UNIVERSIDADE FEDERAL DE JUIZ DE FORA CAMPUS GOVERNADOR VALADARES PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS APLICADAS À SAÚDE

Larissa Torres Fernandes

Betaína como recurso ergogênico na melhora da fadiga muscular em praticantes de exercício físico: uma revisão sistemática de ensaios clínicos randomizados

Governador Valadares

2024

Larissa Torres Fernandes

Betaína como recurso ergogênico na melhora da fadiga muscular em praticantes de exercício físico: uma revisão sistemática de ensaios clínicos randomizados

Dissertação apresentada ao Programa de PósGraduação em Ciências Aplicadas à Saúde, da Universidade Federal de Juiz de Fora, Campus Governador Valadares, como requisito parcial à obtenção do título de Mestre em Ciências Aplicadas à Saúde, área de concentração Biociências.

Orientador(a): Prof. Dr. Ciro José Brito
Coorientador(a): Prof(a). Dr(a). Carina Carvalho Silvestre
Prof(a). Dr(a). Mariana de Melo Cazal

Governador Valadares
2024

Ficha catalográfica elaborada através do programa de geração
automática da Biblioteca Universitária da UFJF,
com os dados fornecidos pelo(a) autor(a)

Fernandes, Larissa Torres.
Betaína como recurso ergogênico na melhora da fadiga muscular em praticantes de exercício físico: uma revisão sistemática de ensaios clínicos randomizados / Larissa Torres Fernandes. -- 2025.
59 p.

Orientador: Ciro José Brito
Coorientadora: Carina Carvalho Silvestre
Dissertação (mestrado acadêmico) - Universidade Federal de Juiz de Fora, Campus Avançado de Governador Valadares, Instituto de Ciências da Vida - ICV. Programa de Pós-Graduação em Ciências Aplicadas à Saúde, 2025.

1. Betaína. 2. Suplementos nutricionais. 3. Efeitos ergogênicos. 4. Desempenho físico. 5. Fadiga muscular . I. Brito, Ciro José, orient. II. Silvestre, Carina Carvalho , coorient. III. Título.

Larissa Torres Fernandes

Betaína como recurso ergogênico na melhora da fadiga muscular em praticantes de exercício físico*: *uma revisão sistemática de ensaios clínicos randomizados

Dissertação apresentada ao Programa de Pós-Graduação em Ciências Aplicadas à Saúde da Universidade Federal de Juiz de Fora como requisito parcial à obtenção do título de Mestre em Ciências Aplicadas à Saúde. Área de concentração: Biociências

Aprovada em 29 de outubro de 2024.

BANCA EXAMINADORA

Prof. Dr. Ciro José Brito - Orientador

Universidade Federal de Juiz de Fora

Profa. Dra. Carina Carvalho Silvestre - Coorientadora

Universidade Federal de Juiz de Fora

Profa. Dra. Mariana de Melo Cazal - Coorientadora

Universidade Federal de Juiz de Fora

Profa. Dra. Andréia Cristiane Carrenho Queiroz

Universidade Federal de Juiz de Fora

Prof. Dr. Destter Álacks Antoniêtto

Univale - Universidade Vale do Rio Doce

Juiz de Fora, 24/09/2024.

Documento assinado eletronicamente por **Andreia Cristiane Carrenho Queiroz**, **Servidor(a)**, em 29/10/2024, às 16:15, conforme horário oficial de Brasília, com fundamento no § 3º do art. 4º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Ciro Jose Brito**, **Servidor(a)**, em 29/10/2024, às 16:20, conforme horário oficial de Brasília, com fundamento no § 3º do art. 4º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Carina Carvalho Silvestre**, **Professor(a)**, em 05/11/2024, às 09:17, conforme horário oficial de Brasília, com fundamento no § 3º do art. 4º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Mariana Melo Cazal**, **Professor(a)**, em 05/11/2024, às 15:59, conforme horário oficial de Brasília, com fundamento no § 3º do art. 4º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Destter Álacks Antoniêtto**, **Usuário Externo**, em 12/11/2024, às 12:56, conforme horário oficial de Brasília, com fundamento no § 3º do art. 4º do Decreto nº 10.543, de 13 de novembro de 2020.

A autenticidade deste documento pode ser conferida no Portal do SEI-Ufjf (www2.ufjf.br/SEI) através do ícone Conferência de Documentos, informando o código verificador **1999842** e o código CRC **D4A63204**.

Dedico este trabalho ao meu pai Antônio João Fernandes (*in menoriam*) e a minha avô Áurea Cota Fernandes.

AGRADECIMENTOS

Primeiramente, à Deus que me permitiu concluir mais essa etapa de minha vida.

Aos meus pais, Antônio João Fernandes e Maria da Penha Torres Fernandes. Ao meu pai, que em vida, sempre acreditou em meu potencial, me estimulando nos estudos e demonstrando orgulho de sua filha como futura farmacêutica e como futura doutora. Como ele sempre dizia: *"Você está estudando bem estudado, um dia ainda vai até ser uma doutora"*. Hoje sei que você é meu maior exemplo de vida, mesmo perante a sua simplicidade e ingenuidade. A minha mãe que sempre demostrou orgulho e positividade perante todas as minhas escolhas.

Agradeço à minha avó Áurea Cota Fernandes pela minha criação e educação, graças a ela desenvolvi disciplina para os estudos, persistência, perseverança e esperança de que somente por meio dos estudos seria possível mudar minha realidade de vida.

Ao meu marido, Alef Ferreira da Silva, que sempre embarcou em minhas aventuras, me apoiando e acreditando ser possível realizar meus sonhos. Hoje tenho certeza de que você é um ótimo marido e amigo, e será um excelente futuro pai. Sem você, não seria possível finalizar essa etapa da minha vida e almejar embarcar na minha futura loucura, que será o doutorado. Obrigada pelo seu suporte emocional e companheirismo.

Ao meu orientador, Ciro José Brito, que sempre acreditou que seria possível desenvolver uma pesquisa com a temática defendida. Mesmo diante dos diversos obstáculos no decorrer de nossa jornada, sempre mostrou positividade e estimulou a buscarmos novas alternativas para concretizar nossa pesquisa. E principalmente, me mostrando na prática que é possível desenvolver uma pesquisa totalmente fora de minha área de formação e zona de conforto.

A minha coorientadora, Mariana de Melo Cazal por todo o suporte direcionado para sua área de atuação. Assim, me mostrando que seria possível ser farmacêutica e desenvolver uma pesquisa apresentando resultados relacionados à nutrição esportiva.

A minha coorientadora Carina Carvalho Silvestre por sempre acreditar em meu potencial desde a graduação. Agradeço o companheirismo, a amizade, a parceria em pesquisas passadas, atuais e futuras. Pelo compartilhamento de seu conhecimento e experiência, enquanto farmacêutica e pesquisadora. Agradeço, também, por acreditar em mim quando nem eu mesma acreditava, e por continuar a acreditar em meu potencial para pesquisas futuras. Sem o seu incentivo, não estaria aqui concluindo o meu mestrado e nem ao menos pensaria em tentar um processo seletivo de doutorado. Saiba que você é minha maior inspiração como profissional e

pesquisadora, almejo um dia ser pelo menos 1% parecida com você. Minha filha, Lívia Maria, terá uma ótima madrinha, enquanto pessoa e quem sabe uma inspiração como profissional.

Aos meus amigos, em especial Lucas Teixeira, Danielle Negri e Deysimara Cássia, obrigada pelas risadas, suporte emocional, companheirismo e pelas parcerias em pesquisas, trabalhos do mestrado e na vida. Sem a dedicação e o apoio de vocês, esta dissertação não teria sido realizada. Obrigada por tornarem de alguma forma esse processo mais leve e divertido.

Agradeço à docente Andréia Cristiane Carrenho Queiroz pelo incentivo, palavras amigas e apontamentos sobre a pesquisa.

Ao Programa de Pós-Graduação em Ciências Aplicadas à Saúde, pelo apoio, incentivo e ensinamentos.

Por fim, a todos os que de alguma forma me impulsionaram, tanto positiva ou negativamente, ou que apoiaram durante esses dois anos de mestrado, e aos leitores dessa tese de mestrado. Meu sincero obrigado!

“A mudança é a forma da continuidade.
Nada se perde, tudo se transforma.
O que muda é o modo de ser,
Mas o ser, este é eterno.”

(Fernando Pessoa)

RESUMO

A Betaína é um derivado da colina encontrado em alguns alimentos e pode ser produzida pela oxidação da colina dietética no fígado e nos rins. Devido as suas propriedades ergogênicas tem sido amplamente utilizada em pesquisas sobre exercício físico. No entanto, existem lacunas no que diz respeito à suplementação com betaína e à melhoria da fadiga muscular. Esta revisão sistemática tem como objetivo investigar a influência da suplementação com betaína na fadiga muscular na prática de exercício. Para isso, foram adotadas as diretrizes PRISMA e o protocolo do estudo foi registrado no PROSPERO (CRD42023469111). As buscas foram realizadas usando palavras-chave específicas de acordo com a estratégia PICOS em 12 de março de 2024, nas bases de dados PubMed, Cochrane Library, Web of Science, Embase e SCOPUS. Foram incluídos ensaios clínicos randomizados (ECRs) em adultos de ambos os sexos que utilizaram betaína como suplemento, comparado ao placebo, para melhorar a fadiga muscular na prática de exercício físico. Estudos com animais e estudos com uso concomitante de betaína e outros suplementos foram excluídos. A fadiga muscular foi avaliada usando o teste de uma repetição máxima (1-RM) e lactato sanguíneo na prática de exercícios de *leg press* ou agachamento e supino. O desfecho da fadiga muscular foi avaliado utilizando o teste de uma repetição máxima (1-RM). O risco de viés dos estudos incluídos foi avaliado utilizando a ferramenta RoB2 da Cochrane e a certeza da evidência foi avaliada usando o GRADE. Foram incluídos cinco ECRs, nos quais um total de 93 participantes foram avaliados; todos eram homens, com 57 indivíduos alocados ao grupo de intervenção com uma média de idade de 19,18±2,67 anos, e 58 indivíduos no grupo controle com uma média de idade de 19,66±2,44 anos. A betaína promoveu mais repetições até a fadiga muscular no *leg press* ou agachamento (n = 3) e no supino (n = 2), com reduções no lactato sérico em dois desses estudos. A betaína parece melhorar a fadiga muscular, proporcionando mais repetições na prática de exercícios de *leg press* e eliminando os níveis de lactato sanguíneo. No entanto, devido ao número reduzidos de estudos incluídos, os resultados apresentados devem ser tratados como descobertas preliminares.

Palavras-chave: Betaína. Suplementos Nutricionais. Efeitos Ergogênicos. Treinamento Físico. Desempenho Físico. Fadiga Muscular.

ABSTRACT

Betaine is a derivative of choline found in some foods and can be produced by the oxidation of dietary choline in the liver and kidneys. It has been widely used in exercise research due to its ergogenic properties. However, there are gaps regarding betaine supplementation and the improvement of muscle fatigue. This systematic review aims to investigate the influence of betaine supplementation on muscle fatigue during exercise. For this purpose, the PRISMA guidelines were adopted, and the study was registered with PROSPERO (CRD42023469111). Searches were conducted using specific keywords according to the PICOS strategy on March 12, 2024, in the PubMed, Cochrane Library, Web of Science, Embase and SCOPUS databases. Randomized clinical trials (RCTs) in adults of both sexes thaused betaine as a supplement, compared to placebo, to improve muscle fatigue during physical exercise were included. Animal studies and studies with concomitant use of betaine and other supplements were excluded. Muscle fatigue was assessed using the one-repetition maximum (1-RM) test and blood lactate during leg press or squat and bench press exercises. The muscular fatigue outcome was assessed using the one repetition maximum test (1-RM). The risk of bias of the included studies was assessed using the Cochrane RoB2 tool and the certainty of the evidence using GRADE. Five RCTs were included, in which a total of 93 participants were evaluated; all were male, with 57 individuals allocated to the intervention group with a mean age of 19.18±2.67 years, and 58 individuals in the control group with a mean age of 19.66±2.44 years. Betaine promoted more repetitions until muscle fatigue in the leg press or squat (n = 3) and bench press (n = 2), with reductions in serum lactate in two of these studies. Betaine seems to improve muscle fatigue, providing more repetitions in leg press exercises and reducing blood lactate levels. However, due to the small number of studies included, the results presented should be treated as preliminary findings.

Keywords: Betaine. Nutritional Supplements. Ergogenic Effects. Physical Training. Physical Performance. Muscle Fatigue.

SUMÁRIO

1 INTRODUÇÃO

Os suplementos alimentares são substâncias ou nutrientes consumidos por via oral com efeito fisiológico que possuem o intuito de complementar uma determinada deficiência dietética (Alves, Portela, Costa, 2022; López-Torres, *et al.,* 2022). Dessa forma, proporcionam aprimoramento físico ou cognitivo, aceleram a recuperação física diante de esforços intensos e previnem doenças nutricionais (Abreu *et al.,* 2023).

Nos últimos anos, observa-se uma popularização mundial quanto ao uso de suplementos nutricionais entre praticantes de atividade física, exercícios físicos e no meio esportivo (Alves, Portela, Costa, 2022; López-Torres, *et al.,* 2022). No mundo, estima-se que o consumo de suplementos alimentares para melhora do desempenho físico aumentará de 10 a 11% no período de 2022 a 2028. Dessa forma, estima-se, também, que até 2030 será gerada uma receita de 75 bilhões de dólares, com a comercialização de suplementos nutricionais direcionados a melhora do desempenho físico (Horizon Database, 2023).

Molin e colaboradores (2019) revelam que o crescimento no consumo de suplementos alimentares deve-se ao aumento de sua disponibilidade no mercado, o elevado número de pontos de comercialização, e a facilidade de aquisição via comércio virtual, que proporcionam maior facilidade para sua aquisição (Molin *et al.,* 2019). O aumento do consumo de suplementos nutricionais sem prescrição profissional, tornou-se um problema de saúde pública. Desse modo, preocupando especialistas e autoridades, devido aos inúmeros relatos de efeitos adversos, problemas de saúde, tanto cardiovasculares, hepáticos e renais, e óbitos (Molin *et al.,* 2019; Alves, Portela, Costa, 2022). Além dos perigos direcionados à saúde, o consumo de suplementos nutricionais sem avaliação profissional promove gastos desnecessários, uma vez a suplementação deve ser baseada na dieta, necessidades nutricionais e estado de saúde individual (Alves, Portela, Costa, 2022).

Os suplementos nutricionais são considerados uma forma de recurso ergogênico do tipo nutricional. Isso deve-se a sua capacidade de promover a melhora do desempenho físico. Os recursos ergogênicos nutricionais incluem qualquer prática nutricional, podendo ser de curto e/ou longo prazo, com o intuito de potencializar o desempenho físico e as adaptações ao treinamento, e otimizar a recuperação pós-exercício (López-Torres *et al.,* 2022).

Para o desempenho físico, o uso de recursos ergogênicos nutricionais proporciona benefícios, como a melhora da modulação da resposta inflamatória, redução do estresse oxidativo e melhora da recuperação da homeostase (López-Torres *et al.,* 2022). Além disso, otimiza aspectos musculares ao intensificar as adaptações das vias de sinalização sobre a

contração muscular, reduzir ou retardar a fadiga muscular, acelerar o tempo de recuperação e aumentar o desempenho aeróbico (López-Torres *et al.,* 2022; Waldman; Bryant; Mcallister, 2023).

Entre os recursos ergogênicos nutricionais, destaca-se a betaína (*N-N-N* trimetilglicina) que pode ser produzida biologicamente a partir da oxidação da colina dietética no fígado e nos rins (Arazi *et al.*, 2022; Machek *et al.*, 2022; Dobrijevic *et al.*, 2023). Entretanto, a síntese endógena de betaína é geralmente insuficiente para atender às necessidades diárias nutricionais. Com isso, a ingestão de betaína via alimentação é considerada essencial. Além disso, a betaína é disponível comercialmente como suplemento nutricional nas formas anidra natural, anidra sintética e cloridrato (Dobrijevic *et al.*, 2023).

A betaína é um aminoácido modificado encontrado em muitos alimentos ricos em betaína e colina, como grãos integrais, beterraba, espinafre, invertebrados, gérmen e farelo de trigo integrais (Kaur *et al.,* 2019; Arazi *et al.*, 2022; Machek *et al.*, 2022; Dobrijevic *et al.*, 2023). As maiores concentrações de betaína em alimentos, comumente consumidos, no Brasil por exemplo, são observadas em grãos de quinoa (610–6300 µg/g), beterraba (750–3337 µg/g), farinha integral (120–1503 µg/g), macarrão (375–1327 µg/g), grãos de trigo mole (490–1320 µg/g), couscous (544–1299 µg/g), espinafre (675–1100 µg/g), pão (499–1000 µg/g) e a aveia (200–1000 µg/g) (Dobrijevic *et al.*, 2023). A ingestão média de betaína via alimentação por adultos pode variar entre 100 a 400 mg/dia. Contudo, pessoas que consomem majoritariamente produtos alimentares integrais e invertebrados, a ingestão pode ser entre 1 a 2,5 gramas (g) por dia (Arazi *et al.*, 2022; Machek *et al.*, 2022; Dobrijevic *et al.*, 2023).

Os efeitos ergogênicos e clínicos da betaína têm sido constantemente investigados em uma variação de consumo entre 500 a 20.000 mg. No desempenho físico, o emprego da suplementação com betaína em doses diárias de 2,5g é a mais comumente investigada em diferentes modalidades esportivas e na prática de exercícios físicos (Cholewa *et al.* 2019). Alguns estudos apontam que, os efeitos ergogênicos da betaína podem ser percebidos a partir de 7 dias e no máximo em 14 dias considerando a ingestão de doses moderadas (2,5g/dia) em populações ativas (Freitas; Barbosa; Ramos, 2015; Waldman; Bryant; Mcallister, 2023; Arazi *et al.*, 2022; Gao *et al.*, 2019; Yang *et al.*, 2020).

Quanto ao metabolismo, a betaína é absorvida no íleo e no duodeno e rapidamente disponível no organismo. Ao ser sintetizada endogenamente no fígado e nos rins a partir da colina dietética, ocorre a oxidação da betaína, e esta é metabolizada em forma de metionina e dimetilglicina (Alvarenga *et al.,* 2022). O metabolismo da betaína é similar em relação ao

consumo da betaína dietética e a suplementação. Isso deve-se a alta solubilidade em água e ao não ligamento a proteínas, proporcionando uma maior biodisponibilidade (Del Favero, 2012).

Os principais mecanismos de ação atribuídos a betaína incluem a sua função de osmólito, agente protetor contra desnaturação de proteínas e doadora de grupo metil (Cholewa *et al.*, 2019; Gao *et al.*, 2019; Kaur *et al.,* 2019; Dobrijevic *et al.*, 2023). Como osmólito atua nos rins, protegendo as células contra o estresse osmótico controlando o gradiente de concentração e o acúmulo de resíduos na urina (Kaur *et al.,* 2019; Dobrijevic *et al.*, 2023). A betaína ao atuar como um agente protetor contra a desnaturação de proteínas, promove a estabilização da estrutura das proteínas e previne sua degradação em condições estressantes (Cholewa *et al.,* 2019; Gao *et al.*, 2019). Ao doar um grupo metil para transmetililação de homocisteína em metionina no fígado e nos rins, reduz os níveis séricos de homocisteína, um aminoácido tóxico, trazendo benefícios para a saúde (Cholewa *et al.,* 2019; Kaur *et al.,* 2019).

Os mecanismos ergogênicos da betaína para o desempenho físico estão principalmente relacionados à sua função como osmólito e doadora de grupo metil (Del Favero, 2012). Como osmólito, nas células musculares a betaína proporciona maior tempo de hidratação celular, substituindo sais inorgânicos e protegendo enzimas intracelulares da pressão osmótica e da inativação por temperatura (Cholewa *et al.*, 2018; Cholewa *et al.*, 2019; Freitas; Barbosa; Ramos, 2015). Ao doar um grupo metil, a betaína contribuí para síntese de proteínas metabólicas essenciais, como a creatina, a qual atua na melhora da força e na potência muscular (Del Favero, 2012; Cholewa *et al.*, 2019). Em condições de estresse, a betaína promove a proteção muscular contra desnaturação acidótica das proteínas intracelulares (Cholewa *et al.*, 2019). Ainda, Waldman; Bryant; Mcallister (2023) apontam que a betaína a nível muscular favorece a estimulação da modulação da função do músculo esquelético, contração, respiração, biogênese mitocondrial e melhora do fluxo sanguíneo (Waldman; Bryant; Mcallister, 2023). Portanto, a betaína pode apresentar o maior potencial ergogênico em protocolos de exercícios que geram altos níveis de estresse metabólico, principalmente, aqueles que empregam períodos de descanso mais curtos e volumes maiores (Cholewa *et al.*, 2014).

No desempenho em exercícios físicos, alguns estudos indicam que o consumo crônico com betaína pode proporcionar melhoras, principalmente direcionadas a força e a potência muscular em indivíduos fisicamente ativos (Ismaeel, 2017; Aguinaga-Ontoso *et al.*, 2023). Del Favero (2012) aponta em seu estudo que ao doar um grupo metil a betaína contribui para formação de fosfadilticolina, que tem um papel importante para a síntese de acetilcolina (Del Favero, 2012). A maior síntese de acetilcolina nos neurônios motores proporciona a melhora do acoplamento excitação-contração durante exercícios físicos intensos, possibilitando o

aumento do trabalho anaeróbico, redução do esforço percebido e da fadiga muscular (Cholewa *et al.*, 2019; Waldman; Bryant; Mcallister, 2023). Desse modo, proporcionando maior força e potência muscular para realização de exercícios físicos (Waldman; Bryant; Mcallister, 2023).

A fadiga muscular é definida como qualquer diminuição da potência muscular durante a prática de exercício físico. Isso deve-se pela redução da capacidade de gerar força dos músculos durante o exercício físico, influenciada por fatores neurais, tipo de fibra muscular e ativação muscular. Ainda, a fadiga muscular pode comprometer o controle e a coordenação muscular, aumentando o risco de lesões articulares (Santos, Júnior e Araujo, 2020; Verschueren *et al.*, 2021). A fadiga muscular é a principal causa da redução do desempenho em praticantes de exercício físico e atletas esportivos, podendo proporcionar alterações no desempenho de um único músculo, desequilíbrio, influenciar no controle postural e alterar padrões de movimentos (Verschueren *et al.*, 2021).

As principais causas da fadiga muscular devem-se principalmente a diminuição das reservas energéticas de trifosfato de adenosina (ATP), fosfocreatina, glicogênio muscular e acúmulo de ácido lático (Santos, Júnior e Araujo, 2018). A diminuição de ATP e fosfocreatina diminuem a força muscular, induzem a queda no estoque de glicogênio e afeta a resistência. O acúmulo de ácido lático causa acidose, diminuindo a eficiência da contração e o desempenho muscular (Dos Santos *et al.*, 2010). Desse modo, interferindo diretamente na eficiência da contração, comprometendo a função muscular. Neste sentindo, estudos apontam que a suplementação com betaína pode influenciar na fadiga muscular (Cholewa *et al.*, 2014; Cholewa *et al.*, 2019; Hoffman *et al.*, 2011, Arazi *et al.*, 2022). Cholewa e colaboradores (2014) em sua revisão sugerem que a suplementação com betaína pode reduzir as percepções da fadiga muscular. Isso ocorre devido a capacidade da betaína em promover o aumento da síntese de acetilcolina no neurônio motor (Cholewa *et al.*, 2014). Ainda, Cholewa e colaboradores (2019) apontam que a suplementação com betaína pode proporcionar maior resistência muscular em exercícios extenuantes (Cholewa *et al.*, 2019). Outros dois estudos, revelam que a suplementação com betaína resulta em redução da fadiga muscular, com o aumento do número de repetições máximas até a falha e redução sérica de lactato pós exercícios (Hoffman *et al.*, 2011, Arazi *et al.*, 2022).

Apesar da existência de revisões sistemáticas direcionadas a investigar os efeitos da suplementação com betaína relacionadas à saúde (Zawieja; Zawieja; Chmurzynska, 2019; Gao *et al.*, 2019; Ashtary-Larky *et al.*, 2022; Xu *et al.*, 2023) e ao desempenho físico (Cholewa *et al.*, 2014; Cholewa *et al.*, 2019) como a força e a potência (Del Favero, 2012; Ismaeel, 2017; Aguinaga-Ontoso *et al.*, 2023), ainda existem lacunas em relação aos seus efeitos em outros

desfechos atrelados ao desempenho físico, como a fadiga muscular. Assim, no melhor de nosso conhecimento, poucos estudos investigaram os efeitos de tal suplementação sob a fadiga muscular na prática de exercício físico. Com isso, não há consenso sobre a relação da suplementação com betaína e a melhora da fadiga muscular. Ante o exposto, o objetivo desta revisão sistemática foi investigar a influência da suplementação com betaína sob a fadiga muscular na prática de exercícios físicos, apresentando evidências sobre o uso desta suplementação.

2 ARTIGO CIENTÍFICO

Artigo científico submetido para publicação no periódico "***"RETOS. Nuevas Tendencias en Educación Física, Deportes y Recreación",*** qualis CAPES Interdisciplinar A4. A estruturação do artigo baseou-se nas instruções aos autores preconizadas pelo periódico (ANEXO A).

FERNANDES Torres, Larissa *et al*. Betaine as an Ergogenic Aid to Improve Muscle Fatigue in Physical Exercise: A Systematic Review of Randomized Clinical Trials. **Retos**, *[S. l.]*, v. 62, p. 341–349, 2024. Disponível em: https://recyt.fecyt.es/index.php/retos/article/view/108391. Acesso em: 18 nov. 2024.

Betaine as an Ergogenic Aid to Improve Muscle Fatigue in Physical Exercise: A Systematic Review of Randomized Clinical Trials

Betaína como ayuda ergogénica para mejorar la fatiga muscular en el ejercicio físico: Una revisión sistemática de ensayos clínicos aleatorizados

*Larissa Torres Fernandes, *Deysimara de Cássia Santos, *Lucas Teixeira Marques, *Danielle Negri Ferreira Neves, **Otávio de Toledo Nóbrega, *Mariana de Melo Cazal, *Carina Carvalho Silvestre, *Ciro José Brito

*Federal University of Juiz de Fora Campus of Governador Valadares (Brazil), **University of Brasilia (Brazil)

Abstract. Objectives: This systematic review aims to investigate the influence of betaine supplementation on muscle fatigue during exercise. Methodology: To this end, the PRISMA guidelines were adopted and the study was registered with PROSPERO (CRD42023469111). Searches were conducted using specific keywords according to the PICOS strategy on March 12, 2024, in the PubMed, Cochrane Library, Web of Science, Embase and SCOPUS databases. Randomized clinical trials (RCTs) in adults of both sexes that used betaine as a supplement, compared to placebo, to improve muscle fatigue during physical exercise were included. Animal studies and studies with concomitant use of betaine and other supplements were excluded. Muscle fatigue was assessed using the one-repetition maximum test and blood lactate during leg press or squat and bench press exercises. The risk of bias of the included studies was assessed using the Cochrane RoB2 tool and the certainty of the evidence using GRADE. Results: Five RCTs were included, in which a total of 93 participants were evaluated; all were male, with 57 individuals allocated to the intervention group with a mean age of 19.18±2.67 years, and 58 individuals in the control group with a mean age of 19.66±2.44 years. Betaine promoted more repetitions until muscle fatigue in the leg press or squat (n = 3) and bench press (n = 2), with reductions in serum lactate in two of these studies. Conclusion: Betaine can be considered as a potential ergogenic resource for improving muscle fatigue, providing a greater number of repetitions in exercises and eliminating lactate in the blood.
Keywords: Betaine, Muscle Fatigue, Exercise, Dietary Supplements, Systematic Review.

Resumen. Objetivos: Esta revisión sistemática investigó la influencia de la suplementación con betaína en la fatiga muscular durante el ejercicio. Metodología: Para ello se ocupó las directrices PRISMA y se registró el estudio en PROSPERO (CRD42023469111). Se realizaron búsquedas utilizando palabras clave específicas según la estrategia PICOS en el 12 de marzo de 2024 en las bases de datos PubMed, Cochrane Library, Web of Science, Embase y SCOPUS. Se incluyeron ensayos clínicos aleatorios (ECA) en adultos de ambos sexos que utilizaron betaína como suplemento, en comparación con placebo, para mejorar la fatiga muscular durante el ejercicio físico. Se excluyeron los estudios en animales y los estudios con uso concomitante de betaína y otros suplementos. La fatiga muscular se evaluó mediante la prueba de una repetición máxima y el lactato sanguíneo durante los ejercicios de leg-press, o sentadilla y press de banca. El riesgo de sesgo de los estudios incluidos se evaluó mediante la herramienta Cochrane RoB2 y la certeza de las pruebas mediante GRADE. Resultados: Se incluyeron cinco ECA, en los que se evaluó a un total de 93 participantes; todos eran varones, con 57 individuos asignados al grupo de intervención con una edad media de 19,18±2,67 años, y 58 individuos en el grupo de control con una edad media de 19,66±2,44 años. La betaína promovió más repeticiones hasta la fatiga muscular en el leg-press o sentadilla (n = 3) y en el press de banca (n = 2), con menores nivels del lactato sérico en dos estudios. Conclusiones: La betaína puede considerarse un potencial recurso ergogénico para mejorar la fatiga muscular, proporcionar un mayor número de repeticiones en los ejercicios y eliminar el lactato en sangre.
Palabras clave: Betaína, Fatiga muscular, Ejercicio, Suplementos Dietéticos, Revisión sistemática.

Fecha recepción: 10-07-24. Fecha de aceptación: 12-10-24
Larissa Torres Fernandes
farm.larissatorresfernandes@gmail.com

Introduction

The use of nutritional supplements as an ergogenic resource promotes improved physical performance. Supplementation can also optimize muscle recovery time, delay fatigue in muscle fibers, and counteract the inhibitory effect of the central nervous system on muscle contraction, resulting in better performance, among other (Waldman, et al. 2023). Betaine (*N-N-N*-trimethylglycine) stands out among ergogenic resources, choline-derived substance that can be found in betaine-rich foods such as whole wheat grains, beets, spinach, invertebrates, whole wheat germ and bran (Kaur, et al. 2019; Arazi, et al. 2022; Machek , et al. 2022; Arumugam, et al. 2021; Dobrijevic, et al. 2023). Betaine can also be produced biologically from the oxidation of dietary choline in the liver and kidneys (Arazi, et al. 2022; Machek, et al. 2022; Dobrijevic, et al. 2023). The average intake of betaine by adults is approximately 100 to 400 mg/day. However, for people who consume mostly whole food products and invertebrates, intake can be between 1 and 2.5 grams (g) per day (Arazi, et al. 2022; Machek, et al. 2022; Arumugam, et al. 2021; Dobrijevic, et al. 2023). As an ergogenic resource, betaine promotes perceived benefits from 7 days and a maximum of 14 days considering the intake of moderate doses (2.5g/day) in active populations (Arazi, et al. 2022; Freitas, et al. 2015; Gao, et al. 2019; Waldman, et al. 2023; Yang, et al. 2020).

The main mechanisms of action attributed to betaine include its function as an osmolyte, protective agent against protein denaturation and methyl group donor (Cholewa, et al. 2019; Gao, et al. 2019; Kaur, et al. 2019; Dobrijevic, et al. 2023). Some studies indicate that chronic consumption of betaine can provide improvements in physical performance, mainly aimed at muscle strength and power in physically active individuals (Ismaeel, 2017; Aguinaga-Ontoso, et al. 2023). In addition, other studies have shown

that chronic betaine consumption can improve muscular endurance, modulate endocrine function and reduce body fat percentage (Arazi, et al. 2022; Freitas, et al. 2015; Gao, et al. 2019; Waldman, et al. 2023). At the muscle level, betaine provides greater cellular hydration time, protection against acidotic denaturation of intracellular proteins and contributes to the synthesis of essential metabolic proteins (Cholewa, et al. 2019; Waldman, et al. 2023). In addition, betaine at the muscle level helps to stimulate the modulation of skeletal muscle function, contraction, respiration, mitochondrial biogenesis and improved blood flow (Waldman, et al. 2023). In the studies carried out by Cholewa et al (2014) and Waldman et al (2023), the authors suggest that betaine supplementation can reduce perceptions of muscle fatigue. This is due to betaine's ability to promote increased acetylcholine synthesis in the motor neuron (Cholewa, et al. 2014; Waldman, et al. 2023).

In this perspective, it is known that muscle fatigue is defined as any decrease in muscle power during physical exercise. Muscle fatigue is the main cause of reduced physical performance in exercise practitioners and sports athletes, and can lead to alterations in the performance of a single muscle, imbalance, influence on postural control, and alteration of movement patterns (Verschueren, et al. 2021; Cervantes Hernández , et al. 2022). Some supplements are capable of providing a reduction in muscle fatigue (Ihsan, et al. 2024). In this sense, studies indicate that betaine supplementation may promote reduced muscle fatigue, with an increase in the number of maximum repetitions until fatigue and a decrease in post-exercise serum lactate. However, few studies have investigated the effects of betaine supplementation on muscle fatigue during physical exercise (Arazi, et al. 2022; Hoffman, et al. 2011). Despite the existence of systematic reviews aimed at investigating the effects of betaine supplementation related to health (Zawieja; Zawieja & Chmurzynska, 2019; Gao, et al. 2019; Ashtary-Larky, et al. 2022; Xu, et al. 2023) and physical performance (Cholewa, et al. 2014; Cholewa, et al. 2019) such as strength and power (Ismaeel, 2017; Aguinaga-Ontoso, et al. 2023), there are still gaps regarding its effects on other outcomes, such as muscle fatigue. Consequently, there is no consensus in the literature regarding the relationship between betaine supplementation and improvement in muscle fatigue. Therefore, this systematic review aims to investigate the influence of betaine supplementation on muscle fatigue during physical exercise, presenting evidence on the use of this supplement.

Materials and methods

This is a systematic review, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA (Page, et al. 2021) (check list in the supplementary material). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023469111).

Data sources and search strategies

The search strategy included terms related to "betaine," "fatigue," and "exercise," standardized by the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS), in different combinations according to the search protocols of each database, without time restrictions (supplementary material). The indexed databases used were: Medical Literature Analysis and Retrieval System Online (PubMed/Medline), Excerpta Medica Database (EMBASE), Web of Science, Scopus, and Cochrane Library. The search in the databases was conducted on March 12, 2024. The search strategies used are detailed in the supplementary material.

Study selection and eligibility criteria

The articles were selected from the databases by two reviewers (DNFN and LTF). All articles found were imported into the Rayyan Reference Manager platform. The process of selecting studies to be included in the review was initially conducted by both authors (DNFN and LTF) reading the titles and abstracts. The full texts of the selected articles were subsequently read (DNFN and LTF). The two authors carried out the process in a standardized and independent manner in both phases. In cases of disagreement, a third author (LTM) was contacted to resolve and clarify such discrepancies.

Studies were included if they met the PICOS criteria, as well as the research question: "Does betaine supplementation improve muscle fatigue in exercise practitioners?" The study population consisted of individuals of both sexes, aged 14 to 60 years, who were physical exercise practitioners. The intervention was betaine supplementation during physical exercise. Studies using some form of placebo were adopted for comparison. The outcome established was reduced muscle fatigue during physical exercise. The type of study used in the review was randomized clinical trials (RCTs) in humans, either parallel or crossover. The following exclusion criteria were adopted: animal studies, studies which were not randomized clinical trials, and studies involving concurrent use of betaine and other supplements.

Data extraction

The data collected from the selected studies were organized and presented in a Microsoft Excel® spreadsheet, independently conducted by two reviewers (LTM and DNFN). In the event of discrepancies, a third author (DCS) was responsible for making decisions. The following data were collected: first author's name; year of publication; country; objective; study design; participant descriptions (number of participants, mean age, participant characteristics); intervention (intervention strategy, dose and supplementation period, evaluation parameters, placebo evaluation form); and results. In terms of evaluation, muscle fatigue was investigated using the one-repetition maximum (1-RM) test, blood lactate levels, and the type of exercise performed for upper limbs (bench

press) and lower limbs (leg press or squat).

Risk of bias analysis

The risk of bias assessment was conducted for the outcome of muscle fatigue using the Cochrane RoB 2.0 tool (Higgins, et al. 2022). The following types of bias for RCTs were assessed: random sequence generation (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and overall risk of bias. In addition to the aforementioned biases, carryover and washout effects were also evaluated for crossover RCTs (selection bias). Domain assessments and overall risk of bias were classified as (L) low, (U) unclear, and (H) high (Higgins, et al. 2022), according to the Cochrane manual criteria. The overall risk of bias was determined by combining the bias domains. The risk of bias analysis was independently and blindly conducted by two reviewers (DCS, DNFN). In case of discrepancies, a third author (LTM) was responsible for making decisions.

Certainty of Evidence

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. This method enables assessing the evidence for each outcome analyzed based on the following domains: study design; methodological limitations (risk of bias); inconsistency; indirect evidence; imprecision and publication bias. The quality of evidence in GRADE is classified into four levels at the end of the evaluation: high, moderate, low and very low (Schünemann, et al. 2013). The outcome adopted for evaluation in GRADE was muscle fatigue. Two researchers independently addressed the five GRADE domains (DNFN, LTF). In case of disagreement, a third author (LTM) was responsible for the decision. We justified all decisions to lower the certainty rating of any study using footnotes at the end of Table 4. The GRADEpro GDT software (https://gdt.gradepro.org/app/) was used to perform the certainty of the evidence.

Results

Selection and identification of studies

The search strategies across different databases yielded a total of 53 studies. After removing duplicate studies, there were 33 studies remaining. Titles and abstracts of these studies were screened, resulting in the exclusion of 28 articles that did not meet the established criteria (supplementary material), leaving five studies eligible for full-text reading. All of these studies (Arazi, et al. 2022; Hoffman, et al. 2009; Lee, et al. 2013; Machek, et al. 2022; Nobari, et al. 2021) were included in this systematic review, as depicted in the PRISMA flow diagram (Figure 1).

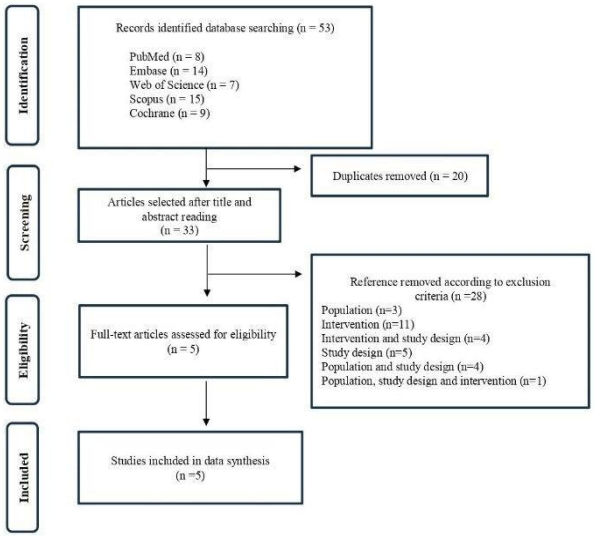

Figure 1. Flow diagram of study selection

Characteristics of studies

The studies included in the review (n = 5) were published between 2009 and 2022, in different countries: two in the United States of America (USA) (Hoffman, et al. 2009; Lee, et al. 2013), one in Iraq (Nobari , et al. 2021), one in Poland (Machek, et al. 2022), and one in Iran (Arazi, et al. 2022). All of them were double-blind RCTs (n = 5), with two being crossover RCTs (n = 2). The total actual sample, without underestimation due to the study design (crossover), involved 93 participants. All participants were men, with 57 individuals allocated to the intervention group, with a mean age of 19.18 ± 2.67 years, and 58 individuals in the control group, with a mean age of 19.66 ± 2.44 years. The intervention period ranged from 14 days to 14 weeks (chronic). The betaine supplementation dose ranged from 2 to 6 g/day, divided into two doses per day in all studies. The main characteristics of the studies are presented in Table 1.

Table 1.
Characteristics of studies

Author, year, country	Objectives	Study design	Participants				
			N		Average age (years)		Characterization of participants
			IG	CG	IG	CG	
Hoffman, et al. 2009, USA	To examine the effectiveness of 15 days of betaine supplementation on muscle endurance, power performance, and fatigue rate in college-aged active men	RCT, double-blind	12	12	20.4 ±1.3	21.4 ±4.7	Male individuals, active in college-age
Lee, et al. 2013, USA	Investigate the ergogenic effects of betaine supplementation on strength and power performance	RCT, Crossover, double-blind	12	12	21±3	21±3	Healthy and recreationally active men
Nobari,	To investigate the effect of betaine	ECR, Double-	14	15	15.5	15.5	Young professional soccer

et al. 2021, Iraq	supplementation on the biomotor abilities of young professional soccer players	blind			±0.3	±0.3	players
Arazi, et al. 2022, Iran	To examine the effects of short-term betaine supplementation on muscle endurance, plasma levels of lactate, testosterone, and cortisol, and the testosterone/cortisol ratio in response to acute resistance exercise	RCT, Crossover, double-blind	10	10	16±1	16±1	Young handball players
Machek, et al. 2022, Polond	To compare the impacts of a potential synergy of blood flow restriction and betaine on leg press performance, lactate concentrations, and exercise-associated biomarkers	ECR, Mixed, double-blind	9	9	23±3	22±1	Young apparently healthy individuals with recreational endurance training

Subtitle: RCT, randomized controlled trial; IG, Intervention Group (betaine supplementation); CG, Control Group (placebo supplementation).

Effects of betaine supplementation on muscle fatigue

Muscle fatigue was assessed in this review using the one-repetition maximum (1-RM) test and blood lactate levels. Among the five studies included, only one directly assessed muscle fatigue (Hoffman, et al. 2009), while four studies indirectly evaluated muscle fatigue (not described as the study objective and not assessed independently)(Arazi, et al. 2022; Lee, et al. 2013; Machek, et al. 2022; Nobari, et al. 2021). Muscle fatigue was assessed in exercises such as bench press, leg press or squat in the studies.

Maximum number of repetitions (1-RM) test

Significant differences were reported in two studies that compared the number of repetitions in bench press exercises between the intervention group (IG) and the control group (CG) and in leg press, between IG and CG after the supplementation period (Arazi, et al. 2022; Nobari, et al. 2021). Only one study reported a significant difference in the number of repetitions solely in the squat exercise, with no significant differences observed in the bench press exercise (Hoffman, et al. 2009). The study by Lee et al. (2013) indicated no significant difference in the total number of repetitions in squats and bench press until muscle fatigue between the IG and CG (Lee, et al. 2013). Finally, one study pointed out that betaine supplementation in IG provided significant effects in performing the 1-RM test in the leg press exercise in terms of exercise and execution time (Machek, et al. 2022), as described in Table 2.

Blood lactate level

Blood lactate levels were assessed in two studies comparing the IG and CG before and after the intervention period (Arazi, et al. 2022; Machek, et al. 2022). Reductions in blood lactate levels were reported in both studies when comparing the IG and CG after betaine supplementation (Table 2).

Table 2.
Characteristics of the interventions and result

Author, year, country	Intervention						Results
	Strategy	Dosage	Assessment points	Duration	Control	Assessment method	
Hoffman, et al. 2009, USA	BET mixed in 240 ml of sports drink	1.25g divided into 2 doses per day	Pre (T1) and 7 days later (T2) and 14 days (T3) after supplementation	14 days	PL	1-RM Bench press and squat	No significant differences were observed in the bench press exercise. The number of repetitions performed in the squat exercise was significantly higher ($p < 0.05$).
Lee, et al. 2013, USA	BET and 300 ml of Gatorade	2.5g divided 2 times a day	Before the ergometric test After the ergometric test	14 days	PL	1-RM Bench press and squat	There were no significant differences in the total number of repetitions of back squats performed at 85% 1-RM until fatigue.
Nobari, et al. 2021, Iraq	BET and 300ml of water, 2 hours before training and 1 hour after training	2g divided into 2 doses per day	P1 pre-season; P2, during the seven weeks following mid-season; and P3, in the week following the end of the season	14 weeks	PL	1-RM Bench press and leg press	There were no significant effects of time on the 1 RM bench press ($p > 0.05$), but there was significance in the group by time interaction ($p = 0.005$). There was significance in time ($p = 0.001$) and group by time ($p < 0.001$) in the leg press.
Arazi, et al. 2022, Iran	BET and warm water after a meal	2.5g divided into 2 doses per day	Pre-supplementation Post-supplementation	14 days	PL	1-RM Bench press and leg press Lactate	There was a significant difference in lactate levels ($p < 0.001$), in the number of repetitions in bench press exercises ($p < 0.001$) and leg press ($p < 0.001$).
Machek,	BET fine white	6g divided into	Blood samples: pre and post-	14 days	PL	1-RM	There were significant

et al. 2022, Poland	powder in transparent gelatin capsules	2 doses per day	supplementation (30 minutes and 3 hours)	Post-exercise Bench press and leg press Lactate	effects of exercise condition (($p = 0.003$) and time ($p < 0.001$) for ΔLactate < in lactate levels.

Assessment of risk of bias

According to the Cochrane RoB 2.0 tool, all studies were classified as having some concern, as at least one of the domains was judged to have some concern (U), with no domain classified as high risk of bias (H), as shown in Figure 2 and 3. The crossover studies (n = 2) did not present the participant allocation sequence in the randomization process, possibly due to the proposed experimental design, and were therefore classified in the Random Sequence Generation domain with some concerns (U) (Arazi, et al. 2022; Lee, et al. 2013). The other RCTs presented a low risk of bias (L) in the Random Sequence Generation domain (Hoffman, et al. 2009a; Machek, et al. 2022; Nobari, et al. 2021). Evaluation of carryover and washout effects in crossover RCTs indicated a low risk of bias (L) (Arazi, et al. 2022; Lee, et al. 2013). All studies (n = 5) presented a low risk of bias for Blinding of Participants and Personnel; Blinding of outcome assessment; and Incomplete outcome data (Arazi, et al. 2022; Hoffman, et al. 2009; Lee, et al. 2013; Machek, et al. 2022; Nobari, et al. 2021). Finally, all studies (n = 5) presented some concerns (U) in relation to selective reporting, as there was no evidence that the RCT research protocol was registered in any database by the authors of the included studies (Arazi, et al. 2022; Hoffman, et al. 2009; Lee, et al. 2013; Machek, et al. 2022; Nobari, et al. 2021). A detailed assessment of the risk of bias is provided in the supplementary material.

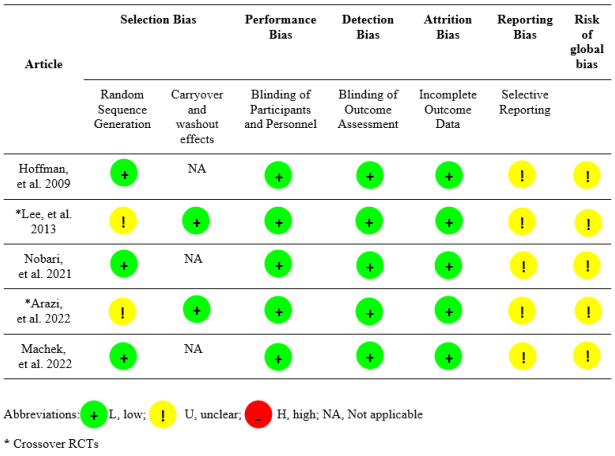

Figure 2. Risk of bias analysis

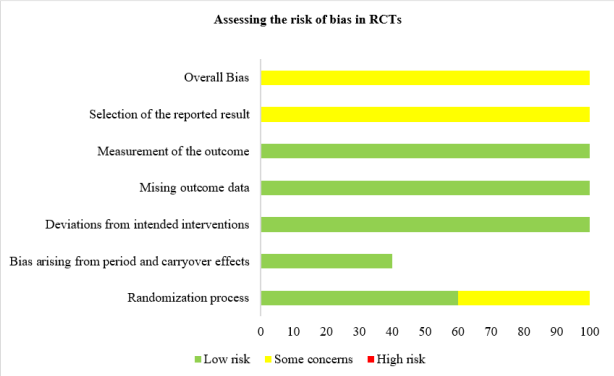

Figure 3. Assessing the risk of bias in RCTs

Certainty of Evidence

The assessment of the certainty of the evidence indicated that there was a degree of uncertainty in the findings regarding the benefit of betaine supplementation in improving muscle fatigue during exercise. The certainty of the evidence was downgraded in the inconsistency (serious) and imprecision (very serious) domains. Table 3 presents a summary of the results, with footnotes explaining the downgrading judgments (decrease in the certainty of the evidence). Therefore, confidence in the estimate of the effect is very limited, in addition to the uncertainties of the results to the detriment of the limitations of the RCTs.

Table 3.
Certainty assessment

Certainty assessment							N° of patients		Effect		
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betaine	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty
5	randomised trials	not serious[a]	serious[b]	not serious	very serious[c]	none[d]	57	58	-	see comment	⨁◯◯◯ Very low

a. Although some studies have considered some concerns regarding the randomization sequence (crossover) and protocol registration (all studies), we believe that this would not influence the lowering of the domain.
b. Although the average age and population show that the sample is homogeneous, the intervention period (14 days to 14 weeks) and the dose of betaine supplementation (2 to 6 g/day) varied greatly.
c. The total actual sample, without underestimation due to the study design, involved 93 participants.
d.Although the gray literature was not used as a database, the databases included in the review were those recommended by the Cochrane Handbook for Systematic Reviews of Interventions (PubMed/Medilene Excerpta Medica Database (EMBASE) and Cochrane Library). In addition, in order to broaden the results found, the following databases were included in the review: Web of Science and Scopus.

Discussion

This systematic review aimed to investigate the influence of betaine supplementation on muscle fatigue during physical exercise, presenting evidence on the use of this supplement. A total of five RCTs were included, involving 93 male participants, over an intervention period of 14 days to 14 weeks and with betaine supplementation doses ranging from 2 to 6 g/day. The results of the studies show a possible effect of betaine supplementation on muscle fatigue indirectly through the greater number of repetitions focused on lower limb exercises, whether in the leg press (Arazi, et al. 2022; Nobari, et al. 2021) or squats (Hoffman, et al. 2009). Furthermore, betaine seems to favor the performance of a greater number of repetitions in bench press exercises (Arazi, et al. 2022; Nobari, et al. 2021). In a direct assessment of muscle fatigue, blood lactate levels were reduced after betaine supplementation (Arazi, et al. 2022; Machek, et al. 2022). The main mechanism described for this effect is suggested by Waldman et al. (2023), who propose that betaine increases free choline, resulting in increased acetylcholine synthesis in motor neurons, reducing perceived effort and muscle fatigue (Waldman, et al. 2023). This enables a greater number of repetitions during physical exercise (Arazi, et al. 2022).

Betaine appears to be an effective ergogenic resource for increasing the number of repetitions in leg press exercises during the 1-RM test aimed at muscle fatigue. However, it is important to note that other factors, beyond muscle fatigue, may directly influence the results of the 1-RM test. Previous studies, such as those by Cholewa et al. (2013) and Cholewa et al. (2018), confirm this hypothesis (Cholewa, et al. 2013; Cholewa, et al. 2018). According to Dias et al. (2013), factors such as stretching, recovery intervals between maximum repetition attempts, ambient temperature, and dehydration can impact the execution of the 1-RM test (Dias, et al. 2013). In the study conducted by Hoffman et al. (2009), which directly assessed muscle fatigue through the 1-RM test, participants underwent a prior warm-up with standardized load, followed by 3 to 4 attempts at 1-RM, with a rest period of 3 to 5 minutes between each attempt (Hoffman, et al. 2009). The warm-up may influence the execution of exercises that require knee extension and flexion movements, as is the case with squats. Despite the warm-up, the study by Hoffman et al. (2009) revealed that it was possible to perform a greater number of repetitions in the 1-RM test (Hoffman, et al. 2009). This improvement may be attributed to the standardization of other variables influencing performance, allowing for a more effective execution of the test (Hoffman, et al. 2009). Furthermore, this study was pioneering in investigating the ergogenic effects of betaine on muscle fatigue. While Hoffman et al. (2009) observed an increase in the number of repetitions, Lee et al. (2013) did not find significant differences in their results (Hoffman, et al. 2009; Lee, et al. .2013). This suggests that factors such as individual variability may be influencing the outcomes and need to be further explored in future investigations.

There are some mechanisms attributed to betaine supplementation that indicate its contribution to reducing muscle fatigue. One of these mechanisms is attributed to its action as a protective agent against the denaturation of intracellular proteins. Betaine helps maintain the stability and conformation of proteins, which can protect intracellular muscle proteins against acidotic denaturation, enhancing greater mechanical tension promoted by attenuated metabolic fatigue and concomitantly prolonged contraction (Cholewa, et al. 2018; Willingham, et al. 2020). Additionally, Willingham et al. (2020) point out in their study that betaine can donate a methyl group for the synthesis of essential metabolic proteins such as creatine and carnitine. This mainly occurs during periods of hypertonicity during physical exercise (Willingham, et al. 2020). Other studies address the ability to promote the elevation of nitric oxide levels provided by betaine supplementation, as it is a compound rich in nitrate (Jones, 2013; Pryor, et al. 2017). Jones (2013) describes that the elevation of nitric oxide levels in the blood under physiological stress conditions promotes modulation of skeletal muscle function, including contraction, respiration, mitochondrial biogenesis, and blood flow (Jones, 2013). This results in improved physical performance and delayed muscle fatigue.

Muscle fatigue can be directly quantified through blood lactate (Hernández-Cruz, et al. 2022). Lactate concentrations reflect the difference between the production and elimination rates of lactate (Theofilidis, et al. 2018; Brooks, 2018; Bartoloni, et al. 2024). This difference is mainly due to oxidation occurring in muscle tissue during exertion, representing a significant source of lactate elimination (Brooks, 2018). In this regard, some studies report significant positive correlations between anaerobic power production and plasma lactate (Temfemo, et al. 2011; Zagatto, et al. 2017). Of the studies included in the review, only two assessed blood lactate before and after exercise, demonstrating a reduction in lactate levels even with an increase in the number of repetitions, reflecting the difference in lactate production and elimination rates, as well as a positive effect on exercise time and condition for lactate during the leg press 1-RM test (Machek, et al. 2022). A study by Trepanowski et al. (2011) indicates a lower accumulation of blood lactate induced by exercise during betaine supplementation versus placebo supplementation. The authors suggest that the lower lactate accumulation, associated with betaine's cellular hydration maintenance effect, may have contributed to exercise performance (Trepanowski, et al. 2011). Arazi et al. (2022) speculate that one possible explanation for post-exercise blood lactate levels being lower may be the ability of betaine supplementation to improve mitochondrial respiration, resulting in increased

lactate oxidation. This leads to lower blood lactate levels, even with increased anaerobic work (Arazi , et al. 2022). However, in the studies by Waldman et al. (2023) and Apicella et al. (2013), the authors point out a higher number of repetitions without changes in lactate concentrations after betaine supplementation (Apicella, et al. 2013; Arazi, et al. 2022).

The supplementation period and dose can significantly impact the effectiveness of the intervention. In this regard, most scientific evidence indicates that betaine's ergogenic resources are pronounced after 14 to 15 days of supplementation, with moderate doses (2.5g/day) administered to active populations (Arazi, et al. 2022; Gao, et al. 2019; Hoffman, et al. 2009; Waldman, et al. 2023; Yang, et al. 2020). However, Hoffman et al. (2009) stated in their study that improvements in physical performance can be perceived with betaine supplementation from 7 days onwards. Thus, the studies included in this review adopted the supplementation period and dose according to the literature to allow for an ergogenic effect of betaine.

There are some limitations to this systematic review, mainly in relation to the generalization and extrapolation of the results. This is due to the small number of studies in the indexed databases, the small sample size, methodological flaws including some concerns about the risk of bias presented by the studies and the very low level of certainty of the evidence. Another important point is that we did not consider gray literature, which can favor publication bias and a lower balanced view of the evidence. In addition, these studies did not directly investigate betaine concentration in plasma and muscle fatigue, so it is impossible to make affirmative and direct inferences about betaine supplementation and the improvement of muscle fatigue in exercisers. In other words, our confidence in the improvement of muscle fatigue through betaine supplementation is limited. Given the limitations of the study, the results presented should be treated as preliminary findings. Moreover, this systematic review presents inferences that are still speculative and indirect about muscle fatigue using the 1-RM test. As the 1-RM test is not only influenced by supplementation, there are other factors and physiological conditions that can influence the performance of a higher number of repetitions. Therefore, this is the first systematic review to investigate the influence of betaine supplementation on muscle fatigue during exercise.

This review has helped to identify the existing gaps in betaine supplementation and muscle fatigue during exercise, encouraging new studies to investigate mainly the effect of betaine supplementation directly on muscle fatigue. Thus, there is a need for studies that assess blood lactate levels; serum betaine concentrations; that better describe the nutritional control of participants to avoid diet-related biases; studies that investigate the specific mechanisms by which betaine impacts muscle fatigue; studies that describe the standardization of the methods used to perform the 1-RM test; and studies that use diverse populations with different age groups.

Conclusions

In conclusion, a betaine can be considered as a potential ergogenic resource for reducing muscle fatigue in exercisers, especially when it comes to increasing the number of repetitions in the 1-RM test in leg press or squat exercises. However, new randomized clinical trials are needed to directly investigate muscle fatigue. This will allow us to affirm the effects of betaine supplementation on muscle fatigue in exercisers with solid scientific evidence.

References

Aguinaga-Ontoso, I., Guillen-Aguinaga, S., Guillen-Aguinaga, L., Alas-Brun, R., & Guillen-Grima, F. (2023). Effects of Nutrition Interventions on Athletic Performance in Soccer Players: A Systematic Review. *Life*, *13*(6), 1271. https://doi.org/10.3390/life13061271

Apicella, J. M., Lee, E. C., Bailey, B. L., Saenz, C., Anderson, J. M., Craig, S. A. S., Kraemer, W. J., Volek, J. S., & Maresh, C. M. (2013). Betaine supplementation enhances anabolic endocrine and Akt signaling in response to acute bouts of exercise. *European Journal of Applied Physiology*, *113*(3), 793–802. https://doi.org/10.1007/s00421-012-2492-8

Arazi, H., Aboutalebi, S., Taati, B., Cholewa, J. M., & Candow, D. G. (2022). Effects of short-term betaine supplementation on muscle endurance and indices of endocrine function following acute high-intensity resistance exercise in young athletes. *Journal of the International Society of Sports Nutrition*, *19*(1), 1–16. https://doi.org/10.1080/15502783.2022.2041988

Arumugam, M. K., Paal, M. C., Donohue, T. M., Jr, Ganesan, M., Osna, N. A., & Kharbanda, K. K. (2021). Beneficial Effects of Betaine: A Comprehensive Review. *Biology*, *10*(6), 456. https://doi.org/10.3390/biology10060456

Ashtary-Larky, D., Bagheri, R., Ghanavati, M., Asbaghi, O., Tinsley, G. M., Mombaini, D., Kooti, W., Kashkooli, S., & Wong, A. (2022). Effects of betaine supplementation on cardiovascular markers: A systematic review and Meta-analysis. *Critical Reviews in Food Science and Nutrition*, *62*(23), 6516–6533. https://doi.org/10.1080/10408398.2021.1902938

Bartoloni, B., Mannelli, M., Gamberi, T., & Fiaschi, T. (2024). The Multiple Roles of Lactate in the Skeletal Muscle. *Cells*, *13*(14), 1177. https://doi.org/10.3390/cells13141177

Brooks, G. A. (2018). The Science and Translation of Lactate Shuttle Theory. *Cell Metabolism*, *27*(4), 757–785. https://doi.org/10.1016/j.cmet.2018.03.008

Cervantes Hernández, N., Hernandez Nájera, N., & Carrasco Legleu, C. E. (2022). Comparación de pruebas para medir la fatiga muscular en el entrenamiento de atletas hombres de CrossFit: una revisión sistemática (Comparison of tests to measure muscle fatigue in training of male CrossFit athlete: a systematic review). *Retos*, *43*, 923–930. https://doi.org/10.47197/retos.v43i0.89787

Cholewa, J. M., Hudson, A., Cicholski, T., Cervenka, A., Barreno, K., Broom, K., Barch, M., & Craig, S. A. S. (2018). The effects of chronic betaine supplementation on body

composition and performance in collegiate females: a double-blind, randomized, placebo controlled trial. *Journal of the International Society of Sports Nutrition*, *15*(1). https://doi.org/10.1186/s12970-018-0243-x

Cholewa, J. M., Wyszczelska-Rokiel, M., Glowacki, R., Jakubowski, H., Matthews, T., Wood, R., Craig, S. A. S., & Paolone, V. (2013). Effects of betaine on body composition, performance, and homocysteine thiolactone. *Journal of the International Society of Sports Nutrition*, *10*, 1–12

Cholewa, J. M., Guimarães-Ferreira, L., & Zanchi, N. E. (2014). Effects of betaine on

performance and body composition: a review of recent findings and potential mechanisms. *Amino acids*, *46*(8), 1785–1793. https://doi.org/10.1007/s00726-014-1748-5

Cholewa, J. M., Newmire, D. E., Rossi, F. E., Guimarães-Ferreira, L., & Zanchi, N. E.

(2019). An overview of betaine supplementation, sports performance, and body composition. Nutrition and Enhanced Sports Performance, 691-706.

Dias, R. M. R., Avelar, A., Menêses, A. L., Salvador, E. P., Silva, D. R. P. da, & Cyrino, E. S. (2013). Segurança, reprodutibilidade, fatores intervenientes e aplicabilidade de testes de 1-RM. *Motriz: Revista de Educação Física*, *19*, 231–242

Dobrijević, D., Pastor, K., Nastić, N., Özogul, F., Krulj, J., Kokić, B., Bartkiene, E., Rocha, J. M., & Kojić, J. (2023). Betaine as a Functional Ingredient: Metabolism, Health-Promoting Attributes, Food Sources, Applications and Analysis Methods. *Molecules (Basel, Switzerland)*, *28*(12), 4824. https://doi.org/10.3390/molecules28124824

Freitas, H. R., Barbosa, M., & Ramos, T. da S. (2015). O papel da suplementação de betaína na atividade física: uma revisão sistemática. *Nutrire*, *40*(2), 246–260. https://doi.org/10.4322/2316-7874.50914

Gao, X., Zhang, H., Guo, X., Li, K., Li, S., & Li, D. (2019). Effect of Betaine on Reducing Body Fat—A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*, *11*(10), 2480. https://doi.org/10.3390/nu11102480

Hernández-Cruz, G., Estrada-Meneses, E. F., Ramos-Jiménez, A., Rangel-Colmenero, B. R., Reynoso-Sánchez, L. F., Miranda-Mendoza, J., & Quezada-Chacón, J. T. (2022). Relación entre el tipo de ejercicio físico y la fatiga cuantificada mediante VFC, CK y el lactato en sangre (Relationship between physical exercise type and fatigue quantified through HRV, CK, and blood lactate). *Retos*, *44*, 176–182. https://doi.org/10.47197/retos.v44i0.89479

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2022). *Manual Cochrane para revisões sistemáticas de intervenções versão 6.3*. Cochrane

Hoffman, J. R., Ratamess, N. A., Kang, J., Gonzalez, A. M., Beller, N. A., & Craig, S. A. (2011). Effect of 15 days of betaine ingestion on concentric and eccentric force outputs during isokinetic exercise. *Journal of Strength and Conditioning Research*, *25*(8), 2235–2241. https://doi.org/10.1519/JSC.0b013e3182162530

Hoffman, J. R., Ratamess, N. A., Kang, J., Rashti, S. L., & Faigenbaum, A. D. (2009). Effect of betaine supplementation on power performance and fatigue. *Journal of the International Society of Sports Nutrition*, *6*, 7. https://doi.org/10.1186/1550-2783-6-7

Ihsan, fadli, Kozina, Z. ., Sukendro, S., Nasrulloh, A. ., Arzhan Hidayat, R. ., & Perdana, satya . (2024). Estrategias nutricionales para una recuperación rápida en el deporte: una revisión de la literatura (Nutritional Strategies for Rapid Recovery in Sport: A Literature Review). *Retos*, *57*, 153–164. https://doi.org/10.47197/retos.v57.105622

Ismaeel, A. (2017). Effects of Betaine Supplementation on Muscle Strength and Power: A Systematic Review. *Journal of Strength and Conditioning Research*, *31*(8), 2338–2346. https://doi.org/10.1519/JSC.0000000000001959

Jones, A. M. (2013). Dietary nitrate: the new magic bullet. *Sports Sci Exch*, *26*(110), 1–5.

Kaur, S., Sharma, N., Vyas, M., Mahajan, R., Satija, S., Mehta, M., & Khurana, N. (2019). A review on pharmacological activities of betaine. *Plant Arch*, *19*, 1021-1034.

Lee, B.-A., Lee, S.-H., & Oh, D.-J. (2013). Effects of peripheral injury in athletes with long-term-exercise participation in modern pentathlons. *Journal of Exercise Rehabilitation*, *9*(5), 481.

Machek, S. B., Harris, D. R., Zawieja, E. E., Heileson, J. L., Wilburn, D. T., Radziejewska, A., Chmurzynska, A., Cholewa, J. M., & Willoughby, D. S. (2022). The Impacts of Combined Blood Flow Restriction Training and Betaine Supplementation on One-Leg Press Muscular Endurance, Exercise-Associated Lactate Concentrations, Serum Metabolic Biomarkers, and Hypoxia-Inducible Factor-1α Gene Expression. *Nutrients*, *14*(23), 5040. https://doi.org/10.3390/nu14235040

Nobari, H., Cholewa, J. M., Castillo-Rodríguez, A., Kargarfard, M., & Pérez-Gómez, J. (2021). Effects of chronic betaine supplementation on performance in professional young soccer players during a competitive season: a double blind, randomized, placebo-controlled trial. *Journal of the International Society of Sports Nutrition*, *18*(1). https://doi.org/10.1186/s12970-021-00464-y

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, n71. https://doi.org/10.1136/bmj.n71

Pryor, J. L., Wolf, S. T., Sforzo, G., & Swensen, T. (2017). The effect of betaine on nitrate and cardiovascular response to exercise. *International Journal of Exercise Science*, *10*(4), 550

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013). *The GRADE handbook*. Cochrane Collaboration London, UK

Temfemo, A., Carling, C., & Ahmaidi, S. (2011). Relationship between Power Output, Lactate, Skin Temperature, and Muscle Activity During Brief Repeated Exercises With Increasing Intensity. *Journal of Strength and Conditioning Research*, *25*(4), 915–921. https://doi.org/10.1519/JSC.0b013e3181d680f0

Theofilidis, G., Bogdanis, G. C., Koutedakis, Y., & Karatzaferi, C. (2018). Monitoring Exercise-Induced Muscle Fatigue and Adaptations: Making Sense of Popular or Emerging Indices and Biomarkers. *Sports (Basel, Switzerland)*, *6*(4), 153. https://doi.org/10.3390/sports6040153.

Trepanowski, J. F., Farney, T. M., McCarthy, C. G., Schilling, B. K., Craig, S. A., & Bloomer, R. J. (2011). The Effects of Chronic Betaine Supplementation on Exercise Performance, Skeletal Muscle Oxygen Saturation and Associated Biochemical Parameters in Resistance Trained Men. *Journal of Strength and Conditioning Research*, *25*(12), 3461–3471. https://doi.org/10.1519/JSC.0b013e318217d48d

Verschueren, J., Tassignon, B., Verhagen, E., & Meeusen, R. (2021). The interaction of acute physical fatigue with three traditional functional performance tests and the reactive balance test. *Physical Therapy in Sport*, *49*, 188–195

Waldman, H. S., Bryant, A. R., & McAllister, M. J. (2023). Effects of Betaine Supplementation on Markers of Metabolic Flexibility, Body Composition, and Anaerobic Performance in Active College-Age Females. *Journal of Dietary Supplements*, *20*(1), 89–105. https://doi.org/10.1080/19390211.2021.1973644

Willingham, B. D., Ragland, T. J., & Ormsbee, M. J. (2020). Betaine Supplementation May Improve Heat Tolerance: Potential Mechanisms in Humans. *Nutrients*, *12*(10), 2939. https://doi.org/10.3390/nu12102939

Xu, J., Nie, Z., Qiu, X., Zhang, J., & Han, S. (2023). Effects of betaine supplementation on inflammatory markers: a systematic review and meta-analysis of randomised controlled trials. *International Journal of Food Sciences and Nutrition*, *74*(7), 721–729. https://doi.org/10.1080/09637486.2023.2257906

Yang, M.-T., Lee, X.-X., Huang, B.-H., Chien, L.-H., Wang, C.-C., & Chan, K.-H. (2020). Effects of Two-Week Betaine Supplementation on Apoptosis, Oxidative Stress, and Aerobic Capacity after Exhaustive Endurance Exercise. *Antioxidants*, *9*(12), 1189. https://doi.org/10.3390/antiox9121189

Zagatto, A. M., Miyagi, W. E., Sousa, F. A. de B., & Gobatto, C. A. (2017). Relationship between anaerobic capacity estimated using a single effort and 30-s tethered running outcomes. *PLOS ONE*, *12*(2), e0172032. https://doi.org/10.1371/journal.pone.0172032

Zawieja, E. E., Zawieja, B., & Chmurzynska, A. (2021). Betaine Supplementation Moderately Increases Total Cholesterol Levels: A Systematic Review and Meta-Analysis. *Journal of Dietary Supplements*, *18*(1), 105–117. https://doi.org/10.1080/19390211.2019.1

Datos de los/as autores/as y traductor/a:

Larissa Torres Fernandes	farm.larissatorresfernandes@gmail.com	Autor/a
Deysimara de Cássia Santos	deysimara16@gmail.com	Autor/a
Lucas Teixeira Marques	lucastmarques@yahoo.com	Autor/a
Danielle Negri Ferreira Neves	danielle.negri@ufjf.br	Autor/a
Otávio de Toledo Nóbrega	otnobrega@gmail.com	Autor/a
Mariana de Melo Cazal	mariana.cazal@ufjf.br	Autor/a
Carina Carvalho Silvestre	silvestre.carina@ufjf.br	Autor/a
Ciro José Brito	cirojbrito@gmail.com	Autor/a
Christopher James Quinn	englishconsultingbrazil@gmail.com	Traductor/a

3 CONCLUSÃO GERAL

A revisão sistemática indica que a betaína pode ser um potencial recurso ergogênico nutricional promotor de redução da fadiga muscular na prática de exercícios físicos, principalmente em exercícios de *leg press* ou agachamento, proporcionando o maior número de repetições no teste de 1-RM. Ainda, a betaína parece favorecer o maior número de repetições no teste de 1-RM para exercícios de supino e a redução dos níveis de lactato sanguíneo. Vale ressaltar, esta é a primeira revisão sistemática que investiga a influência da suplementação de betaína na fadiga muscular durante o exercício. Contudo, esses resultados são considerados preliminares, devido ao número reduzido de estudos incluídos e a falta de estudos que investigassem diretamente a fadiga muscular.

A presente revisão ajudou a identificar as lacunas existentes sobre a suplementação com betaína e a fadiga muscular durante a prática de exercícios físicos, estimulando a realização de novos estudos que investiguem, principalmente, o efeito da suplementação de betaína de forma direta na fadiga muscular, com ensaios clínicos mais robustos e menor fragilidade metodológica. Assim, demostrando a necessidade de estudos que avaliem os níveis de lactato sanguíneo correlacionado com as concentrações séricas de betaína, que melhor descrevam o controle nutricional dos participantes a fim de evitar viés proveniente da alimentação, estudos que descrevam a padronização em relação aos métodos de execução do teste de 1-RM, e estudos com diferentes populações.

REFERÊNCIAS GERAIS

1. ABREU, Rodrigo et al. Effects of dietary supplements on athletic performance in elite soccer players: a systematic review. **Journal of the International Society of Sports Nutrition**, v. 20, n. 1, p. 2236060, 2023.

2. AGUINAGA-ONTOSO, Ines *et al.* Effects of Nutrition Interventions on Athletic Performance in Soccer Players: A Systematic Review**. Life**, v. 13, n. 6, p. 1271, 2023.

3. ALVARENGA, L *et al.* O papel da betaína em pacientes com doença renal crônica: uma revisão narrativa. **Curr Nutr Rep** v.11, p 395–406, 2022.

4. ALVES, Deborah; PORTELA, Felipe Augusto Sousa; COSTA, Flávia Nunes. Suplementação alimentar orientada para atletas: uma revisão integrativa. **Research, Society and Development**, v. 11, n. 16, p. e125111638086-e125111638086, 2022.

5. ARAZI, Hamid *et al.* Effects of short-term betaine supplementation on muscle endurance and indices of endocrine function following acute high-intensity resistance exercise in young athletes. **Journal of the International Society of Sports Nutrition**, v. 19, n. 1, p. 1–16, 2022.

6. ASHTARY-LARKY, Damoon *et al.* Effects of betaine supplementation on cardiovascular markers: A systematic review and Meta-analysis. **Critical Reviews in Food Science and Nutrition**, v. 62, n. 23, p. 6516–6533, 2022.

7. CHOLEWA, Jason Michael.; GUIMARAES-FERREIRA, Lucas; ZANCHI, Nelo Eidy. Effects of betaine on performance and body composition: a review of recent findings and potential mechanisms. **Aminoácidos** , v. 46, p. 1785-1793, 2014.

8. CHOLEWA, Jason Michael *et al.* The effects of chronic betaine supplementation on body composition and performance in collegiate females: a double-blind, randomized, placebo-controlled trial. **Journal of the International Society of Sports Nutrition**, v. 15, n. 1, 2018.

9. CHOLEWA, Jason Michael. et al. An overview of betaine supplementation, sports performance, and body composition. **Nutrition and Enhanced Sports Performance**, p. 691-706, 2019.

10. DEL FAVERO, Serena Menegassi**. Efeitos da suplementação de betaína, combinada ou não com a suplementação de creatina, sobre a força máxima, potência e concentrações intramusculares de fosforilcreatina, em indivíduos não treinados em força.** 2012. Tese de Doutorado. Universidade de São Paulo.

11. DOBRIJEVIĆ, Dejan *et al.* Betaine as a Functional Ingredient: Metabolism, Health-Promoting Attributes, Food Sources, Applications and Analysis Methods. **Molecules,** v. 28, n. 12, p. 4824, 2023.

12. DOS SANTOS, Artur Bonezi et al. Aspectos biomecânicos e Fisiológicos da fadiga na locomoção humana: conceitos, mecanismos e aplicações. 2010.

13. FREITAS, Hércules Rezende; BARBOSA, Myleide; RAMOS, Thaynan da Silva. O papel da suplementação de betaína na atividade física: uma revisão sistemática. **Nutrire,** v. 40, n. 2, p. 246–260, 2015.

14. GAO, Xiang *et al.* Effect of Betaine on Reducing Body Fat—A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Nutrients**, v. 11, n. 10, p. 2480, 2019.

15. HORIZON DATABASE. Sports Nutrition Market Size, Share & Trends Analysis Report By Product Type (Sports Supplements, Sports Drinks), By Formulation, By Consumer Group, By Sales Channel, By Region, And Segment Forecasts, 2024 – 2030. Disponível em: https://www.grandviewresearch.com/industry-analysis/sports-nutrition-market .Acesso em 24 de agosto de 2024.

16. HOFFMAN, Jay R *et al.* Effect of 15 Days of Betaine Ingestion on Concentric and Eccentric Force Outputs During Isokinetic Exercise. **Journal of Strength and Conditioning Research**, v. 25, n. 8, p. 2235–2241, 2011

17. ISMAEEL, Ahmed. Effects of Betaine Supplementation on Muscle Strength and Power: A Systematic Review. **Journal of Strength and Conditioning Research**, v. 31, n. 8, p. 2338–2346, 2017.

18. KAUR, Satinder et al. A review on pharmacological activities of betaine. **Plant Arch**, v. 19, p. 1021-1034, 2019.

19. LÓPEZ-TORRES, Olga et al. Ergogenic aids to improve physical performance in female athletes: a systematic review with meta-analysis. **Nutrients,** v. 15, n. 1, p. 81, 2022.

20. FERNANDES Torres, Larissa *et al*. Betaine as an Ergogenic Aid to Improve Muscle Fatigue in Physical Exercise: A Systematic Review of Randomized Clinical Trials. **Retos**, *[S. l.]*, v. 62, p. 341–349, 2025. Disponível em: https://recyt.fecyt.es/index.php/retos/article/view/108391. Acesso em: 18 nov. 2024.

21. MACHEK, Steven B *et al.* The Impacts of Combined Blood Flow Restriction Training and Betaine Supplementation on One-Leg Press Muscular Endurance, Exercise-Associated Lactate Concentrations, Serum Metabolic Biomarkers, and Hypoxia-Inducible Factor-1α Gene Expression. **Nutrients,** v. 14, n. 23, p. 5040, 2022.

22. MOLIN, Thaís Ramos Dal *et al.* Marco regulatório dos suplementos alimentares e o desafio à saúde pública. **Revista de Saúde Pública**, v. 53, p. 90, 2019.

23. SANTOS, Raynara Fonsêca dos; FREITAS JÚNIOR, William Monteiro de; ARAÚJO, Rogério Olmedija de. Avaliação do índice de fadiga muscular de flexores e extensores de joelho em indivíduos ativos e sedentários**. Revista Brasileira de Ciências do Esporte**, v. 42, p. e2008, 2020.

24. VERSCHUEREN, Jo *et al.* The interaction of acute physical fatigue with three traditional functional performance tests and the reactive balance test. **Physical therapy in sport**, v. 49, p. 188–195, 2021.

25. WALDMAN, Hunter S; BRYANT, Andrea R; MCALLISTER, Matthew J. Effects of Betaine Supplementation on Markers of Metabolic Flexibility, Body Composition, and Anaerobic Performance in Active College-Age Females. **Journal of Dietary Supplements**, v. 20, n. 1, p. 89–105, 2023.

26. XU, Jiaoyang *et al.* Effects of betaine supplementation on inflammatory markers: a systematic review and meta-analysis of randomised controlled trials. **International Journal of Food Sciences and Nutrition**, v. 74, n. 7, p. 721–729, 2023.

27. YANG, Ming-Ta *et al.* Effects of Two-Week Betaine Supplementation on Apoptosis, Oxidative Stress, and Aerobic Capacity after Exhaustive Endurance Exercise. **Antioxidants,** v. 9, n. 12, p. 1189, 2020.

28. ZAWIEJA, Emilia E; ZAWIEJA, Bogna; CHMURZYNSKA, Agata. Betaine Supplementation Moderately Increases Total Cholesterol Levels: A Systematic Review and Meta-Analysis. **Journal of Dietary Supplements**, v. 18, n. 1, p. 105–117, 2021.

APÊNDICE A – Material suplementar do artigo

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Lines 1-2 title page/ Line 26-27 pages 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstract's checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Lines 94-101 pages 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Lines 101-103 pages 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Lines 129-138 pages 5 and 6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Lines 115-118 pages 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Lines 112-115 pages 5

Topic	No.	Item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 122-128 pages 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Lines 141-150 pages 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Lines 144-150 pages 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	No applied
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 153-164 pages 6 e 7

Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	No applied

Topic	No.	Item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Lines 141-150 pages 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	No applied
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Lines 141-150 pages 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	No applied
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	No applied
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	No applied
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	No applied

Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Lines 167-168 pages 7
RESULTS			

Topic	No.	Item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Lines 190-199 pages 8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	The PRISMA flow diagram (Figure 1), pages 23
Study characteristics	17	Cite each included study and present its characteristics.	Lines 190-199 pages 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Lines 226-239 pages 9-10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	No applied
Results of syntheses	20a	For each synthesis, briefly summaries the characteristics and risk of bias among contributing studies.	Lines 226-239 pages 9-10

	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	No applied
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	No applied
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	No applied

Topic	No.	Item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	No applied
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Lines 243-250 pages 10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Lines 253-329 pages 11-14
	23b	Discuss any limitations of the evidence included in the review.	Liness 330-346 pages 14
	23c	Discuss any limitations of the review processes used.	Lines 330-346 pages 14
	23d	Discuss implications of the results for practice, policy, and future research.	Lines 347-349 pages 14
OTHER INFORMATION			

Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Lines 108-109 pages 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Lines 108-109 pages 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No applied
Support	25	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review.	Lines 369-370 pages 15
Competing interests	26	Declare any competing interests of review authors.	Lines 373-374 pages 15
Topic	**No.**	**Item**	**Location where item is reported**
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Indicated throughout the text (supplementary material)

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			

Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summaries relevant characteristics of studies.	Yes
Topic	**No.**	**Item**	**Reported?**
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favored).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Search strategies used in the databases

Search date: March 12, 2024

Databases	Search strategy
PubMed (n=8)	**#1**("Betaine"[MeSH Terms]) OR ("Betaine"[Title/Abstract])
	#2((((((("Fatigue"[Mesh]) OR ("Fatigue"[Title/Abstract])) OR ("Muscle Fatigue"[Mesh])) OR ("Muscle Fatigue"[Title/Abstract])) OR ("Muscle Fatigue"[Title/Abstract])) OR ("Fatigue, Muscular"[Title/Abstract])) OR ("Fatigue, Muscle"[Title/Abstract])
	#3((((((((((((((((((((((((("exercise"[MeSH Terms]) OR ("exercise"[Title/Abstract])) OR ("exercises"[Title/Abstract])) OR ("Physical Activity"[Title/Abstract])) OR ("Activities, Physical"[Title/Abstract])) OR ("Activity, Physical"[Title/Abstract])) OR ("Physical Activities"[Title/Abstract])) OR ("Exercise, Physical"[Title/Abstract])) OR ("Exercises, Physical"[Title/Abstract])) OR ("Physical Exercise"[Title/Abstract])) OR ("Physical Exercises"[Title/Abstract])) OR ("Acute Exercise"[Title/Abstract])) OR ("Acute Exercises"[Title/Abstract])) OR ("Exercise, Acute"[Title/Abstract])) OR ("Exercises, Acute"[Title/Abstract])) OR ("Exercise, Isometric"[Title/Abstract])) OR ("Exercises, Isometric"[Title/Abstract])) OR ("Isometric Exercises"[Title/Abstract])) OR ("Isometric Exercise"[Title/Abstract])) OR ("Exercise, Aerobic"[Title/Abstract])) OR ("Aerobic Exercise"[Title/Abstract])) OR ("Aerobic Exercises"[Title/Abstract])) OR ("Exercises, Aerobic"[Title/Abstract])) OR ("Exercise Training"[Title/Abstract])) OR ("Exercise Trainings"[Title/Abstract])) OR ("Training, Exercise"[Title/Abstract])) OR ("Trainings, Exercise"[Title/Abstract])
	#4 #1 AND #2 AND #3

Cochrane Library (n= 9)	**#1** #1betaine #2Fatigue #3Muscle Fatigue #4Fatigue, Muscular #5Fatigue, Muscle #6exercise #7Exercises #8Physical Activity #9Activities, Physical #10Activity, Physical #11Physical Activities #12 Exercise, Physical #13Exercises, Physical #14Physical Exercise #15Physical Exercises #16Acute Exercise #17Acute Exercises #18Exercise, Acute #19Exercises, Acute #20Exercise, Isometric #21Exercises, Isometric #22Isometric Exercises #23Isometric Exercise #24 Exercise, Aerobic #25Aerobic Exercise #26Aerobic Exercises 27#Exercises, Aerobic Exercise Training #28Exercise Trainings #29Training, Exercise #30Trainings, Exercise
	#2(#1) AND (#2 OR #3 OR #04 OR #5) AND (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
Web of Science (n = 7)	**#1**betaine (Title) and betaine (Title) and betaine (Abstract)
	#2(((ALL=("Fatigue")) OR ALL=("Muscle Fatigue")) OR ALL=(“Fatigue, Muscular”)) OR ALL=(“Fatigue, Muscle”)
	#3((((((((((((((((((((((((((ALL=("exercise")) OR ALL=(“Exercises”)) OR ALL=(“Physical Activity”)) OR ALL=(“Activities, Physical”)) OR ALL=(“Activity, Physical”)) OR ALL=(“Physical Activities”)) OR ALL=(“Exercise, Physical”)) OR ALL=(“Exercises, Physical”)) OR ALL=(“Physical Exercise”)) OR ALL=(“Physical Exercises”)) OR ALL=(“Acute Exercise”)) OR ALL=(“Acute Exercises”)) OR ALL=(“Exercise, Acute”)) OR ALL=(“Exercises, Acute”)) OR ALL=(“Exercise, Isometric”)) OR ALL=(“Exercises, Isometric”)) OR ALL=(“Isometric Exercises”)) OR ALL=(“Isometric Exercise”)) OR ALL=(“Exercise, Aerobic”)) OR ALL=(“Aerobic Exercise”))
	OR ALL=(“Aerobic Exercises”)) OR ALL=(“Exercises, Aerobic”)) OR ALL=(“Exercise Training”)) OR ALL=(“Exercise Trainings”)) OR ALL=(Training, Exercise)) OR ALL=(Trainings, Exercise)
	#4 #3 AND #2 AND #1
EMBASE (n = 14)	**#1** 'betaine'/exp OR 'betaine'
	#2 'fatigue'/exp OR 'fatigue' OR 'muscle fatigue'/exp OR 'muscle fatigue' OR 'fatigue, muscular' OR 'fatigue, muscle'/exp OR 'fatigue, muscle'

	#3 'exercise'/exp OR 'exercise' OR 'exercises' OR 'physical activity'/exp OR 'physical activity' OR 'activities, physical' OR 'activity, physical'/exp OR 'activity, physical' OR 'physical activities' OR 'exercise, physical' OR 'exercises, physical' OR 'physical exercise'/exp OR 'physical exercise' OR 'physical exercises' OR 'acute exercise'/exp OR 'acute exercise' OR 'acute exercises' OR 'exercise, acute' OR 'exercises, acute' OR 'exercise, isometric'/exp OR 'exercise, isometric' OR 'exercises, isometric' OR 'isometric exercises' OR 'isometric exercise'/exp OR 'isometric exercise' OR 'exercise, aerobic'/exp OR 'exercise, aerobic' OR 'aerobic exercise'/exp OR 'aerobic exercise' OR 'aerobic exercises' OR 'exercises, aerobic' OR 'exercise training'/exp OR 'exercise training' OR 'exercise trainings' OR 'training, exercise' OR 'trainings, exercise'
	#4 #1 AND #2 AND #3
Scopus (n = 15)	**#1** ALL("Betaine")
	#2 ALL ("fatigue") OR ALL ("muscle fatigue") OR ALL ("fatigue, muscular") OR ALL ("fatigue, muscle")
	#3 ALL ("exercise") OR ALL ("exercises") OR ALL ("physical activity") OR ALL ("activities, physical") OR ALL ("activity, physical") OR ALL ("physical activities") OR ALL ("exercise, physical") OR ALL ("exercises, physical") OR ALL ("physical exercise") OR ALL ("physical exercises") OR ALL ("acute exercise") OR ALL ("acute exercises") OR ALL ("exercise, acute") OR ALL ("exercises, acute") OR ALL ("exercise, isometric") OR ALL ("exercises, isometric") OR ALL ("isometric exercises") OR ALL ("isometric exercise") OR ALL ("exercise, aerobic") OR ALL ("aerobic exercise") OR ALL ("aerobic exercises") OR ALL ("exercises, aerobic") OR ALL ("exercise training") OR ALL ("exercise trainings") OR ALL ("training, exercise") OR ALL ("trainings, exercise")
	#4 #3 AND #2 AND #1

Exclusion criteria

Study	Exclusion criteria
[1] Stratton MT, Siedler MR, Harty PS, Rodriguez C, Boykin JR, Green JJ, et al. The influence of caffeinated and noncaffeinated multi-ingredient pre-workout supplements on resistance exercise performance and subjective outcomes. J Int Soc Sports Nutr. 2022;19:126–49.	Intervention
[2] Battillo DJ, Malin SK. Impact of Caloric Restriction and Exercise on Trimethylamine N-Oxide Metabolism in Women with Obesity. Nutrients. 2023;15:1455.	Intervention

[3] van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen AP, Arents BW. Emollients and moisturisers for eczema. Cochrane Database of Systematic Reviews. 2017;2020.	Intervention
[4] Ortega MA, Alvarez-Mon MA, García-Montero C, FraileMartinez O, Guijarro LG, Lahera G, et al. Gut Microbiota Metabolites in Major Depressive Disorder—Deep Insights into Their Pathophysiological Role and Potential Translational Applications. Metabolites. 2022;12:50.	Intervention
[5] Kistner S, Rist MJ, Krüger R, Döring M, Schlechtweg S, Bub A. High-Intensity Interval Training Decreases Resting Urinary Hypoxanthine Concentration in Young Active Men—A Metabolomic Approach. Metabolites. 2019;9:137.	Intervention
[6] Ostojic SM. Guanidinoacetic acid as a performanceenhancing agent. Amino Acids. 2016;48:1867–75.	Intervention
[7] Kedia AW, Hofheins JE, Habowski SM, Ferrando AA, Gothard MD, Lopez HL. Effects of a Pre-workout Supplement on Lean Mass, Muscular Performance, Subjective Workout Experience and Biomarkers of Safety. Int J Med Sci. 2014;11:116–26.	Intervention
[8] Kraemer WJ, Hatfield DL, Spiering BA, Vingren JL, Fragala MS, Ho J-Y, et al. Effects of a multi-nutrient supplement on exercise performance and hormonal responses to resistance exercise. Eur J Appl Physiol. 2007;101:637–46.	Intervention
[9] Mofrad PS, SAJ. Gastroenterology Expert Column - Nonalcoholic fatty liver disease. Medgenmed Medscape Gen Med . 2003;5:2.	Intervention
[10] Duarte D, Castro B, Pereira JL, Marques JF, Costa AL, Gil AM. Evaluation of Saliva Stability for NMR Metabolomics: Collection and Handling Protocols. Metabolites. 2020;10:515.	Intervention
[11] Dror Y, Rimon E, Vaida R. Whole-Wheat Bread for Human Health. Cham: Springer International Publishing; 2020.	Intervention
[12] Chen H, Ma X, Cao L, Zhao S, Zhao C, Yin S, et al. A Multi-Ingredient Formula Ameliorates Exercise-Induced Fatigue by Changing Metabolic Pathways and Increasing Antioxidant Capacity in Mice. Foods. 2021;10:3120.	Population
[13] Warren LLLTKN. The influence of betaine on untrained and trained horses exercising to fatigue. J Anim Sci. 1999;77:677–84.	Population
[14] Banks Q, Pratt SJP, Iyer SR, Lovering RM, HernándezOchoa EO, Schneider MF. Optical Recording of Action Potential Initiation and Propagation in Mouse Skeletal Muscle Fibers. Biophys J. 2018;115:2127–40.	Population

[15] Andras A, Stansby G, Hansrani M. Homocysteine lowering interventions for peripheral arterial disease and bypass grafts. Cochrane Database of Systematic Reviews. 2013	Study design
[16] de Souza RAS, da Silva AG, de Souza MF, Souza LKF, Roschel H, da Silva SF, et al. A Systematic Review of CrossFit® Workouts and Dietary and Supplementation Interventions to Guide Nutritional Strategies and Future Research in CrossFit®. Int J Sport Nutr Exerc Metab. 2021;31:187–205.	Study design
[17] Pasumarthy L, Srour J. Nonalcoholic Steatohepatitis: A Review of the Literature and Updates in Management. South Med J. 2010;103:547–50.	Study design
[18] Iles R. Nuclear Magnetic Resonance Spectroscopy and Genetic Disorders. Curr Med Chem. 2008;15:15–36.	Study design
[19] Moreira L de SG, Fanton S, Cardozo L, Borges NA, Combet E, Shiels PG, et al. Pink pressure: beetroot (*Beta vulgaris rubra*) as a possible novel medical therapy for chronic kidney disease. Nutr Rev. 2022;80:1041–61.	Study design
[20] Kedia AW, Hofheins JE, Habowski SM, Ferrando AA, Gothard MD, Lopez HL. Effects of a Pre-workout Supplement on Lean Mass, Muscular Performance, Subjective Workout Experience and Biomarkers of Safety. Int J Med Sci. 2014;11:116–26.	Intervention and study design
[21] Guasch-Ferre MHFR-CMBMYEZYTEWDHACD et al. Gut microbiota related plasma metabolites and risk of cardiovascular disease in the PREDIMED study. Circulation . 2017;135.	Intervention and study design
[22] Smith S, Rowbotham NJ. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. Cochrane Database of Systematic Reviews. 2022;2022.	Intervention and study design
[23] Christoffers WA, Coenraads P-J, Svensson Å, Diepgen TL, Dickinson-Blok JL, Xia J, et al. Interventions for hand eczema. Cochrane Database of Systematic Reviews. 2019;2019.	Intervention and study design
[24] Elsheikh E, Henry LL, Younossi ZM. Current management of patients with nonalcoholic fatty liver disease. Expert Rev Endocrinol Metab. 2013;8:549–58.	Population and study design
[25] Li Z-Y, He P, Sun H-F, Qin X-M, Du G-H. ^{1}H NMR based metabolomic study of the antifatigue effect of Astragali Radix. Mol BioSyst. 2014;10:3022–30.	Population and study design
[26] Chen H, Ma X, Cao L, Zhao S, Zhao C, Yin S, et al. A Multi-Ingredient Formula Ameliorates Exercise-Induced Fatigue by Changing Metabolic Pathways and Increasing Antioxidant Capacity in Mice. Foods. 2021;10:3120.	Population and study design

[27] Chen H, Ma X, Cao L, Zhao S, Zhao C, Yin S, et al. A Multi-Ingredient Formula Ameliorates Exercise-Induced Fatigue by Changing Metabolic Pathways and Increasing Antioxidant Capacity in Mice. Foods. 2021;10:3120.	Population and study design
[28] 28. Tan L-C, Yang W-J, Fu W-P, Su P, Shu J-K, Dai LM. ^{1}H-NMR-based metabolic profiling of healthy individuals and high-resolution CT-classified phenotypes of COPD with treatment of tiotropium bromide. Int J Chron Obstruct Pulmon Dis. 2018;Volume 13:2985–97.	Population, study design and intervention

ANEXO A- Instruções aos autores preconizadas pelo periódico

Link de acesso: https://recyt.fecyt.es/index.php/retos/envios

Normas para autores

Normas generales de publicación

1.Los autores deben certificar que sus manuscritos son su obra original. Estamos especialmente sensibilizados por los plagios o autoplagios. Los revisores utilizarán los diferentes programas para detección de plagio a lo largo del proceso de evaluación de los textos. Serán sancionados con cinco años sin poder enviar artículos a la revista Retos aquellos autores que inflijan este aspecto. Los autores que hayan utilizado inteligencia artificial, deberán indicar qué aplicaciones y en qué procesos y apartados han sido utilizados. Igualmente, serán retirados todos los artículos publicados por el/los autores implicados.

2.Los autores deben certificar que el manuscrito no ha sido previamente publicado en otra parte.

3.Los autores deben certificar que el manuscrito no está siendo considerado para su publicación en otros lugares.

4.Los autores deben participar en el proceso de revisión por pares; es decir, son los responsables de responder las observaciones, sugerencias y comentarios de los evaluadores del manuscrito.

5.Los autores están obligados a proporcionar retractaciones o correcciones de errores.

6.Todos los autores mencionados en el documento deben haber contribuido de manera significativa a la investigación.

7.Los autores deben declarar que todos los datos en el documento son reales y auténticos.

8.Los autores deben notificar a los editores de cualquier conflicto de intereses.

9.Los autores deben identificar todas las fuentes utilizadas en la creación de su manuscrito.

10.Los autores deben informar de cualquier error que descubren en su artículo publicado a los Editores.

11.Los autores conocen la tarifa de publicación para una revisión normal que se encuentra aquí: https://recyt.fecyt.es/index.php/retos/Cuota Por tanto, la aceptan pagar en el caso de ser aceptado el artículo.

Remisión de manuscritos

En la actualidad, Retos solamente acepta manuscritos remitidos para su evaluación a través de la plataforma web de Retos, dejando sin efecto la remisión en papel o por correo electrónico, y que sigan correctamente las Normas de Publicación.

Para remitir un manuscrito a Retos es necesario registrarse e identificarse en la plataforma como autor, así como para llevar a cabo el seguimiento del estado de su manuscrito. Todo manuscrito enviado para su consideración a Retos debe ir acompañado de una carta al editor (que se adjuntará como archivo complementarios), firmada por los autores, en la que se indicará:

- El manuscrito es original y no ha sido publicado previamente, completo o en parte, o en otro idioma, ni está siendo considerado para publicación en otra revista.
- Si ha existido financiación relacionada con el trabajo plasmado en el manuscrito, así se indica en el texto.
- Que todos los autores han leido el texto, son co-responsables, y que la autoría es compartida por todos.
- Que se han cumplido los principios éticos y deontológicos en relación a las personas participantes en el estudio remitido.
- Que la correspondencia referente al manuscrito remitido se realizará con el autor de la correspondencia del que se indicará el nombre, dirección completa postal, teléfono y correo electrónico, y que será esta persona la encargada de mantenerse en contacto con los demás autores para la revisión y aprobación final del artículo.
- Las principales razones y motivos por las que los autores creen que el manuscrito debería ser publicado en Retos.

Normas específicas de publicación

1. ***"Retos"*** publica trabajos que estén realizados con rigor metodológico y que supongan una contribución al progreso de cualquier ámbito de la actividad físico-deportiva científica, en alguna de las siguientes secciones:
   - De carácter científico: trabajos de investigaciones básicas y/o aplicadas.
   - Divulgación y/o experiencias didácticas empíricas. Intercambio de propuestas y experiencias desarrollas e investigadas.
   - Revisiones sistemáticas cuantitativas y/o metaanálisis, exclusivamente.

Debe tenerse en cuenta que según los criterios de **calidad de revistas** asumidos por nuestra revista desde 2006, el porcentaje de artículos de revisiones teóricas, sobre el total publicado por número, no podrá ser superior al 25%, es decir, al menos el 75% deben ser artículos originales que comunican resultados de investigación. Igualmente, al menos el 80% de los autores deberán serán externos al comité editorial y virtualmente ajenos a la organización editorial de la revista.

2. **Los trabajos serán originales e inéditos**, no admitiéndose aquellos que hayan sido publicado total o parcialmente, ni los que están en proceso de publicación o hayan sido presentados a otra revista para su valoración. Se asume que todas las personas que figuran como autores han dado su conformidad y que cualquier persona citada como fuente de comunicación personal consiente tal citación. Es responsabilidad de los autores las posibles anomalías o plagios que de ello se derive. Estamos especialmente sensibilizados por los plagios o autoplagios. Los revisores utilizarán los diferentes programas para detección de plagio a lo largo del proceso de evaluación de los textos. Serán sancionados con cinco años sin poder enviar artículos a la revista Retos aquellos autores que inflijan este aspecto. Los autores que hayan utilizado inteligencia artificial, deberán indicar qué aplicaciones y en qué procesos y apartados han sido utilizados. Igualmente, serán retirados todos los artículos publicados por el/los autores implicados.

Por esta razón, se exigirá que se envíe junto al artículo una **certificación** fechada y firmada por el autor principal, donde se indique expresamente que el artículo que se adjunta es original, inédito, no ha sido publicado y no está siendo examinado por ninguna otra revista o publicación. Del mismo modo, que se ostenta la legítima titularidad de uso sobre todos los derechos de propiedad intelectual e industrial correspondientes al artículo. Igualmente, que se aceptan las normas de publicación y que se solicita la evaluación del artículo por el Comité Editorial/Científico de «Retos» para su publicación.

Se deberán indicar tres posibles revisores que sean especialistas en el tema sobre el versa el artículo, distintos de la institución a la que pertenece el autor/es y externos al Comité Científico de la revista Retos. Es necesario incluir nombre, institución y e-mail de contacto de los revisores propuestos.

3. **Deberán escribirse en un lenguaje claro y directo**, sin notas a pié de página, estando mecanografiados en hojas DIN-A-4 por una sola cara, con letra tipo Times New Roman y tamaño 12 puntos, interlineado sencillo, con márgenes superior, inferior, derecha e izquierda de 3 cm, numeración en la parte superior derecha y líneas de página. Los títulos, apartados y subapartados se pondrán en negrita y nunca en mayúsculas. Para el inicio de cada párrafo se sangrará con 0,5 cm.

Los trabajos, elaborados en formato Word para PC, tendrán una extensión aproximada de 7.500 palabras (es orientativo). Previa solicitud y autorización del Consejo de Redacción, podrá tener el artículo una extensión superior a la indicada.

4. Los manuscritos constarán de las siguientes partes:

A. En la primera página se incluirá: **título** (idioma original del artículo e inglés, en minúsculas, sin cursiva, ni negrita –cuando el idioma original sea inglés, francés o portugués deberá ir también en español-), un **resumen** (idioma original del artículo e inglés, en minúsculas, sin cursiva, ni negrita –cuando el idioma original sea inglés, francés o portugués deberá ir también en español-) que tendrá una extensión mínima de 150 palabras y máxima de 250, que deberá reflejar el objetivo del estudio, el método, los resultados más destacados y principales conclusiones. Al pie de cada resumen se especificarán de cinco a ocho **palabras clave** (idioma original del artículo e inglés, en minúsculas, sin cursiva, ni negrita –cuando el idioma original sea inglés, francés o portugués, deberá ir también en español-), que aludan al contenido del trabajo, las cuales deben ser extraídas de tesauros o clasificaciones propias del ámbito de la actividad física y del deporte. El idioma con el que se presentará el trabajo será español, inglés, francés ó portugués.

B. A continuación, a partir de la **segunda página**, figurará el **texto** completo del artículo. En el caso de utilizar siglas, éstas deberán ser explicadas entre paréntesis la primera vez que aparezcan en el texto.

5. **Todas las tablas, figuras, gráficos, …** deben ponerse en el interior del texto, en el lugar que los autores consideran que deben ir. Para su elaboración se seguirán las normas de publicación de la APA (Publication Manual of the American Psychological Association, 2009, 7ª edición).

Las tablas deberán llevar numeración y título en la parte superior de las mismas, en la primera línea en letra normal Tabla y su número correspondiente, un la siguiente línea deberá ir el título de la tabla en cursiva. En el caso de utilizar abreviaturas, se deberán aclarar a pie de tabla o figura.Las figuras deberán llevar la numeración y título en la parte inferior. En el caso de no ser originales, aún siendo del mismo autor, se deberá reseñar también su procedencia y referencia bibliográfica. Las tablas y figuras se numerarán consecutivamente en el texto según su ubicación (tabla 1 o figura 1), respetando una numeración correlativa para cada tipo. Deberán ser compuestas por los autores del modo definitivo como deseen que aparezcan, evitar colores siempre que sea posible. Su tamaño tendrá una base de 7 ó 14 cm y deberán de ser legibles las letras y signos que en ellas aparezcan, evitando espacios vacíos y aprovechando al máximo el espacio ocupado. La manera aproximada de calcular el espacio ocupado por las tablas y figuras sigue la equivalencia de dos figuras de 14 x 20 cm. es igual a una página impresa de «Retos» y a una página y media de texto a interlineado espacio.

6. **En el caso de las fotografías**, su tamaño tendrá una base de 7 ó 14 cm y una altura máxima de 20 cm y se deberán enviar en archivo a parte, en formato jpg o similar, ya que pueden existir problemas con la publicación de imágenes obtenidas de Internet, o entregadas en archivos de imagen que no den buena calidad a la hora del proceso de impresión, en ese caso no serán publicadas. Se recomienda que las fotografías sean originales. Las fotografías reciben el tratamiento de figuras, por lo que el autor deberá atenerse a las normas establecidas a tal efecto anteriormente. En las fotografías que aparezcan personas se deberán adoptar las medidas necesarias para que éstas no puedan ser identificadas.

El Consejo de redacción se reserva el derecho a reducir el número de tablas, figuras y fotografías propuestas por el autor si se consideran irrelevantes para la comprensión del texto. En este caso se notificará al autor la decisión tomada.

7. La estructura del texto variará según la sección a que se destine.

A. De carácter científico: trabajos de investigaciones básicas y/o aplicadas. Constará de una *introducción*, que será breve y contendrá la intencionalidad del trabajo: panorama general del tema o problema abordado, estado de la cuestión o revisión de la literatura, laguna

del conocimiento, objetivos y justificación. *Material y método*: se expondrá el material utilizado en el trabajo, sus características, criterios de selección y técnicas empleadas, herramientas, procedimientos y límites de la metodología empleada facilitando los datos necesarios, bibliográficos o directos, para que la experiencia relatada pueda ser repetida por el lector (se da cuenta del qué, cómo, con qué y para qué de la estrategia con la que se resolvió la pregunta de investigación o se llegó a los objetivos). *Resultados*: se relatan, no interpretan, las observaciones efectuadas con el material y método empleados. Estos datos pueden publicarse en detalle en el texto o bien en forma de tablas y figuras, gráficas, esquemas, mapas, etc.; siempre y cuando esté debidamente justificado su uso. *Discusión*: los autores expondrán sus opiniones sobre la base de aquellos resultados, posible interpretación de los mismos, aplicación con los resultados obtenidos por otros autores en publicaciones similares, sugerencias para futuros trabajos sobre el tema, etc. *Conclusiones*. *Agradecimientos*. *Referencias bibliográficas.*

B. Divulgación y/o experiencias didácticas empíricas. Intercambio de propuestas y experiencias desarrollas e investigadas. El texto se dividirá en todos aquellos apartados que consideren los autores necesarios para una perfecta comprensión del tema tratado. Como referencia, se pueden tener en consideración los siguientes apartados: *presentaciónintroducción, contexto, planteamiento didáctico-experiencia, resultados más relevantes (diferenciando entre ventajas y problemáticas surgidas), decisiones de acción para la próxima puesta en práctica, conclusiones, referencias bibliográficas y posibles anexos.*

C. Revisiones teóricas. El texto se dividirá en todos aquellos apartados que consideren los autores necesarios para una perfecta comprensión del tema tratado. A modo de referencia, pueden contener los siguientes apartados: *introducción (antecedentes, estado actual del tema), métidología empleada, resultados, dicusión, conclusiones, aplicaciones prácticas, futuras líneas de investigación, agradecimientos, referencias y tablas/gráficos*.

8. La preparación de los manuscritos ha de atenerse a las normas de publicación de la APA (Publication Manual of the American Psychological Association, 2009, 7ª edición).

Normas APA; los 20 errores más frecuentes en un artículo.

1º) Cuando cite en el texto a dos o más autores entre paréntesis, antes del último se escribe "&", no "y" ni ", y".

2º) No se emplea "y cols." sino ", et al.", que nunca va en cursivas.

3º) Los apellidos de los autores citados van siempre en mayúscula y sólo se cita el primero de sus apellidos (no el nombre o inicial), salvo que el propio autor original los escriba separados por un guión. Las iniciales de los autores sólo se ponen en el listado final de referencias, y no en el texto. 4º) Dentro de una cita en un paréntesis, cada "et al." va precedido siempre de coma. En el texto, fuera de paréntesis, "et al." no va precedido de coma. Además, Para citar un trabajo con uno o dos autores, incluya el nombre del autor(s) en cada citación. Para un trabajo con tres o más autores, incluya solo el nombre del primer autor más "et al." en cada cita, incluida la primera cita. A partir de la segunda cita, se pone el apellido del primero y "et al.".

5º) En la lista de referencias se proporciona el apellido e iniciales del autor hasta con 20 autores inclusive. Cuando haya 21 o más autores, incluya los nombres de los primeros 19 autores, inserte puntos suspensivos (pero no ampersand) y luego agregue el nombre del autor final. 6º) En el texto (no en tablas ni en expresiones matemáticas), desde el número cero hasta el nueve se escribe con letras, no con números. Por ejemplo: no se escribe "*desde los 4 a los 18 años*", sino "*desde los cuatro a los 18 años*".

7º) "kg", "km", "h", etc., al ser abreviaturas, no acaban nunca en punto.

8º) El número cero, antes de un punto decimal, se debe escribir en los números que son menores de 1 cuando el resultado estadístico puede exceder de 1. En caso contrario, NO se debe escribir el número cero antes de una fracción decimal cuando el resultado estadístico no puede exceder de 1. Por ejemplo, resultados de correlaciones, proporciones o nivel de significancia estadística.

9º) Procure emplear sólo abreviaturas conocidas, sin abusar en cuanto a su cantidad en el texto. Cerciórese de que la primera vez que escribe una abreviatura es porque antes ya ha indicado en el texto qué significa.

10º) Cuando cita en un paréntesis dos obras del mismo autor, los años van separados por una coma, no por una "y".

11º) El número de las tablas debe aparecer encima de la tabla escrito en negrilla, sin punto final (e.g., **Tabla 3**). El título de la tabla debe aparecer debajo del número de la tabla escrito en letra cursiva. NO se debe escribir un punto al finalizar el título. El título de las figuras se escribe de la misma manera.

12º) En el listado final de referencias, aunque sólo sean dos, antes del último autor siempre se escribe ", &", y no "y" ni “, y”.

13º) En el listado final de referencias, tras el número de la revista y antes del issue, no va espacio alguno. La revista y su número (entre paréntesis) se escriben en cursiva, el issue y el número de páginas no.

14º) No se debe abusar del empleo de las palabras en cursiva, así como de las expresiones latinas. Las cursivas sólo se emplean la primera vez que se mencionan palabras especiales en otro idioma, como el nombre de un Instrumento (cuestionario) o un título como por ejemplo: *Spalding's Official Basket Ball Guide.* 15º) No debe subrayar en ningún lugar del texto.

16º) En el listado final de referencias, cuando añade una referencia de una revista electrónica, al final de la referencia debe escribir: "Recuperado de" se usan solo cuando la fecha de recuperación es también necesaria. En la escritura de una referencia, la fecha de recuperación debe aparecer antes de la URL. Por ejemplo: Recuperado Mayo 21, 2021, de https://xxxx. Otro ejemplo: Recuperado Abril 18, 2020, de https://xxxx.

17º) Las unidades de millar deben llevar coma. Utilice comas entre grupos de tres dígitos en la mayoría de las cifras de 1,000 o más. Algunas excepciones son las siguientes: números de página (página 1029), dígitos binarios (00110010), números seriales (29046694), grados de temperatura (1440 °C), designaciones acústicas de frecuencia (2000 Hz), grados de libertad (F(24, 1000).

18º) *"p"* (significatividad) va siempre en minúscula y en cursiva.

19º) Debe indicar las páginas exactas de una cita o referencia separadas por un guión. Para indicar varios números de páginas de una cita, debe escribir "pp." y no "p." o “p.p.”. Cuando la página aludida es sólo una, se pone "p." y sin espacio ninguno el número de la página correspondiente.

20º) Para escribir citas de menos de 40 palabras en su texto, encierre la cita en comillas dobles. Proporcione el autor, el año y la página específica de la cita en el texto, e incluya una referencia completa en la lista final de referencias. Signos de puntuación, como puntos, comas y puntos y comas, deben aparecer después del paréntesis de la referencia. Los signos de interrogación y de exclamación deben aparecen dentro de las comillas y son parte de la cita pero después del paréntesis de la referencia si son parte del texto de usted. Ejemplos:

* Textual corta, énfasis en el contenido, un autor.

"Deseaba morirse para alejarse de sí mismo, para no ser él, para encontrar la tranquilidad en el corazón vacío, para permanecer abierto al milagro a través del pensamiento puro" (Hesse, 1990, p.12).

* Textual corta, énfasis en el contenido, más de tres a cinco autores.

"En todos los niveles, la familia es la institución más importante por medio de la cual el sistema de clases se reproduce" (Worsley, et al., 1979, p.147). * Textual corta, énfasis en el contenido, seis o más autores.

"En todos los niveles, la familia es la institución más importante por medio de la cual el sistema de clases se reproduce" (Worsley, et al., 1979, p.147).

* Textual corta, énfasis en el autor.

Rivas (1985) dijo: "Cuando el hombre razona sobre el principio de libertad y ve que su persona está sujeta a normas de conducta no tolerables es cuando empieza a rebelarse" (p.175).

Algunas consideraciones finales

El primer comentario, se refiere a que cada una de las secciones de un artículo se debe escribir en un tiempo verbal específico, que recomienda las normas APA. La información de los tiempos verbales recomendados se ilustra en la Tabla 1.

Tabla 1

Tiempos verbales recomendados en la escritura de documentos

Sección del artículo	Tiempo recomendado	Ejemplo
Introducción	Pasado	Pérez (2020) presentó...
	Presente perfecto*	Algunos investigadores han usado...
Metodología	Pasado	Los participantes completaron una encuesta...
	Presente perfecto*	Otros han usado similares enfoques...
Resultados	Pasado	Los resultados fueron significativos…
Discusión	Presente	Los resultados indican...
Conclusiones	presente	Las limitaciones del estudio son...

Nota. *: el tiempo verbal *presente perfecto* también se conoce con el nombre de tiempo pretérito perfecto compuesto en el idioma Español.

ANEXO B- Protocolo de registro no PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Betaine as an ergogenic resource for improving muscle fatigue in exercisers: systematic review with meta-analysis of randomized clinical trials

Citation

Larissa Torres Fernandes, Danielle Negri Ferreira Neves, Deysimara de Cássia Santos, Lucas Teixeira Marques, Otávio de Toledo Nóbrega, Mariana de Melo Cazal, Carina Carvalho Silvestre, Ciro José Brito. Betaine as an ergogenic resource for improving muscle fatigue in exercisers: systematic review with meta-analysis of randomized clinical trials. PROSPERO 2023 CRD42023469111 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023469111

Review question

Does betaine supplementation improve muscle fatigue during and/or after exercise?

Searches

The database searches took place between October and November 2023.

A comprehensive bibliographic search will be carried out systematically in five databases: PubMed, Cochrane Library, Web of Science, Embase and Scopus.

The search terms that will be used follow the descriptors DeCS/MESH: "betaine and fatigue and exercise", betaine and fatigue and physical activity", betaine and fatigue and physical training", "betaine and lactate and exercise", "betaine and lactate and physical activity", " betaine and lactate and physical training", "betaine and lactic acid and exercise" and "betaine and lactic acid and physical training".

Studies without language restrictions and published between 1995 and 2023 will be considered eligible for review.

Types of study to be included

The type of study used in the review will be a randomized clinical trial (RCT) in humans, parallel or cross-over.

The exclusion criteria will be: duplicate studies, animal studies, studies that were not randomized clinical trials and studies with concomitant use of betaine and other supplements.

Condition or domain being studied

In recent years, the consumption of dietary supplements in conjunction with physical activity has become more popular. Betaine supplementation associated with physical activity has been highlighted in some studies. Betaine is a compound derived from choline found in many foods such as beet, saccharin and spinach. The main mechanisms of action attributed to betaine are its function as an organic osmolyte, a protective agent against the denaturation of intracellular

proteins, a methyl group donor and an increase in serum nitric oxide levels. The ergogenic and clinical effects of betaine are observed from the consumption of 2, 5 grams daily, for an average time of 14 days.Betaine consumption can chronically promote improvements in muscular endurance, modulate endocrine function, and reduce the percentage of fat. In addition, betaine can promote increased anaerobic work, reduced perceived exertion and muscle fatigue. In this context, some studies indicate that betaine supplementation can promote a reduction in muscle fatigue, a greater number of repetitions until muscle fatigue and a serious reduction in post-exercise lactate. However, there is no consensus in the literature on the relationship between betaine supplementation and an improvement in muscle fatigue.

Participants/population

The study population will be individuals of both sexes, aged between 14 and 60, who practice physical exercise.

Intervention(s), exposure(s)

The intervention will be betaine supplementation through physical exercise.

Comparator(s)/control

For comparison purposes, studies that used some kind of placebo will be used as a comparative method in relation to the possible effects of betaine supplementation.

Main outcome(s)

The outcome was improvement in muscle fatigue during and/or after exercise.

Additional outcome(s)

None

Measures of effect

None

Data extraction (selection and coding)

Identification of possible RCTs according to DeSC/MESH search terms.

All possible RCTs will be identified independently by two researchers and entered into the Ryyan review software.

Two researchers will independently assess all the RCTs. In the event of disagreements, these will be discussed by the two authors of the review; when no agreement is reached, a third author will be in charge of deciding.

The following data will be extracted from each study: the name of the first author; year of publication; country; name of the journal; study design; sample size; descriptions of the participants; the interventions used (including type, dose, duration); and the placebo interventions.

Risk of bias (quality) assessment

The risk of bias assessment will be carried out using the Cochrane RoB 2.0 Tool (HIGGINS et al., 2023).

The performance and methods of randomization, the confidentiality of allocation, the extent of blinding (participants, data collectors, outcome assessors and data analysis), incomplete outcome data, selective reporting and other biases will be assessed.

The evaluations will be classified according to the criteria for judging the risk of bias provided by the Cochrane manual (HIGGINS et al. 2023).

Strategy for data synthesis

We will provide a narrative synthesis of the results of the included studies with: age range, gender, number of individuals in the exposed and control population, dose/composition of the supplement administered and periods of administration and timing. The characteristics of the population, the content of the intervention and the outcome measures for each study will be reported.

Studies that meet the inclusion criteria will have their data extracted by two reviewers. Any discrepancies will be resolved, if necessary, by a third reviewer.

If meta-analyses are possible, a random effects meta-analysis will be performed on the change in each outcome. Effect sizes will be presented as mean difference (MD) with means ± SD and 95% CI for fatigue variable. Relevant statistical tests will be used according to the data.

Analysis of subgroups or subsets

- dose

- supplementation time

- number of repetitions until muscle fatigue

Contact details for further information

Larissa Torres Fernandes

larissatorresfernandes@hotmail.com

Organisational affiliation of the review

Universidade Federal de Juiz de Fora

Review team members and their organisational affiliations [2 changes]

Larissa Torres Fernandes. Universidade Federal de Juiz de Fora

Danielle Negri Ferreira Neves. Universidade Federal de Juiz de Fora

Deysimara de Cássia Santos. Universidade Federal de Juiz de Fora

Lucas Teixeira Marques. Universidade Federal de Juiz de Fora

Dr Otávio de Toledo Nóbrega. Universidade de Brasília

Dr Mariana de Melo Cazal. Universidade Federal de Juiz de Fora

Dr Carina Carvalho Silvestre. Universidade Federal de Juiz de Fora

Dr Ciro José Brito. Universidade Federal de Juiz de Fora

Type and method of review

Systematic review

Anticipated or actual start date

25 September 2023

Anticipated completion date [1 change]

30 June 2024

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Brazil

Published protocol

https://www.crd.york.ac.uk/PROSPEROFILES/469111_PROTOCOL_20240607.pdf

Stage of review [1 change]

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

14 October 2023

Date of first submission

03 October 2023

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Correcting authors' orders

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

14 October 2023
14 October 2023
07 June 2024
07 June 2024

ANEXO C- Comprovante de submissão do artigo

Gmail Larissa Torres Fernandes <farm.larissatorresfernandes@gmail.com>

[Retos] Agradecimento pela submissão

1 mensagem

recyt@recyt.fecyt.es <recyt@recyt.fecyt.es> 10 de julho de 2024 às 18:13
Responder a: Francisco Ruiz Juan <retosfeadef@gmail.com>
Para: Larissa Torres Fernandes <farm.larissatorresfernandes@gmail.com>

Larissa Torres Fernandes,

Agradecemos a submissão do seu manuscrito "Betaína como um auxílio ergogênico para melhorar a fadiga muscular no exercício físico: Uma revisão sistemática de ensaios clínicos randomizados" à revista Retos. Através do sistema de gestão editorial online que estamos a utilizar, conseguirá acompanhar o progresso no processo editorial, bastando entrar no sistema disponível em:

URL do Manuscrito: https://recyt.fecyt.es/index.php/retos/authorDashboard/submission/108391
Nome de utilizador: 1larissatorres2

Desde 1° de janeiro de 2024, ativamos um serviço de revisão Express, que consiste em responder à revisão no prazo máximo de 15/20 dias a partir do envio do artigo para revisão. Os autores terão uma decisão editorial, caso tenhamos resposta. dos revisores, enviaremos mais cedo. Os autores que possam ter interesse deverão entrar em contato com o editor da revista, escrevendo uma mensagem para Retosfeadef@gmail.com, para saber as tarifas adicionais deste serviço em um prazo não superior a 48 horas a partir do recebimento desta mensagem. , enviamos imediatamente o manuscrito aos revisores para que seja avaliado pelo procedimento normal.
A revista está sempre atenta ao processo de revisão, a resposta vai demorar dependendo da resposta dos revisores, temos uma média de cerca de dois meses, às vezes um pouco mais de tempo e outras vezes um pouco menos. Informamos isso aos autores para que não fiquem impacientes e não enviem e-mails continuamente para verificar o status do artigo, pois a revista acompanha periodicamente todos os artigos em revisão. Após esse horário, se desejar, entre em contato com a revista para solicitar informações, e não antes.
É muito importante que todos os autores tenham sido inseridos nos metadados; após o envio do artigo para revisão, os autores não poderão ser incluídos ou excluídos a menos que haja justificativa expressa para isso, para evitar más práticas, como algumas que detectamos. Já está claramente especificado nas regras que devem ser respeitadas pelos autores.
Da mesma forma, todos os trabalhos deverão ter a autorização de todas as pessoas que neles tenham participado, e a revista não se responsabilizará pelas más práticas dos autores, deixando de fora as pessoas que trabalharam nas referidas obras ou que foram incluídas sem terem participado ativamente. neles. Caso algo disso seja detectado e comprovado, todos os autores serão punidos com cinco anos sem poder enviar artigos para a revista Retos.
Se você tiver alguma dúvida, não hesite em entrar em contato comigo. Agradecemos por escolher esta revista para divulgar seu trabalho.

Francisco Ruiz Juan

Francisco Ruiz Juan

Director de Retos

retosfeadef@gmail.com