2013) foram os primeiros a investigar os efeitos do enxágue bucal de cafeína e compará-lo com o enxágue bucal com carboidratos. No entanto, não foi verificado diferença estatística entre as condições avaliadas. Em seguida, Bottoms *et al.* (2014) encontraram melhora no desempenho usando uma solução de 25ml com cafeína (0,032%) para realização de enxágues bucais repetidos durante um teste contrarrelógio de ciclismo. A distância percorrida na condição CAF foi maior em comparação com o placebo (16,2 ± 2,8 vs. 14,9 ± 2,6 km, respectivamente) e, embora não tenha sido verificado diferença estatística entre as condições carboidratos e cafeína, observou-se que dez dos doze indivíduos que percorreram uma distância maior na condição cafeína. Sinclair e Bottoms (2014) avaliaram o efeito do enxágue bucal com cafeína (0,032%) no desempenho físico durante exercícios para membros superiores. Esses autores encontraram uma melhora de 16% na distância percorrida durante 30 minutos de contrarrelógio (CAF: 15,43 ± 3,27 km vs PLA: 13,15 ± 3,36 km). Curiosamente, em ambos os estudos não foram observadas diferenças na RPE entre as condições, promovendo uma redução na razão RPE/potência, o que sustenta a hipótese de que os efeitos do enxague bucal com cafeína ocorrem por meio da estimulação de regiões do cérebro associadas a recompensa e motivação (FREDHOLM *et al.*, 1999). Alguns estudos que avaliaram os efeitos do enxágue bucal com cafeína também verificaram melhora no desempenho cognitivo durante o exercício (POMPORTES *et al.*, 2017) e redução da fadiga mental (VAN CUTSEM *et al.*, 2018), o que fortalece a hipótese de que os efeitos ergogênicos do enxágue bucal com cafeína acontecem principalmente em nível cerebral, traduzindo-se em aumento do desempenho físico.

2.4 Enxágue bucal com cafeína e mecanismos

Os mecanismos envolvidos em um potencial efeito ergogênico do enxágue bucal com cafeína não são completamente conhecidos. No entanto, dois possíveis mecanismos têm sido propostos na literatura. O primeiro deles envolve a ligação da CAF com os receptores de adenosina localizados na cavidade oral (KAMIMORI *et al.*, 2002), enquanto o segundo trata-se dos efeitos associados aos receptores de sabor amargo localizados na boca que possuem uma conexão direta com regiões do cérebro relacionado ao processamento de informações e recompensa (GAM; GUELFI; FOURNIER, 2014; ZALD; HAGEN; PARDO, 2002).

A cavidade oral possui receptores de gosto amargo localizados no epitélio orofaríngeo (MATSUMOTO, 2013) que podem ser ativados através de substâncias como a cafeína (MEYERHOF *et al.*, 2010). Tem sido observado que a ativação destes receptores pode estimular o sistema nervoso simpático e regiões do cérebro associadas ao controle motor e recompensa (GAM; GUELFI; FOURNIER, 2016). A cafeína também exerce importantes funções no sistema nervoso central através do antagonismo aos receptores de adenosina (FREDHOLM *et al.*, 1999), modulando as concentrações de neurotransmissores (dopamina, acetilcolina, serotonina, norepinefrina e glutamato) e promovendo efeitos positivos no estado de alerta, humor e concentração (GUEST *et al.*, 2021).

2.5 Receptores de gosto amargo

A percepção do sabor é uma função que permite decidir o que comer, além de preceder e sinalizar o posterior processo de digestão alimentar (BRESLIN, 2013). A avaliação das respostas fisiológicas desencadeadas pela percepção de sabor tem sido discutida na área do desempenho esportivo (BEST, 2020b). A cafeína é um composto capaz de ativar receptores de gosto amargo (CHANDRASHEKAR *et al.*, 2000). Estes, por sua vez, são detectados por receptores acoplados a proteína G (BEHRENS; ZIEGLER, 2020) e codificados pelos genes TAS2R (MEYERHOF *et al.*, 2010). Alguns trabalhos apontam que variações genéticas, especialmente no gene TAS2R38 podem afetar a detecção de compostos de sabor amargo (feniltiocarbamida e 6-n-propiltiouracil) (DUFFY *et al.*, 2004) o que pode tornar alguns indivíduos mais sensíveis a exposição a compostos de sabor amargo, nomeados como "*super-tasters*" (BARTOSHUK; DUFFY; MILLER, 1994). Além disso, alguns fatores como exposição frequente a cafeína (TANIMURA; MATTES, 1993), tabagismo (KAPLAN; GLANVILLE; FISCHER, 1964) e envelhecimento (MENNELLA *et al.*, 2010) parecem modificar a percepção ao sabor amargo.

Evidências mostram que o sabor doce e amargo são capazes de ativar áreas do cérebro semelhantes (córtex cingulado anterior, amigdala e estriado) associadas ao controle motor e processamento de informações (ZALD; HAGEN; PARDO, 2002). Além disso, foi também verificado que substâncias de sabor amargo (ex: quinina), quando comparada a outros quatro saborizantes (salgado, doce, azedo e água), promove uma maior ativação do sistema nervoso autonômico (ROUSMANS *et al.*, 2000). Juntas, estas evidências mostram o importante papel dos receptores de sabor amargo na ativação de áreas do cérebro associadas ao controle motor e processamento de informações, bem como estimulação do sistema nervoso autonômico, o que pode ter implicações diretas no desempenho físico e cognitivo.

3 OBJETIVOS

A presente dissertação teve como objetivo realizar uma revisão sistemática sobre os efeitos do enxágue bucal de cafeína sob a performance física e cognitiva

4 METODOLOGIA

O protocolo deste estudo foi desenhado de acordo com as diretrizes PRISMA. Uma pesquisa bibliográfica sistemática foi realizada em abril de 2020 usando as bases de dados: Pubmed, Web of Science, Science Direct e Cochrane para identificar pesquisas originais. A estratégia de pesquisa usada foi (conceito 1) *CAF mouth rinse* OR *caffeine mouth rinse* OR *CAF mouthwash* OR *caffeine mouth rinse* e (conceito 2) *performance* OR *CAF mouth rinse* AND *performance*. A análise restringiu-se ao "idioma inglês" e a artigos de pesquisa originais publicados em periódico de revisão por pares. Além disso, foi realizada uma revisão das referências bibliográficas dos artigos selecionados e não houve restrição de ano aplicada à busca.

4.1 Critérios de Elegibilidade

Os critérios de inclusão e exclusão foram determinados com a aplicação do PICOS (Participantes, Intervenção, Comparação, Resultado e Desenho do Estudo).

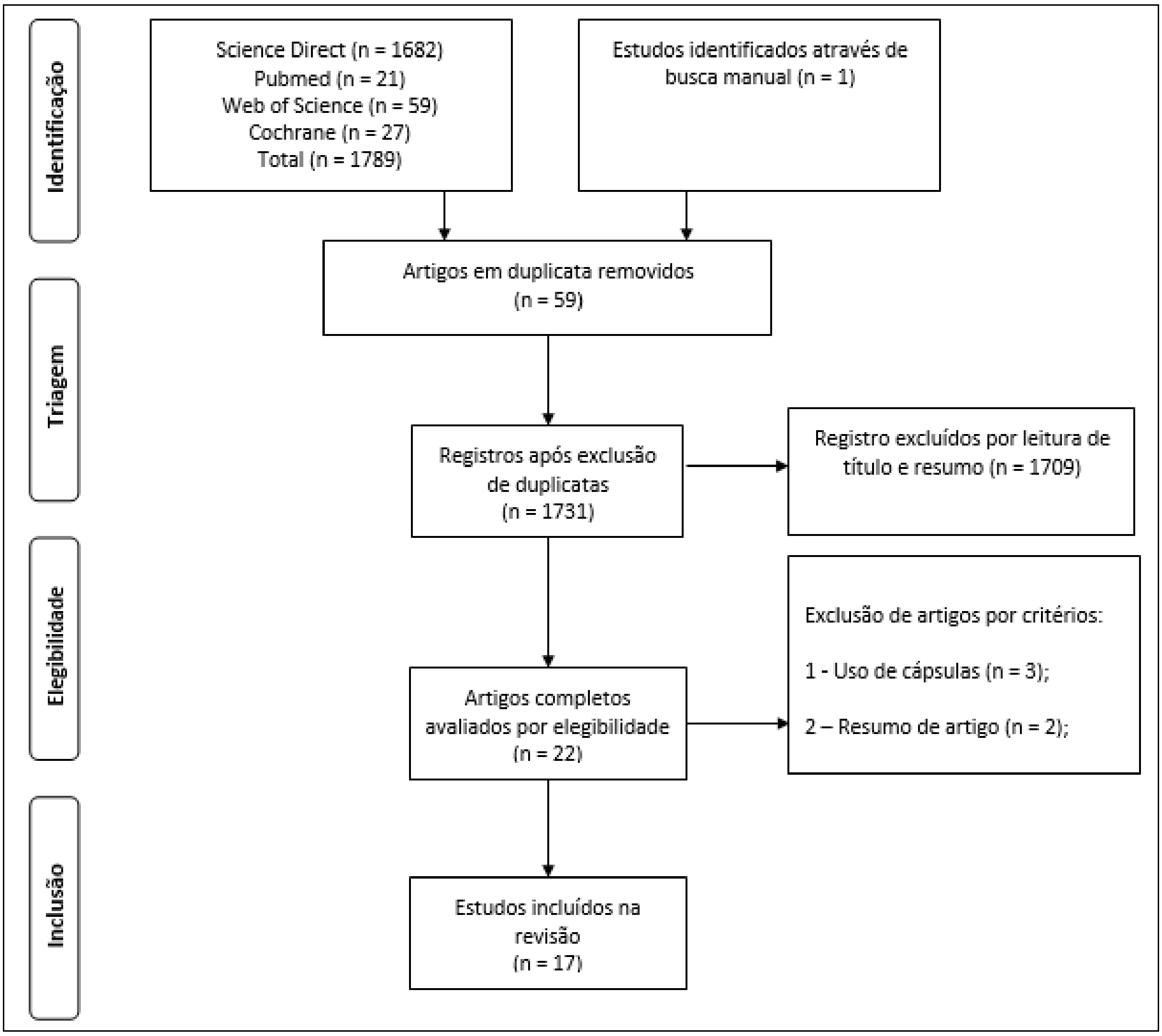
4.2 Seleção de estudos e coleta de dados

Os títulos, resumos e textos completos dos artigos selecionados foram revisados de forma independente por dois pesquisadores para verificação dos critérios de elegibilidade. O processo de extração de dados se concentrou nas seguintes informações: (1) título, tipo de publicação (original), informações sobre a publicação (ano, país, centro de pesquisa ou departamento), declaração de financiamento e divulgação de potenciais conflitos de interesse; e (2) desenho e métodos do estudo, participantes selecionados (tamanho da amostra, idade, sexo dos participantes), grupo de controle (randomização, tipo de placebo), intervenção (concentração de solução de cafeína) e resultados relatados (tempo, potência média, fadiga mental, força, e velocidade).

4.3 Avaliação de Qualidade

A escala Physiotherapy Evidence Database (PEDro) foi utilizada para avaliar a qualidade dos artigos. Esta escala foi desenvolvida pelo Center for Evidence-Based Physiotherapy e é projetada para avaliar a validade interna dos trabalhos. Cada estudo foi classificado em vários critérios previamente estabelecidos para produzir uma pontuação máxima de 10. A escala PEDro varia de 0 a 10, onde 9 a 10 pontos correspondem a qualidade excelente, 6 a 8 pontos correspondem a boa qualidade, 4 a 5 pontos correspondem a uma qualidade razoável, e menos de 3 pontos correspondendo à qualidade metodológica ruim. Todos os estudos classificados pela escala PEDro foram incluídos.

Figura 1 – Fluxograma da estratégia de busca e seleção de estudos



5 RESULTADOS E DISCUSSÃO

Os resultados e discussão serão apresentados na forma de artigo de revisão sistemática.

5.1 Artigo de revisão sistemática

IS CAFFEINE MOUTH RINSING AN EFFECTIVE STRATEGY TO IMPROVE PHYSICAL AND COGNITIVE PERFORMANCE? A SYSTEMATIC REVIEW

Authors:

Widemar Ferraz da Silva[1], João Paulo Lopes-Silva[2], Leandro José Camati Felippe[1], Guilherme Assunção Ferreira[1, 3], Adriano Eduardo Lima-Silva[4], Marcos David Silva-Cavalcante[1]

Institution:

[1]Department of Physical Education and Sport Science, CAV Federal University of Pernambuco, Brazil. [2]Department of Physical Education, University Center CESMAC, Maceió, Alagoas, Brazil. [3]Associated Program of Post-Graduation in Physical Education UPE/UFPB, University of Pernambuco, Recife, Pernambuco, Brazil. [4]Human Performance Research Group, Federal University of Technology Parana, Parana, Brazil.

Corresponding author:

Marcos David Silva-Cavalcante
cavalcantemds@hotmail.com

ABSTRACT:

Background: Caffeine ingestion is one of the most used ergogenic aid for improving athletic and cognition performance. However, the use of alternative forms of caffeine administration has recently been proposed as a form to mitigate possible side effects. *Objective:* To conduct a systematic review of the studies examining the effects of caffeine mouth rinsing on physical and cognitive performance. *Methods*: Using the PRISMA guidelines, we identified 1790 studies on four electronics databases (Cochrane, Pubmed, Science Direct and Web of Science). From these, 17 articles fulfilled the inclusion criteria (14 for physical performance and 3 for cognitive performance). *Results*: Four studies found positive effects of caffeine mouth rinsing on physical performance when repeated mouth rinse was performed during exercise, while one study detected a positive effect of caffeine mouth rinsing with a single mouth rinse before exercise, but only in a fasted state. In contrast, all selected studies found an improvement in cognitive performance with caffeine mouth rinsing. *Conclusion*: The effects of caffeine mouth rinsing on physical performance is uncertain. However, a potential ergogenic effect of caffeine mouth rinse might be present when exercise is performed in a fasted state and/or caffeine mouth rinse is repeated many times during exercise. In relation to cognitive performance, caffeine mouth rinsing seems to be a beneficial strategy.

Keywords: bitter tastant, ergogenic aids, sports nutrition.

1. INTRODUCTION

Many nutrients and substances such as carbohydrate, creatine, sodium bicarbonate, β-alanine, nitrate, and caffeine have widely been used in an athletic environment to enhance physical performance [1]. Caffeine is one of the most ergogenic aids used by athletes [2, 3], especially after its removal in 2004 from the prohibited substances list of the World Anti-Doping Agency (WADA) [4]. It has been reported that ~76% of professional athletes use caffeine in endurance sports (cycling, rowing, athletics, and triathlon) [2], which can be administered via different routes (capsules, tablets with water, drink coffee, energy drinks, gels bars, and gums) [5].

In addition to physical performance, it has been suggested that caffeine ingestion also appears to enhance cognitive performance. It is in line with findings from a recent meta-analysis [6] examining the impact of acute caffeine ingestion on cognitive parameters during different cognitive tests. This meta-analysis found that, following a period of sleep deprivation, caffeine ingestion has a moderate to large (Hedges' g=0.68-1.95) on the speed component of information processing tasks, reaction time (speed), and attention (speed and accuracy). These findings are especially important since some athletes are involved in activities that require periods of sustained cognitive function and vigilance under sleep-deprived conditions due to, for example, their job (e.g., Special Forces military athletes). Furthermore, caffeine ingestion also appears to be beneficial for cognitive aspects of sports performance also seems to benefit different cognitive aspects of the sport (e.g., ball passing accuracy) [7, 8]. Thus, caffeine use could improve performance in sport modalities involving cognitive aspects.

Although the most common route of caffeine administration is ingestion [9] and promotes beneficial effects on both physical and cognitive performance [10, 11], some side effects are often reported (e.g., anxiety, headaches, and increased blood pressure) [9]. Therefore, new caffeine use strategies that may mitigate its side effect and improve physical and/or cognitive performance would be of interest. In this context, it has been proposed that caffeine mouth rinsing could also be effective for the improvement of both physical and cognitive performance [12, 13]. Unlike caffeine ingestion, the mouth rinse is a promising strategy to reduce the possible side effects of its intake because it does not increase plasma caffeine concentration [14]. Another advantage of using caffeine mouth rinsing would be its immediate action, enabling repeated use during sports competitions and/or cognitive tasks. Mouth rinsing strategy involves the mouth rinse caffeine for few seconds (5-20 s) without further ingestion [12] This strategy emerged from studies that investigated the effect of carbohydrate mouth rinsing on physical performance [15]. The mechanisms involved in a potential ergogenic effect of mouth rinse with caffeine are not entirely known, but two possible mechanisms have been proposed. The first mechanism involves caffeine binding with adenosine receptors located in the oral cavity, promoting an increase in neurotransmitters' release and muscle firing rates [16]. The second mechanism refers to bitter taste receptors located in the mouth directly connected to regions of the brain related to information processing and reward [17, 18]. These, in turn, are activated when exposed to caffeine, improving mental alertness through dopamine transmission by activation of sensory neurons in the mouth, starting a cascade of transduction events towards the brain [19].

Some systematic reviews have shown improved physical and cognitive performance with caffeine ingestion [20-24], but so far, alternative methods (chewing gum, mouth rinse, and nasal aerosol) have been poorly addressed [25]. In this context, only a systematic review examined the effects of caffeine mouth rinsing on physical performance and found a mixed result [25]. However, since this systematic review, recent studies have been published [26-29]. Furthermore, the effect of caffeine mouth rinsing on cognitive performance has not been critically reviewed. Thus, this systematic review aims to summarize the studies investigating the effects of caffeine mouth rinsing on physical and cognitive performance.

2. MATERIAL AND METHODS

The present study' protocol was designed following PRISMA (Preferred Reporting Items for Systematic Review, and Meta-Analysis) guidelines. Systematic research literature was performed in March 2021 in the databases of Pubmed, Web of Science, Science Direct and Cochrane to identify original research. The search strategy used was (concept 1) CAF mouth rinse OR caffeine mouth rinse OR CAF mouthwash OR caffeine mouth rinse AND (concept 2) performance OR CAF mouth rinse AND performance. The analysis was restricted to "English language" and original research articles published in the peer-review journal. Besides, a review of the selected articles' references was performed, and there was no year restriction applied to the search.

2.1 Eligibility Criteria

Inclusion and exclusion criteria were determined through the PICOS (Participants, Intervention, Comparison, Outcome, and Study Design) application. The PICOS strategy utilized is reported in Table 1.

Table 1: Description of the PICOS strategy.

PICOS Components	Detail
Participants	Healthy humans (men or female)
Intervention	Caffeine mouth rinse before and/or during exercise and/or cognitive task
Comparison	Placebo condition
Outcome	Physical and/or cognitive performance (time-based, mean of power/velocity, strength, speed, reaction time, mental fatigue and cognitive control)
Study design	Single and double-blind, randomized controlled trials with crossover design or counterbalanced

2.2 Study Selection and Data Collection

Two researchers independently reviewed the titles, abstracts, and full texts of the selected articles to check for eligibility criteria. The data extraction process was focused on the following information: (1) title, type of publication (original), information on publication (year, country, research center, or department), funding statement, and disclosure of potential conflicts of interest; and (2) design and methods of the study, participants selected (sample size, age, sex of participants), control condition (randomization, type of placebo), intervention (concentration of caffeine solution), and outcomes reported (time, mean power, strength, speed, reaction time, mental fatigue and cognitive control).

2.3 Quality Assessment

The Physiotherapy Evidence Database (PEDro) scale was used to assess the quality of the articles. Each study was rated on several previously established criteria to yield a maximum score of 10. The PEDro scale ranges from 0 to 10, where 9-10 points correspond to excellent quality, 6-8 points corresponding to good quality, 4-5 points corresponding to fair quality, and less than 3 points corresponding to poor methodological quality. Studies with PEDro scale above 3 points were included.

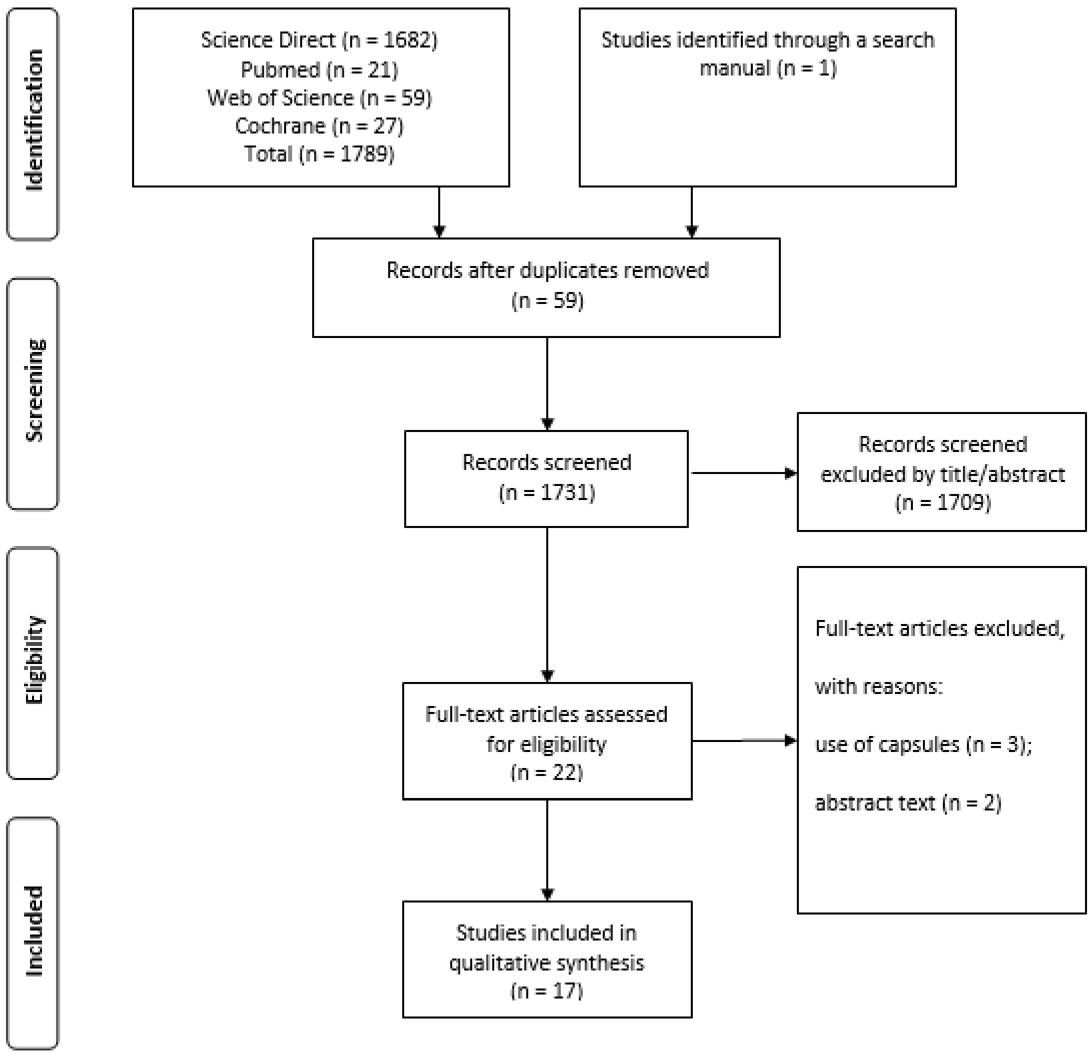


Figure 1: Flowchart of search strategy and selection of studies.

3. RESULTS

Study selection

A total of 1790 articles were initially identified. Of 1731 that remained after removing 59 duplicates, 1709 articles did not fit with the purpose of the present review. Thus, we evaluated 22 full-text articles, and after applying inclusion and exclusion criteria, we included 17 articles in qualitative synthesis (Figure 1).

Study methodological quality

Among the studies that evaluated physical performance, nine articles reached 9-10 points [14, 26, 28-34], two studies 8-7 points [11, 35] and three studies 6-5 [27, 36, 37] in PEDro scale (see in Table 2). Concerning studies that verified cognitive performance, two studies reached 9-10 points [10, 38], while a study scored 5-6 points [39] on PEDro scale (see in Table 3). None of the 17 selected studies reported conflicts of interest or funding related to commercial interest.

Study characteristics

Of the 17 studies selected, 14 studies evaluated the effects of caffeine mouth rinsing on performance. The total of participants was 197, where 175 were men whereas only 22 were women included in only study [27]. A total of eight studies performed the caffeine mouth rinsing before exercise [26, 27, 31-34, 37], four studies during exercise [11, 30, 35, 36] and two studies before and during exercise [14, 28]. These solutions were rinsed for 5-s mouth rinse in five studies [11, 27, 30, 34, 36] and 10-s mouth rinse in nine studies [14, 26, 28, 29, 31-33, 35, 37]. Regarding to mode of exercise, two studies utilized a repeated maximal sprint test [5x6 maximal sprints (24s active recovery)] [30, 35], six studies utilized a time trial protocol [11, 14, 26, 29, 34, 36], whereas others utilized Yo-Yo Intermittent Recovery Test Level 1 [32], Wingate test [33, 37], Taekwondo Anaerobic Intermittent Kick Test [27], maximal strength and resistance exercise [31] and time exhaustion [28].

Three studies evaluated the effects of caffeine mouth rinse on cognitive performance [10, 38, 39]. The total number of participants was 42 and only one study included women with a total of 6 participants [39]. One study used a single mouth rinse immediately before cognitive task [38] and other two performed repeated mouth rinses before and during cognitive task [10, 39]. Regarding the mouth rinse protocols adopted, two studies used 20s mouth rinse [38, 39] and one study used 10s mouth rinse [10]. Cognitive performance was assessed using the Stroop task [38], Flanker task [10], Simon task and duration-production task [39].

Caffeine solution concentration ranged from 0.032 [14] to 2% [35]. The placebo condition included microcrystalline cellulose [26, 29], water [37], flavored water [17, 30, 39], artificial saliva [10] distilled water [38], non-caloric mint essence [28] and decaffeinated diet cola [40].

Physical performance

Five out 14 selected studies involving physical performance found a positive effect with caffeine mouth rising compared to placebo [11, 27, 28, 35, 41] (Table 2). Of these studies, four used repeated caffeine mouth rising [11, 28, 35, 41] and one used single mouth rinsing before exercise [27]. In contrast, of the nine studies that found no improvement in physical performance with caffeine mouth rinse, seven studies used a single mouth rising before exercise [26, 29, 31-34, 37] and two adopted repeated caffeine mouth rising strategy [14, 30].

Cognitive performance

All studies found positive effects of caffeine mouth rinse on cognitive performance (Table 3). It was observed that, when compared to placebo, caffeine mouth rinse promoted a decrease in mental fatigue [10], reaction time [38], and an increase in cognitive control [39].

Table 2: Summary and results of the studies reviewed assessing the effect of caffeine mouth rinsing on physical performance.

Study	Study design	N/Sample	Age (years) (mean ± SD)	PEDro Scale	Exercise protocol	Mouth rinse protocol	Mouth rinsing time	Control	Performance improvement
BEAVEN, et al. 2013	DB	12M/recreationally trained	32 ± 7.5	10/10	5x6 maximal sprints (24s active recovery)	CAF 1.2% MR prior each sprint	5s	PLA (non-caloric saccharin solution)	↔ any of the performance variables examined
BOTTOMS, et al. 2014	SB	12M/healthy active	20.5 ± 0.7	7/10	30-min cycling TT	CAF (128mg) 0.032% MR every 6min of exercise	5s	PLA (water bolus)	↑ distance covered in CAF
CLARKE, et al. 2015	DB	15M/recreationally resistance-trained	21 ± 2	10/10	Leg Press 1RM + 60% of 1RM to failure	CAF (300mg; 0,3g/Kg) 1.2% MR before test	10s	PLA (water)	↔ any of the performance variables examined
DOERING, et al. 2014	DB	10M/trained cyclists	32.9 ± 7.5	10/10	0.75 x Wmax x 3.600 kJ cycling TT	CAF (35mg) MR before and every 12.5% of exercise completion	10s	PLA (diet cola beverage decaffeinated and decarbonated)	↔ any of the performance variables examined
DOLAN, et al. 2017	DB	14M/competitive lacross players	19.9 ± 1.3	10/10	Yo-Yo Intermittent Recovery Test-Level 1	CAF 1.2% MR before test	10s	PLA (flavored water)	↔ any of the performance variables examined
KIZZI, et al. 2016	DB	8M/recreationally active	23 ± 2	8/10	5x6 maximal sprints (24s active recovery)	CAF 2% MR prior each sprint	10s	PLA (non-caloric solution)	↑ mean power output in CAF
MARINHO, et al. 2019	DB	10M/healthy	24.8 ± 3.7	10/10	Wingate test	CAF 1.2% MR (300mg) before test	10s	PLA (non-caloric mint essence solution)	↔ any of the performance variables

									examined
PAK, et al. 2020	SB	18M and 9F/ taekwondo athletes	17 ± 3	5/10	Taekwondo anaerobic intermittent test	CAF (6mg/kg) MR before test	5s	PLA (25ml water containing sweetener)	↑ success full kicks
PATAKY, et al. 2017	DB	25M and 13F/ recreationally trained 13F	21 ± 1	10/10	3-km TT	CAF 1.14% MR before test	5s	PLA (flavor-matched placebo containing 6g of saccharine)	↔ any of the performance variables examined
KARAYIGIT et al, 2017	DB	10M/recreationally active	20.50 ± 1.58	5/10	Wingate test	CAF 2% MR before test (500mg)	10s	PLA (water)	↔ any of the performance variables examined
SINCLAIR, et al. 2014	SB	12M/ND	21.54 ± 1.28	5/10	30-min arm crank TT	CAF 0.032% MR every 6 minutes of exercise	5s	PLA (water bolus)	↑ distance covered in CAF
BARBOSA, et al. 2020	DB	7M/recreationally trained	24.6 ±11.5	9/10	800-m running TT	CAF 0.6% MR (300mg) immediately before test	10s	PLA (300mg of microcrystalline cellulose (0.6%))	↔ any of the performance variables examined
MELO, et al. 2020	SB	12M/physically active	22 ± 2.8	9/10	Cycling TE	CAF 1,2% MR before the test and every 15 minutes during the trial	10s	PLA (non-caloric mint essence)	↑ TE
FIGUEIREDO , et al. 2021	DB	10M/trained healthy subjects	30.1 ± 6.4	10/10	10-km running TT	CAF 1,2% (300mg) MR 10s before the test	10s	PLA (300mg of microcrystalline cellulose)	↔ any of the performance variables examined

CAF: caffeine, DB: double-blinded, SB: single blinded, ES: Effect size, F: females, M: males, MR: mouth rinse, MD: maltodextrin, NR: not reported, RM: repetition maximum PLA: placebo, PT: peak torque, SD: standard deviation, TE: time exhaustion, TT: time trial.

Table 3: Summary and results of the studies reviewed assessing the effect of caffeine mouth rinsing on cognitive performance.

Study	Study design	N/Sample	Age (years) (mean ± SD)	PEDro Scale	Task	Mouth rinse protocol	Mouth rinsing time	Control	Performance improvement
CUTSEM, et al. 2017	DB	10M/healthy subjects	23 ± 2	10/10	Flanker test (2x3min) and Stroop task (90 min)	CAF 1.2% + MD 6,4% MR before the Stroop test and every 12.5% of completion	10s	Artificial saliva	↓ mental fatigue
DE PAW, et al. 2015	DB	10M/ healthy subjects	27 ± 3	10/10	Stroop task (90 min)	CAF 1.2% MR before test	20s	Artificial saliva	↓ reaction time
POMPORTES, et al, 2017	SB	16M 6F/physically active	26 ± 8	6/10	Simon task (3x 3min) and duration-production task (3x3min)	CAF 67mg before and twice during the exercise	20s	Tap water added orange sugarless syrup	↑ temporal performance and cognitive control

CAF: caffeine, DB: double-blinded, SB: single blinded, MD: maltodextrin, MR: mouth rinse, M: males, F: females.

4. DISCUSSION

The present systematic review investigated the effects of caffeine mouth rinsing on physical and cognitive performance. The main finding was that caffeine mouth rinse effects on physical performance are uncertain, showing positive effects only in five out 14 studies reviewed. In contrast, all studies assessing cognitive performance showed a reduction in mental fatigue [10], reduction in reaction time [38] and improved temporal performance, and cognitive control [39] with caffeine mouth rinse.

Beaven, Maulder [30] were the first to investigate caffeine mouth rinsing effects on physical performance and compare it to carbohydrate mouth rinse in recreationally trained participants. However, they found no statistical differences ($p > 0.05$) in physical performance between conditions. On the other hand, Bottoms, Hurst [11], using five caffeine mouth rinses (0.032%) during a 30-min cycling time-trial found a significant improvement (~8%) in physical performance (CAF: 16.2 ± 2.8 km vs. PLA: 14.9 ± 2.6 km). Using similar concentrations of caffeine (0.032%), Sinclair and Bottoms [36] evaluated the effect of mouth rinsing during a 30-min arm crank time trial and found an increase of 16% on covered distance (CAF: 15.43 ± 3.27 km vs PLA: 13.15 ± 3.36 km). Interestingly, even with greater power output with caffeine in these two studies [11, 36] no differences in perceived exertion were found between caffeine and placebo. These results suggest that caffeine mouth rinsing reduces RPE/power ratio by stimulating reward centers in the brain [11]. It is line with previous findings [38] demonstrating a greater activation in brain areas involved in reward and attention (i.e., dorsolateral prefrontal cortex and orbitofrontal cortex) immediately after 20 s of caffeine mouth rinsing.

Similar to mouthwash with carbohydrate [42, 43], the magnitude of physical performance improvement promoted by caffeine mouth rinse may also be related to endogenous glycogen stores (i.e., liver and muscle) [44]. While Beaven, Maulder [30] found no improvement on repeated-sprint performance, Kizzi, Sum [35] observed an increase in both peak (sprints 3, 4 and 5) and mean power (sprints 3 and 4) during 5 maximal sprint cycling, but under low muscle glycogen availability. Pak, Cuğ [27] observed that a single exposure to caffeine mouth rinse before exercise improved performance of successful kicks compared to glucose and placebo (CAF: 38.3 ± 6.8%, GLU: 36.4 ± 6.9%, PLA: 36.0 ± 6.5%) during a taekwondo test in a fasted but not in a fed state. It is also important to note that most studies [14, 31-34] with no caffeine mouth rinse effect on physical performance were performed in individuals under a fed state. Therefore, the use of caffeine mouth rinsing before exercise seems to be effective in improving physical performance to a greater extent under low carbohydrate availability [14, 35]. From an evolutionary viewpoint, bitter taste receptors may respond better in conditions where muscle and liver glycogen stores are depleted since such receptors' sensitivity may be reduced in a fed state [45]. In supported of this, increased activation of the primary taste cortex (i.e. insular cortex) with the presence of caffeine in the mouth has been found only in a fasted state [46].

Nevertheless, it has been demonstrated that caffeine mouth rinsing, when made several times throughout exercise, improves physical performance regardless of the carbohydrate stores levels [11, 36]. Therefore, repeated oral cavity exposure to caffeine may promote a cumulative effect on improving physical performance. Sinclair, Bottoms [41] found that more extended (10 s) exposition to CHO mouth rinsing has a greater effect on cycling performance when compared to shorter exposition (5 s). The ergogenic effect of caffeine mouth rinsing could be similar to carbohydrate since that also is associated with the activation of receptors located in the mouth. Therefore, it is probable that more frequent and/or prolonged exposures to caffeine in the oral cavity are needed to increase exercise performance. However, Doering, Fell [14] no reported improving exercise performance after 10s mouth rinsing with diet cola beverage (35 mg caffeine) every 12.5% of completion cycling time trial. One factor that may have influenced is the time between the last meal and exercise. While participants from Doering's study performed a cycling time trial 1 hour after the last meal of the participants, other studies found improvement in physical performance with caffeine mouth rinsing 4 h postprandial [11, 36]. Therefore, it is probable that a prolonged period between the last meal and exercise (~4 hours) is necessary for a beneficial effect of caffeine mouth rinsing on physical performance. However, further studies are needed to confirm this hypothesis.

Clarke, Kornilios [31] found no effects of caffeine mouth rinsing on strength performance using the leg press until failure. Marinho, Mendes [33], using a similar concentration of caffeine (1.2%) used in Clarke's study, assessed the effects of mouth rinsing on Wingate performance and found no improvement on performance compared to placebo. KARAYİĞİT, YAŞLI [37] evaluated if serial caffeine mouth rinsing (6 times) would be able to improve performance during the Wingate test. However, there was no improvement in performance during the Wingate test compared to placebo. On the other hand, using caffeine intake (5mg/kg), Duncan, Eyre [47] verified an increased peak power on the upper and low body during the Wingate test compared to placebo. Together, these results suggest that caffeine mouth rinsing does not promote physical performance improvement during short high-intensity exercise and that caffeine ingestion seems to be a better strategy.

While the studies involving caffeine mouth rinse to improve physical performance showed an unclear direction, studies have been successfully demonstrated caffeine mouth rinse's effectiveness to improve cognitive performance. Pomportes, Brisswalter [38] compared the effects of caffeine (67mg), carbohydrate (7%), and guarana (400mg) mouth rinse on cognitive performance during 40min of submaximal cycling. The participants repeated a duration-production task (time perception) and Simon task (cognitive control and information processing) two times during the trial. During the duration-production task, cognitive performance improved in all conditions (caffeine, carbohydrate, and guarana) when compared to the placebo. Besides, an improvement in the mean incongruent reaction time and mean congruent reaction time during the Simon task was also found in caffeine compared to placebo, indicating improved cognitive control. De Pauw, Roelands [38] verified an increase in brain regions' activity associated with reward and problem solving (i.e., orbitofrontal cortex and dorsolateral prefrontal cortex) with caffeine mouth rinsing (20s). These brain alterations resulted in an improvement in the reaction time during the Stroop test. Finally, Van Cutsem, De Pauw [10] used a mouth rinse protocol involving a combination of caffeine (1.2%) and carbohydrate (6.4%) during cognitive tests (Stroop test and Flanker test) and verified reduced mental fatigue compared to the placebo. Despite a reduced number of studies, the findings indicate that caffeine mouth rinse is a promising strategy to improve cognitive performance, which can be beneficial for sports, for example, where success depends on quick decision making.

Although the effects of caffeine ingestion on physical performance are well established [48], some findings suggest that there is interindividual variation in response to caffeine ingestion [49]. This interindividual variation seems to be explained by CYP1A2 gene polymorphism that encodes the cytochrome P450 1A2 enzyme, found mainly in the liver, responsible for caffeine's metabolism[50]. Individuals with the AC or CC genotype are categorized as slow metabolizers, whereas those with the AA genotype are fast metabolizers [51]. However, mouth rinse avoids hepatic metabolism, giving an advantage to some individuals. Here, only two studies [29, 34] have evaluated caffeine mouth rinse effect on physical performance in individuals with different CYP1A2 genotypes. Pataky, Womack [34] verified that caffeine mouth rinses no promoted physical performance improvement during a 3km cycling time trial regardless of CYP1A2 polymorphism. These findings are consistent with those recently presented by Figueiredo, Queiroz [29], where caffeine mouth rinse also did not demonstrate an effect on performance during 10-km running or vertical jump in individuals CC homozygotes or AC heterozygotes. Thus, these results suggest that a possible ergogenic effect of caffeine mouth rinse on physical is independent of the CYP1A2 genotype.

5. LIMITATIONS AND FUTURE STUDIES

It is necessary to acknowledge some of the limitations of the studies selected in the present systematic review. Starting with the sample of studies summarized here, we can observe a high prevalence of males. It can be due to complexity in evaluating the effects of caffeine in women since oral contraceptives [52] and different phases of the menstrual cycle [53] can directly affect the caffeine metabolism. However, caffeine mouth rinse can be a practical strategy to avoid these disadvantages associated with changes in caffeine metabolism since the ergogenic effect of mouth rinse would not be affected by liver clearance. In addition, some evidence shows that caffeine ingestion in capsules does not present a gender bias [54]; therefore, futures studies could verify whether the same happens with caffeine mouth rinse. The degree of training has also been suggested as a factor that could affect the ergogenic effects mediated by caffeine [55]. This becomes important since most studies here recruited recreationally active volunteers. Another factor that may interfere with the effectiveness of the caffeine mouth rinse would be the habitual consumption of caffeine; however, only 4 studies [26, 29, 32, 34] reported participant's habitual caffeine intake. The studies used dietary control strategies concerning the interval between the postprandial period and the beginning of physical performance tests. Overnight fasting [32], 16h [27], 10h [37], 4h [11, 36], 2h [30, 33] and 1h [14, 35] postprandial period were used, while others working did not report [26, 28, 29, 31, 34]. The fasting time may likely impact the effectiveness of the caffeine mouth rinse in a similar way to what was seen during the mouth rinse with carbohydrates [44]. The expectancy (placebo effect) cannot be ruled out since that physiological permutations (e.g., changes in motivation and mood states) associated with expectancy of caffeine use may influence physical and cognitive performance [24]. In this systematic review, 4 studies reported blinding effectiveness [11, 30, 35, 36]. Thus, it is likely that some studies will have their results influenced by an expectancy, which could explain the mixed results. In relation to cognitive performance, although all the data points in a single direction, it is important to highlight the small number of studies is found in the literature. Therefore, it is important more studies must be carried out to confirm these findings. Finally, future studies should evaluate the influence of other factors on the effectiveness of the caffeine mouth rinse, such as, for example, optimal dose, ideal frequency of rinses, sex, habitual caffeine consumption, interindividual variation in the ability to detect a bitter taste, and different periods between the last meal and exercise.

6. CONCLUSION

The present review suggests that the effectiveness of caffeine mouth rinse on physical performance is uncertain. A potential ergogenic effect of caffeine mouth rinse might be present when exercise is performed in a fasted state and/or caffeine mouth rinse is repeated during exercise. Finally, although there are few studies, our results suggest a beneficial caffeine mouth rinse effect on cognitive performance.

7. REFERENCES

1. Thomas DT, Erdman KA, Burke LM. American college of sports medicine joint position statement. Nutrition and athletic performance. Medicine and science in sports and exercise 48(3):543-568, 2016.
2. Aguilar-Navarro M, Muñoz G, Salinero JJ, Muñoz-Guerra J, Fernández-Álvarez M, Plata MdM, Del Coso J. Urine caffeine concentration in doping control samples from 2004 to 2015. Nutrients 11(2):286, 2019.
3. Desbrow B, Leveritt M. Awareness and use of caffeine by athletes competing at the 2005 ironman triathlon world championships. International journal of sport nutrition and exercise metabolism 16(5):545-558, 2006.
4. Chester N, Wojek N. Caffeine consumption amongst british athletes following changes to the 2004 wada prohibited list. International journal of sports medicine 29(06):524-528, 2008.
5. Wickham KA, Spriet LL. Administration of caffeine in alternate forms. Sports Medicine 48:S79-S91, 2018.
6. Irwin C, Khalesi S, Desbrow B, McCartney D. Effects of acute caffeine consumption following sleep loss on cognitive, physical, occupational and driving performance: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 108:877-888, 2020.
7. Foskett A, Ali A, Gant N. Caffeine enhances cognitive function and skill performance during simulated soccer activity. International journal of sport nutrition and exercise metabolism 19(4):410-423, 2009.
8. Stuart GR, Hopkins WG, Cook C, Cairns SP. Multiple effects of caffeine on simulated high-intensity team-sport performance. Medicine and science in sports and exercise 37(11):1998, 2005.
9. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacological reviews 51(1):83-133, 1999.
10. Van Cutsem J, De Pauw K, Marcora S, Meeusen R, Roelands B. A caffeine-maltodextrin mouth rinse counters mental fatigue. Psychopharmacology 235(4):947-958, 2018.
11. Bottoms L, Hurst H, Scriven A, Lynch F, Bolton J, Vercoe L, Shone Z, Barry G, Sinclair J. The effect of caffeine mouth rinse on self-paced cycling performance. Comparative exercise physiology 10(4):239-245, 2014.
12. Wickham KA, Spriet LL. Administration of caffeine in alternate forms. Sports Med, Review, 48(Suppl 1):79-91, 2018.

13. Best R, McDonald K, Hurst P, Pickering C. Can taste be ergogenic? European Journal of Nutrition, 2020.
14. Doering TM, Fell JW, Leveritt MD, Desbrow B, Shing CM. The effect of a caffeinated mouth-rinse on endurance cycling time-trial performance. Int J Sport Nutr Exerc Metab, Randomized Controlled Trial, 24(1):90-97, 2014.
15. Carter JM, Jeukendrup AE, Jones DA. The effect of carbohydrate mouth rinse on 1-h cycle time trial performance. Medicine and science in sports and exercise 36(12):2107-2111, 2004.
16. Kamimori GH, Karyekar CS, Otterstetter R, Cox DS, Balkin TJ, Belenky GL, Eddington ND. The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. International journal of pharmaceutics 234(1-2):159-167, 2002.
17. Gam S, Guelfi KJ, Fournier PA. Mouth rinsing and ingesting a bitter solution improves sprint cycling performance. Medicine and science in sports and exercise 46(8):1648-1657, 2014.
18. Zald DH, Hagen MC, Pardo JV. Neural correlates of tasting concentrated quinine and sugar solutions. Journal of neurophysiology 87(2):1068-1075, 2002.
19. Pickering C. Are caffeine's performance-enhancing effects partially driven by its bitter taste? Medical Hypotheses 131:109301, 2019.
20. Grgic J. Caffeine ingestion enhances wingate performance: A meta-analysis. European journal of sport science 18(2):219-225, 2018.
21. Grgic J, Trexler ET, Lazinica B, Pedisic Z. Effects of caffeine intake on muscle strength and power: A systematic review and meta-analysis. Journal of the International Society of Sports Nutrition 15(1):11, 2018.
22. Mielgo-Ayuso J, Calleja-Gonzalez J, Del Coso J, Urdampilleta A, León-Guereño P, Fernández-Lázaro D. Caffeine supplementation and physical performance, muscle damage and perception of fatigue in soccer players: A systematic review. Nutrients 11(2):440, 2019.
23. Salinero JJ, Lara B, Del Coso J. Effects of acute ingestion of caffeine on team sports performance: A systematic review and meta-analysis. Research in Sports Medicine 27(2):238-256, 2019.
24. Shabir A, Hooton A, Tallis J, F Higgins M. The influence of caffeine expectancies on sport, exercise, and cognitive performance. Nutrients 10(10):1528, 2018.
25. Ehlert AM, Twiddy HM, Wilson PB. The effects of caffeine mouth rinsing on exercise performance: A systematic review. International Journal of Sport Nutrition and Exercise Metabolism 30(5):362-373, 2020.
26. Barbosa TN, Parreira LK, Mota JF, Kalman D, Saunders B, Pimentel GD. Acute caffeine mouth rinse does not improve performance in recreationally trained runners: A pilot study. Nutrire 45(2):1-6, 2020.
27. Pak İE, Cuğ M, Volpe SL, Beaven CM. The effect of carbohydrate and caffeine mouth rinsing on kicking performance in competitive taekwondo athletes during ramadan. Journal of Sports Sciences:1-6, 2020.
28. Melo AdA, Bastos-Silva VJ, Moura FA, Bini RR, Lima-Silva AE, Araujo GGd. Caffeine mouth rinse enhances performance, fatigue tolerance and reduces muscle activity during moderate-intensity cycling. Biology of Sport 38(4):9, 2021.
29. Figueiredo N, Queiroz M, Felício FP, Ferreira J, Gerosa-Neto J, Mota JF, da Silva CR, Ghedini PC, Saunders B, Pimentel GD. Acute caffeine mouth rinsing does not improve 10-km running performance in cyp1a2 c-allele carriers. Clinical Nutrition ESPEN, 2021.
30. Beaven CM, Maulder P, Pooley A, Kilduff L, Cook C. Effects of caffeine and carbohydrate mouth rinses on repeated sprint performance. Appl Physiol Nutr Metab 38(6):633-637, 2013.

31. Clarke ND, Kornilios E, Richardson DL. Carbohydrate and caffeine mouth rinses do not affect maximum strength and muscular endurance performance. J Strength Cond Res, Randomized Controlled Trial, 29(10):2926-2931, 2015.
32. Dolan P, Witherbee KE, Peterson KM, Kerksick CM. Effect of carbohydrate, caffeine, and carbohydrate + caffeine mouth rinsing on intermittent running performance in collegiate male lacrosse athletes. J Strength Cond Res, Randomized Controlled Trial, 31(9):2473-2479, 2017.
33. Marinho A, Mendes E, Vilela R, Bastos-Silva V, Balikian P. Caffeine mouth rinse has no effects on anaerobic energy yield during a wingate test. The Journal of sports medicine and physical fitness, 2019.
34. Pataky MW, Womack CJ, Saunders MJ, Goffe JL, D'Lugos AC, El-Sohemy A, Luden ND. Caffeine and 3-km cycling performance: Effects of mouth rinsing, genotype, and time of day. Scand J Med Sci Sports, Randomized Controlled Trial, 26(6):613-619, 2016.
35. Kizzi J, Sum A, Houston FE, Hayes LD. Influence of a caffeine mouth rinse on sprint cycling following glycogen depletion. Eur J Sport Sci, Randomized Controlled Trial, 16(8):1087-1094, 2016.
36. Sinclair J, Bottoms L. The effects of carbohydrate and caffeine mouth rinsing on arm crank time-trial performance. J Sports Res 1(2):34-44, 2014.
37. KARAYİĞİT R, YAŞLI BÇ, KARABIYIK H, KOZ M, ERSÖZ G. Effect of serial caffeine mouth rinse on wingate anaerobic performance.
38. De Pauw K, Roelands B, Knaepen K, Polfliet M, Stiens J, Meeusen R. Effects of caffeine and maltodextrin mouth rinsing on p300, brain imaging, and cognitive performance. Journal of applied physiology (bethesda, md : 1985), Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't, 118(6):776-782, 2015.
39. Pomportes L, Brisswalter J, Casini L, Hays A, Davranche K. Cognitive performance enhancement induced by caffeine, carbohydrate and guarana mouth rinsing during submaximal exercise. Nutrients, Randomized Controlled Trial, 9(6), 2017.
40. Silva-Cavalcante MD, Correia-Oliveira CR, Santos RA, Lopes-Silva JP, Lima HM, Bertuzzi R, Duarte M, Bishop DJ, Lima-Silva AE. Caffeine increases anaerobic work and restores cycling performance following a protocol designed to lower endogenous carbohydrate availability. PLoS One 8(8):e72025, 2013.
41. Sinclair J, Bottoms L, Flynn C, Bradley E, Alexander G, McCullagh S, Finn T, Hurst HT. The effect of different durations of carbohydrate mouth rinse on cycling performance. European journal of sport science 14(3):259-264, 2014.
42. Ataide-Silva T, Ghiarone T, Bertuzzi R, Stathis CG, Leandro CG, Lima-Silva AE. Cho mouth rinse ameliorates neuromuscular response with lower endogenous cho stores. Medicine and science in sports and exercise 48(9):1810-1820, 2016.
43. Lane SC, Bird SR, Burke LM, Hawley JA. Effect of a carbohydrate mouth rinse on simulated cycling time-trial performance commenced in a fed or fasted state. Applied Physiology, Nutrition, and Metabolism 38(2):134-139, 2013.
44. Lane SC, Areta JL, Bird SR, Coffey VG, Burke LM, Desbrow B, Karagounis LG, Hawley JA. Caffeine ingestion and cycling power output in a low or normal muscle glycogen state. Medicine & Science in Sports & Exercise 45(8):1577-1584, 2013.
45. Beelen M, Berghuis J, Bonaparte B, Ballak SB, Jeukendrup AE, van Loon LJ. Carbohydrate mouth rinsing in the fed state: Lack of enhancement of time-trial performance. International journal of sport nutrition and exercise metabolism 19(4):400-409, 2009.
46. Haase L, Cerf-Ducastel B, Murphy C. Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. Neuroimage 44(3):1008-1021, 2009.

47. Duncan MJ, Eyre E, Grgic J, Tallis J. The effect of acute caffeine ingestion on upper and lower body anaerobic exercise performance. European journal of sport science 19(10):1359-1366, 2019.
48. Grgic J, Grgic I, Pickering C, Schoenfeld BJ, Bishop DJ, Pedisic Z. Wake up and smell the coffee: Caffeine supplementation and exercise performance—an umbrella review of 21 published meta-analyses. British journal of sports medicine 54(11):681-688, 2020.
49. Del Coso J, Lara B, Ruiz-Moreno C, Salinero JJ. Challenging the myth of non-response to the ergogenic effects of caffeine ingestion on exercise performance. Nutrients 11(4):732, 2019.
50. Rahimi R. The effect of cyp1a2 genotype on the ergogenic properties of caffeine during resistance exercise: A randomized, double-blind, placebo-controlled, crossover study. Irish Journal of Medical Science (1971-) 188(1):337-345, 2019.
51. Guest N, Corey P, Vescovi J, El-Sohemy A. Caffeine, cyp1a2 genotype, and endurance performance in athletes. Medicine & Science in Sports & Exercise 50(8):1570-1578, 2018.
52. Abernethy D, Todd E. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. European journal of clinical pharmacology 28(4):425-428, 1985.
53. Lane J, Steege J, Rupp S, Kuhn C. Menstrual cycle effects on caffeine elimination in the human female. European journal of clinical pharmacology 43(5):543-546, 1992.
54. Skinner TL, Desbrow B, Arapova J, Schaumberg MA, Osborne J, Grant GD, Anoopkumar-Dukie S, Leveritt MD. Women experience the same ergogenic response to caffeine as men. Medicine and science in sports and exercise 51(6):1195-1202, 2019.
55. Brooks JH, Wyld K, Chrismas BC. Acute effects of caffeine on strength performance in trained and untrained individuals. 2015.

6 CONSIDERAÇÕES FINAIS

Na presente dissertação, foi realizado uma revisão sistemática com o objetivo de avaliar os efeitos do enxágue bucal no desempenho físico e cognitivo. O nosso estudo mostrou que a efetividade do enxágue bucal com cafeína no desempenho físico permanece incerto e que um potencial efeito ergogênico pode ser obtido quando esta estratégia é realizada em jejum e/ou quando o enxágue é repetido diversas vezes durante o exercício. Em relação aos efeitos do enxágue bucal com cafeína na performance cognitiva, poucos estudos têm sido realizados. Porém, todos encontraram melhora no desempenho cognitivo com enxágue de cafeína, demonstrando que essa é uma estratégia promissora em esportes que demandam tomadas de decisão rápida.

REFERÊNCIAS

AGUILAR-NAVARRO, M. *et al.* Urine caffeine concentration in doping control samples from 2004 to 2015. **Nutrients**, Basel, Switzerland, v. 11, n. 2, p. 286, 2019.

ALLEN, D. G.; LAMB, G. D.; WESTERBLAD, H. Skeletal muscle fatigue: cellular mechanisms. **Physiological reviews**, Bethesda, EUA. v. 88, n. 1, p. 287-332, 2008.

ASTORINO, T. A.; ROBERSON, D. W. Efficacy of acute caffeine ingestion for short-term high-intensity exercise performance: a systematic review. **The Journal of Strength & Conditioning Research**, Champaign, EUA, v. 24, n. 1, p. 257-265, 2010.

ATAIDE-SILVA, T. *et al.* CHO Mouth Rinse Ameliorates Neuromuscular Response with Lower Endogenous CHO Stores. **Medicine and science in sports and exercise**, Hagerstown,EUA, v. 48, n. 9, p. 1810-1820, 2016.

BARBOSA, T. N. *et al.* Acute caffeine mouth rinse does not improve performance in recreationally trained runners: a pilot study. **Nutrire**, [São Paulo], v. 45, n. 2, p. 1-6, 2020.

BARTOSHUK, L. M.; DUFFY, V. B.; MILLER, I. J. PTC/PROP tasting: anatomy, psychophysics, and sex effects. **Physiology & behavior**, New York, EUA, v. 56, n. 6, p. 1165-1171, 1994.

BAZZUCCHI, I. *et al.* Caffeine improves neuromuscular function during maximal dynamic exercise. **Muscle & nerve**, Hoboken, EUA, v. 43, n. 6, p. 839-844, 2011.

BAZZUCCHI, I. *et al.* Carbohydrate mouth rinsing: improved neuromuscular performance during isokinetic fatiguing exercise. **International journal of sports physiology and performance**, Champaign, EUA, v. 12, n. 8, p. 1031-1038, 2017.

BEAVEN, C. M. *et al.* Effects of caffeine and carbohydrate mouth rinses on repeated sprint performance. **Appl Physiol Nutr Metab**, Ottawa, Canada, v. 38, n. 6, p. 633-637, 2013.

BEELEN, M. *et al.* Carbohydrate mouth rinsing in the fed state: lack of enhancement of time-trial performance. **International journal of sport nutrition and exercise metabolism**, Champaign, EUA, v. 19, n. 4, p. 400-409, 2009.

BEHRENS, M.; ZIEGLER, F. Structure-Function Analyses of Human Bitter Taste Receptors—Where Do We Stand? **Molecules**, Basel, Switzerland, v. 25, n. 19, p. 4423, 2020.

BEST, R. *et al.* Can taste be ergogenic? **European Journal of Nutrition**, Darmstadt, Germany, n. 1, p. 45-54, 2021.

BOTTOMS, L. *et al.* The effect of caffeine mouth rinse on self-paced cycling performance. **Comparative exercise physiology**, Wageningen, Netherlands, v. 10, n. 4, p. 239-245, 2014.

BOWTELL, J. L. *et al.* Improved exercise Tolerance with caffeine is associated with Modulation of both Peripheral and central neural Processes in human Participants. **Frontiers in Nutrition**, Lausanne, Switzerland, n. 5, p. 6, 2018.

BRESLIN, P. A. An evolutionary perspective on food and human taste. **Current Biology**, Cambridge, UK, v. 23, n. 9, p. R409-R418, 2013.

CARTER, J. M.; JEUKENDRUP, A. E.; JONES, D. A. The effect of carbohydrate mouth rinse on 1-h cycle time trial performance. **Medicine and science in sports and exercise**, Hagerstown, EUA, v. 36, n. 12, p. 2107-2111, 2004.

CHANDRASHEKAR, J. *et al.* T2Rs function as bitter taste receptors. **Cell**, Cambridge, EUA, v. 100, n. 6, p. 703-711, 2000.

CHESTER, N.; WOJEK, N. Caffeine consumption amongst British athletes following changes to the 2004 WADA prohibited list. **International journal of sports medicine**, Stuttgart, Germany, v. 29, n. 06, p. 524-528, 2008.

CLARKE, N. D. *et al.* Carbohydrate mouth rinse improves morning high-intensity exercise performance. **European journal of sport science**, Abingdon, UK, v. 17, n. 8, p. 955-963, 2017.

CLARKE, N. D.; KORNILIOS, E.; RICHARDSON, D. L. Carbohydrate and Caffeine Mouth Rinses Do Not Affect Maximum Strength and Muscular Endurance Performance. **J Strength Cond Res**, Champaign, EUA, v. 29, n. 10, p. 2926-2931, 2015. Randomized Controlled Trial.

COOPER, R. *et al.* Effects of a carbohydrate and caffeine gel on intermittent sprint performance in recreationally trained males. **European journal of sport science**, Abingdon, UK, v. 14, n. 4, p. 353-361, 2014.

CRAWFORD, C. *et al.* Caffeine to optimize cognitive function for military mission-readiness: a systematic review and recommendations for the field. **Nutrition reviews**, Oxford, EUA, v. 75, n. supl. 2, p. 17-35, 2017.

DAVIS, J.; GREEN, J. M. Caffeine and anaerobic performance. **Sports Medicine**, Auckland, New Zealand, v. 39, n. 10, p. 813-832, 2009.

SANTOS, R. de A. *et al.* Caffeine alters anaerobic distribution and pacing during a 4000-m cycling time trial. **PloS one**, San Francisco, EUA, v. 8, n. 9, p. e75399, 2013.

DE PAUW, K. *et al.* Effects of caffeine and maltodextrin mouth rinsing on P300, brain imaging, and cognitive performance. **Journal of applied physiology**, Bethesda, EUA, v. 118, n. 6, p. 776-782, 2015.

DE PAUW, K. *et al.* Do Glucose and Caffeine Nasal Sprays Influence Exercise or Cognitive Performance? **International journal of sports physiology and performance**, Champaign, EUA, v. 12, n. 9, p. 1186-1191, 2017.

DESBROW, B.; LEVERITT, M. Awareness and use of caffeine by athletes competing at the 2005 Ironman Triathlon World Championships. **International journal of sport nutrition and exercise metabolism**, Champaign, EUA, v. 16, n. 5, p. 545-558, 2006.

DOERING, T. M. *et al.* The effect of a caffeinated mouth-rinse on endurance cycling time-trial performance. **Int J Sport Nutr Exerc Metab**, Champaign, EUA, v. 24, n. 1, p. 90-97, 2014.

DOHERTY, M.; SMITH, P. Effects of caffeine ingestion on rating of perceived exertion during and after exercise: a meta-analysis. **Scandinavian journal of medicine & science in sports**, Copenhagen, Denmark, v. 15, n. 2, p. 69-78, 2005.

DOLAN, P. *et al.* Effect of Carbohydrate, Caffeine, and Carbohydrate + Caffeine Mouth Rinsing on Intermittent Running Performance in Collegiate Male Lacrosse Athletes. **J Strength Cond Res**, Champaign, EUA, v. 31, n. 9, p. 2473-2479, 2017.

DUFFY, V. B. *et al.* Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. **Alcoholism: Clinical and Experimental Research**, Oxford, UK, v. 28, n. 11, p. 1629-1637, 2004.

DUNCAN, M. J. *et al.* The effect of acute caffeine ingestion on upper and lower body anaerobic exercise performance. **European journal of sport science**, Abingdon, EUA, v. 19, n. 10, p. 1359-1366, 2019.

DURKALEC-MICHALSKI, K. *et al.* Dose-dependent effect of caffeine supplementation on judo-specific performance and training activity: a randomized placebo-controlled crossover trial. **Journal of the International Society of Sports Nutrition**, London, v. 16, n. 1, p. 1-14, 2019.

ECKERSON, J. M. *et al.* Acute ingestion of sugar-free red bull energy drink has no effect on upper body strength and muscular endurance in resistance trained men. **The Journal of Strength & Conditioning Research**, Champaign, EUA, v. 27, n. 8, p. 2248-2254, 2013.

EHLERT, A. M.; TWIDDY, H. M.; WILSON, P. B. The Effects of Caffeine Mouth Rinsing on Exercise Performance: A Systematic Review. **International Journal of Sport Nutrition and Exercise Metabolism**, Champaign, EUA, v. 30, n. 5, p. 362-373, 2020.

FELIPPE, L. C. *et al.* Caffeine increases both total work performed above critical power and peripheral fatigue during a 4-km cycling time trial. **Journal of Applied Physiology**, Bethesda, EUA, v. 124, n. 6, p. 1491-1501, 2018.

VIANA, B. F. *et al.* Caffeine increases motor output entropy and performance in 4 km cycling time trial. **Plos one**, San Francisco, EUA, v. 15, n. 8, p. e0236592, 2020.

FOSKETT, A.; ALI, A.; GANT, N. Caffeine enhances cognitive function and skill performance during simulated soccer activity. **International journal of sport nutrition and exercise metabolism**, Champaign, EUA, v. 19, n. 4, p. 410-423, 2009.

FREDHOLM, B. B. *et al.* Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. **Pharmacological reviews**, Bethesda, EUA, v. 51, n. 1, p. 83-133, 1999.

GAM, S.; GUELFI, K. J.; FOURNIER, P. A. Mouth rinsing and ingesting a bitter solution improves sprint cycling performance. **Medicine and science in sports and exercise**, Hagerstown, EUA, v. 46, n. 8, p. 1648-1657, 2014.

GAM, S.; GUELFI, K. J.; FOURNIER, P. A. New insights into enhancing maximal exercise performance through the use of a bitter tastant. **Sports medicine**, Auckland, New Zealand, v. 46, n. 10, p. 1385-1390, 2016.

GRAHAM, T. E.; RUSH, J. W.; SOEREN, M. H. Caffeine and exercise: metabolism and performance. **Canadian Journal of Applied Physiology**, Champaign, EUA, v. 19, n. 2, p. 111-138, 1994.

GRGIC, J. Caffeine ingestion enhances Wingate performance: a meta-analysis. **European journal of sport science**, Abingdon, UK, v. 18, n. 2, p. 219-225, 2018.

GRGIC, J. *et al.* Effects of caffeine intake on muscle strength and power: a systematic review and meta-analysis. **Journal of the International Society of Sports Nutrition**, [*s. l.*], v. 15, n. 1, p. 11, 2018.

GUEST, N. S. *et al.* International society of sports nutrition position stand: caffeine and exercise performance. **Journal of the International Society of Sports Nutrition**, [*s. l.*], v. 18, n. 1, p. 1-37, 2021.

HAASE, L.; CERF-DUCASTEL, B.; MURPHY, C. Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. **Neuroimage**, Orlando, EUA, v. 44, n. 3, p. 1008-1021, 2009.

IRWIN, C. *et al.* Effects of acute caffeine consumption following sleep loss on cognitive, physical, occupational and driving performance: A systematic review and meta-analysis. **Neuroscience & Biobehavioral Reviews**, New York, v. 108, p. 877-888, 2020.

KALMAR, J. M. The influence of caffeine on voluntary muscle activation. **Medicine & Science in Sports & Exercise**, Hagerstown, EUA, v. 37, n. 12, p. 2113-2119, 2005.

KAMIMORI, G. H. *et al.* The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. **International journal of pharmaceutics**, Amsterdam, Netherlands, v. 234, n. 1-2, p. 159-167, 2002.

KAMMERER, M. *et al.* Effects of energy drink major bioactive compounds on the performance of young adults in fitness and cognitive tests: a randomized controlled trial. **Journal of the International Society of Sports Nutrition**, London, v. 11, n. 1, p. 44, 2014.

KAPLAN, A. R.; GLANVILLE, E. V.; FISCHER, R. Taste thresholds for bitterness and cigarette smoking. **Nature**, London, v. 202, n. 4939, p. 1366-1366, 1964.

KARAYİĞİT, R. *et al.* Effect Of Serial Caffeine Mouth Rinse On Wingate Anaerobic Performance. **SPORMETRE**, Ankara, Turkey, v. 15, n. 4, p. 191-196, 2017.

KIZZI, J. *et al.* Influence of a caffeine mouth rinse on sprint cycling following glycogen depletion. **Eur J Sport Sci**, Abingdon, UK., v. 16, n. 8, p. 1087-1094, 2016.

LANE, S. C. *et al.* Caffeine ingestion and cycling power output in a low or normal muscle glycogen state. **Medicine & Science in Sports & Exercise**, Hagerstown, EUA, v. 45, n. 8, p. 1577-1584, 2013.

LANE, S. C. *et al.* Effect of a carbohydrate mouth rinse on simulated cycling time-trial performance commenced in a fed or fasted state. **Applied physiology, nutrition, and metabolism**, Ottawa, Canada, v. 38, n. 2, p. 134-139, 2012.

LIEBERMAN, H. R. *et al.* Effects of caffeine, sleep loss, and stress on cognitive performance and mood during US Navy SEAL training. **Psychopharmacology**, Berlin, v. 164, n. 3, p. 250-261, 2002.

LOPES-SILVA, J. *et al.* Caffeine ingestion after rapid weight loss in judo athletes reduces perceived effort and increases plasma lactate concentration without improving performance. **Nutrients**, Basel, Switzerland, v. 6, n. 7, p. 2931-2945, 2014.

LUDEN, N.*et al.* Carbohydrate mouth rinsing enhances high intensity time trial performance following prolonged cycling. **Nutrients**, Basel, Switzerland, v. 8, n. 9, p. 576, 2016.

MACINTOSH, B. R.; GARDINER, P. F. Posttetanic potentiation and skeletal muscle fatigue: interactions with caffeine. **Canadian journal of physiology and pharmacology**, Ottawa, Canada, v. 65, n. 2, p. 260-268, 1987.

MARINHO, A.*et al.* Caffeine mouth rinse has no effects on anaerobic energy yield during a Wingate test. **The Journal of sports medicine and physical fitness**, Torino, Italy, v. 60, n. 1, p.69-74, 2020.

MATSUMOTO, I. Gustatory neural pathways revealed by genetic tracing from taste receptor cells. **Bioscience, biotechnology, and biochemistry**, Oxford, UK, v. 77, n. 7, p. 1359-1362, 2013.

MCLELLAN, T. M.; CALDWELL, J. A.; LIEBERMAN, H. R. A review of caffeine's effects on cognitive, physical and occupational performance. **Neuroscience & Biobehavioral Reviews**, New York, v. 71, p. 294-312, 2016.

MELO, A. d. A. *et al.* Caffeine mouth rinse enhances performance, fatigue tolerance and reduces muscle activity during moderate-intensity cycling. **Biology of Sport**, Poznań, Poland, v. 38, n. 4, p. 9, 2021.

MENNELLA, J. A. *et al.* Age modifies the genotype-phenotype relationship for the bitter receptor TAS2R38. **BMC genetics**, London, v. 11, n. 1, p. 1-9, 2010.

MEYERHOF, W. *et al.* The molecular receptive ranges of human TAS2R bitter taste receptors. **Chemical senses**, Oxford, UK, v. 35, n. 2, p. 157-170, 2010.

MIELGO-AYUSO, J. *et al.* Caffeine supplementation and physical performance, muscle damage and perception of fatigue in soccer players: A systematic review. **Nutrients**, Basel. Switzerland, v. 11, n. 2, p. 440, 2019.

MOHR, M.; NIELSEN, J. J.; BANGSBO, J. Caffeine intake improves intense intermittent exercise performance and reduces muscle interstitial potassium accumulation. **Journal of applied physiology**, Bethesda, EUA, v. 111, n. 5, p. 1372-1379, 2011.

PAK, İ. E. *et al.* The effect of carbohydrate and caffeine mouth rinsing on kicking performance in competitive Taekwondo athletes during Ramadan. **Journal of Sports Sciences**, London, v. 38, n. 7, p. 795-800, 2020.

PATAKY, M. W. *et al.* Caffeine and 3-km cycling performance: Effects of mouth rinsing, genotype, and time of day. **Scand J Med Sci Sports**, Copenhagen, Denmark, v. 26, n. 6, p. 613-619, 2016.

PICKERING, C. Are caffeine's performance-enhancing effects partially driven by its bitter taste? **Medical hypotheses**, 131, p. 109301, 2019.

POMPORTES, L. *et al.* Cognitive Performance Enhancement Induced by Caffeine, Carbohydrate and Guarana Mouth Rinsing during Submaximal Exercise. **Nutrients**, Basel. Switzerland, v. 9, n. 6, 2017.

ROUSMANS, S. *et al.* Autonomic nervous system responses associated with primary tastes. **Chemical Senses**, Oxford, UK, v. 25, n. 6, p. 709-718, 2000.

RYAN, E. J. *et al.* Caffeine gum and cycling performance: a timing study. **The Journal of Strength & Conditioning Research**, [*s. l.*], v. 27, n. 1, p. 259-264, 2013.

SALINERO, J. J.; LARA, B.; DEL COSO, J. Effects of acute ingestion of caffeine on team sports performance: A systematic review and meta-analysis. **Research in Sports Medicine**, Abingdon, UK, v. 27, n. 2, p. 238-256, 2019.

SHABIR, A. *et al.* The influence of caffeine expectancies on sport, exercise, and cognitive performance. **Nutrients**, Basel, Switzerland, v. 10, n. 10, p. 1528, 2018.

SILVA-CAVALCANTE, M. D. *et al.* Caffeine increases anaerobic work and restores cycling performance following a protocol designed to lower endogenous carbohydrate availability. **PloS one**, San Francisco, EUA, v. 8, n. 8, p. e72025, 2013.

SINCLAIR, J.; BOTTOMS, L. The effects of carbohydrate and caffeine mouth rinsing on arm crank time-trial performance. **J Sports Res**, [*s. l.*], v. 1, n. 2, p. 34-44, 2014.

SINCLAIR, J. *et al.* The effect of different durations of carbohydrate mouth rinse on cycling performance. **European journal of sport science**, Abingdon, UK, v. 14, n. 3, p. 259-264, 2014.

STUART, G. R. *et al.* Multiple effects of caffeine on simulated high-intensity team-sport performance. **Medicine and science in sports and exercise**, Hagerstown, EUA, v. 37, n. 11, p. 1998, 2005.

TALLIS, J. *et al.* The effect of physiological concentrations of caffeine on the power output of maximally and submaximally stimulated mouse EDL (fast) and soleus (slow) muscle. **Journal of applied physiology**, Bethesda, EUA, v. 112, n. 1, p. 64-71, 2012.

TANIMURA, S.; MATTES, R. D. Relationships between bitter taste sensitivity and consumption of bitter substances. **Journal of Sensory Studies**, [*s. l.*], v. 8, n. 1, p. 31-41, 1993.

TARNOPOLSKY, M.; CUPIDO, C. Caffeine potentiates low frequency skeletal muscle force in habitual and nonhabitual caffeine consumers. **Journal of applied physiology**, Bethesda, EUA, v. 89, n. 5, p. 1719-1724, 2000.

THOMAS, D. T.; ERDMAN, K. A.; BURKE, L. M. American College of Sports Medicine Joint Position Statement. Nutrition and Athletic Performance. **Medicine and science in sports and exercise**, Hagerstown, EUA, v. 48, n. 3, p. 543-568, 2016.

VAN CUTSEM, J. *et al.* A caffeine-maltodextrin mouth rinse counters mental fatigue. **Psychopharmacology**, Berlin, v. 235, n. 4, p. 947-958, 2018.

WESTERBLAD, H.; ALLEN, D. Changes of myoplasmic calcium concentration during fatigue in single mouse muscle fibers. **The Journal of General Physiology**, New York, v. 98, n. 3, p. 615-635, 1991.

WHALLEY, P. J.; DEARING, C. G.; PATON, C. D. The effects of different forms of caffeine supplement on 5-km running performance. **International journal of sports physiology and performance**, Champaign, EUA, v. 15, n. 3, p. 390-394, 2020.

WICKHAM, K. A.; SPRIET, L. L. Administration of Caffeine in Alternate Forms. **Sports Med**, Auckland, New Zealand, v. 48, n. supl. 1, p. 79-91, 2018a.

WILSON, P. B. Dietary and non-dietary correlates of gastrointestinal distress during the cycle and run of a triathlon. **European journal of sport science**, Abingdon, UK, v. 16, n. 4, p. 448-454, 2016.

ZALD, D. H.; HAGEN, M. C.; PARDO, J. V. Neural correlates of tasting concentrated quinine and sugar solutions. **Journal of neurophysiology**, Bethesda, EUA, v. 87, n. 2, p. 1068-1075, 2002.