PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
DOUTORADO EM FISIOPATOLOGIA E SAÚDE ANIMAL

EMILI BRUNA TOSO BUENO

Pediococcus acidilactici CE51 E SEUS PÓS-BIÓTICOS: EFEITOS NA INTEGRIDADE INTESTINAL, INFLAMAÇÃO E COMPLICAÇÕES MUSCULARES ASSOCIADAS À DOENÇA INFLAMATÓRIA INTESTINAL

Presidente Prudente – SP
2026

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DEDICATÓRIA

Dedico-o a Deus, fonte de força e sabedoria, sem o qual não teria sido possível trilhar este caminho e concluir esta etapa tão desafiadora.

Aos meus pais, pelo amor incondicional, pelos valores transmitidos e por serem sempre meu alicerce. Ao meu esposo, companheiro de todas as horas, pelo apoio, incentivo e compreensão ao longo dessa jornada.

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“Por vezes sentimos que aquilo que fazemos não é senão uma gota de água no mar. Mas o
mar seria menor se lhe faltasse uma gota.”

Madre Tereza de Calcutá

RESUMO

Pediococcus acidilactici CE51 e seus pós-bióticos: efeitos na integridade intestinal, inflamação e complicações musculares associadas à doença inflamatória intestinal

As doenças inflamatórias intestinais (DII) são condições crônicas caracterizadas por inflamação persistente do trato gastrointestinal, frequentemente associadas a alterações sistêmicas, como disbiose intestinal e comprometimento metabólico. Entre essas complicações, destaca-se a sarcopenia, que impacta negativamente a qualidade de vida e o prognóstico dos pacientes. Nesse contexto, cresce o interesse por estratégias terapêuticas inovadoras, como o uso de probióticos e, mais recentemente, de pós-bióticos, devido ao seu potencial de modulação da microbiota e da resposta inflamatória. Esta tese teve como objetivo geral investigar o potencial terapêutico de *Pediococcus acidilactici* CE51 e de seus pós-bióticos na modulação da inflamação intestinal e de complicações sistêmicas associadas às doenças inflamatórias intestinais (DII), com ênfase na sarcopenia. O Artigo 1, de caráter revisional, teve como objetivo analisar criticamente as evidências científicas sobre o papel dos pós-bióticos derivados de bactérias ácido-láticas no manejo das complicações musculares associadas às DII. A metodologia consistiu em uma revisão narrativa da literatura, abordando estudos experimentais e clínicos relacionados à fisiopatologia da sarcopenia, microbiota intestinal e mecanismos de ação dos pós-bióticos. Os resultados demonstraram que a inflamação crônica intestinal, a disbiose e alterações metabólicas contribuem diretamente para a perda de massa e função muscular, e que, pós-bioticos, como ácidos graxos de cadeia curta, peptídeos bioativos e exopolissacarídeos exercem efeitos anti-inflamatórios, antioxidantes e moduladores do metabolismo muscular, destacando seu potencial na prevenção e atenuação da sarcopenia associada às DII. O Artigo 2 teve como objetivo avaliar os efeitos do probiótico *Pediococcus acidilactici* CE51 e de seu sobrenadante livre de células em modelo experimental de enteropatia induzida por indometacina. Foram utilizados 45 ratos Wistar machos, distribuídos em cinco grupos: CMC (controle – 200 µL/kg), I (indometacina 10 mg/kg), IP (indometacina + probiótico 10^8 UFC), ICFS (indometacina + sobrenadante livre de células 200 µL/kg) e IS (indometacina + sulfassalazina 10 mg/kg). Os animais foram pré-tratados por 28 dias e submetidos à indução inflamatória por 4 dias, totalizando aproximadamente 32

dias de experimento. A inflamação promoveu redução significativa do ganho de peso ($p<0,05$), inflamação intestinal moderada e alterações sistêmicas importantes, incluindo anemia, trombocitopenia e hipoproteinemia. Observou-se aumento expressivo de danos genotóxicos no grupo I, com elevação significativa da frequência de micronúcleos em comparação ao controle ($p<0,05$). Em relação aos tratamentos, os grupos ICFS e IS apresentaram recuperação significativa da contagem de plaquetas ($p<0,05$) e aumento de leucócitos quando comparados ao grupo inflamatório. O grupo IS demonstrou melhora mais pronunciada nos níveis de albumina e proteína total ($p<0,05$), enquanto o grupo ICFS se destacou pela modulação da microbiota intestinal, com aumento significativo de Lactobacillaceae e do gênero *Lactobacillus* ($p<0,05$) e redução de grupos associados à disbiose. Além disso, os grupos tratados (IP, ICFS e IS) apresentaram redução significativa na frequência de micronúcleos em relação ao grupo I ($p<0,05$), com valores próximos ao grupo controle. De forma geral, o sobrenadante livre de células (ICFS) demonstrou maior efeito benefico em comparação ao probiótico, especialmente na modulação da microbiota e na redução de danos sistêmicos, embora sem reversão completa de todas as alterações induzidas. Esses achados reforçam o potencial dos pós-bióticos como alternativa terapêutica mais estável e eficaz, contribuindo para o avanço de estratégias inovadoras no manejo das DII e de suas complicações sistêmicas.

Palavras-chave: Doença inflamatória intestinal; Pós-bióticos; *Pediococcus acidilactici*; Inflamação intestinal; Imunomodulação; Sarcopenia.

ABSTRACT

Pediococcus acidilactici CE51 and its postbiotics: effects on the intestinal integrity, inflammation and muscle complications associated with inflammatory bowel disease

Inflammatory bowel diseases (IBD) are chronic conditions characterized by persistent inflammation of the gastrointestinal tract, often associated with systemic alterations such as intestinal dysbiosis and metabolic impairment. Among these complications, sarcopenia stands out, negatively impacting patients' quality of life and prognosis. In this context, there is a growing interest in innovative therapeutic strategies, such as the use of probiotics and, more recently, postbiotics, due to their potential to modulate the microbiota and the inflammatory response. This thesis aimed to investigate the therapeutic potential of *Pediococcus acidilactici* CE51 and its postbiotics in modulating intestinal inflammation and systemic complications associated with inflammatory bowel diseases (IBD), with emphasis on sarcopenia. Article 1, a review study, aimed to critically analyze the scientific evidence regarding the role of postbiotics derived from lactic acid bacteria in the management of muscle complications associated with IBD. The methodology consisted of a narrative literature review, including experimental and clinical studies related to the pathophysiology of sarcopenia, intestinal microbiota, and mechanisms of action of postbiotics. The results demonstrated that chronic intestinal inflammation, dysbiosis, and metabolic alterations directly contribute to the loss of muscle mass and function, and that metabolites such as short-chain fatty acids, bioactive peptides, and exopolysaccharides exert anti-inflammatory, antioxidant, and muscle metabolism-modulating effects, highlighting their potential in the prevention and attenuation of sarcopenia associated with IBD. Article 2 aimed to evaluate the effects of the probiotic *Pediococcus acidilactici* CE51 and its cell-free supernatant in an experimental model of indomethacin-induced enteropathy. A total of 45 male Wistar rats were used, distributed into five groups: CMC (control – 200 µL/kg), I (indomethacin 10 mg/kg), IP (indomethacin + probiotic 10^8 CFU), ICFS (indomethacin + cell-free supernatant 200 µL/kg), and IS (indomethacin + sulfasalazine 10 mg/kg). The animals were pretreated for 28 days and then subjected to inflammatory induction for 4 days, totaling approximately 32 days of experimentation. Inflammatory

induction resulted in a significant reduction in weight gain ($p<0.05$), moderate intestinal inflammation, and important systemic alterations, including anemia, thrombocytopenia, and hypoproteinemia. A marked increase in genotoxic damage was observed in the I group, with a significant elevation in micronucleus frequency compared to the control ($p<0.05$). Regarding treatments, the ICFS and IS groups showed significant recovery in platelet counts ($p<0.05$) and increased leukocyte levels compared to the inflammatory group. The IS group demonstrated more pronounced improvement in albumin and total protein levels ($p<0.05$), while the ICFS group stood out for its modulation of the intestinal microbiota, with a significant increase in Lactobacillaceae and the genus *Lactobacillus* ($p<0.05$), along with a reduction in dysbiosis-associated groups. Additionally, the treated groups (IP, ICFS, and IS) showed a significant reduction in micronucleus frequency compared to the I group ($p<0.05$), with values close to the control group. Overall, the cell-free supernatant (ICFS) demonstrated greater biological consistency compared to the probiotic, particularly in microbiota modulation and reduction of systemic damage, although without complete reversal of all induced alterations. These findings reinforce the potential of postbiotics as a more stable and effective therapeutic alternative, contributing to the advancement of innovative strategies for the management of IBD and its systemic complications.

Keywords: Inflammatory bowel disease; Postbiotics; *Pediococcus acidilactici*; Intestinal inflammation; Immunomodulation; Sarcopenia.

LISTA DE SIGLAS

AA – Ácido acético

AMPK – Proteína quinase ativada por AMP

DII – Doença inflamatória intestinal

EPS – Exopolissacarídeos

IL-1β – Interleucina-1 beta

IL-10 – Interleucina-10

IL-6 – Interleucina-6

BAL – Bactérias ácido-láticas

mTOR – Alvo mecanístico da rapamicina

AP – Ácido propiônico

PCR – Proteína C-reativa

EROS – Espécies reativas de oxigênio

AGCC – Ácidos graxos de cadeia curta

LISTA DE FIGURAS

ARTIGO 1 – PÓS-BIÓTICOS DERIVADOS DA FERMENTAÇÃO DE BACTÉRIAS DO ÁCIDO LÁTICO: POTENCIAL TERAPÊUTICO NO TRATAMENTO DE COMPLICAÇÕES MUSCULARES EM DOENÇA INFLAMATÓRIA INTESTINAL

LISTA DE TABELAS

ARTIGO 1 - PÓS-BIÓTICOS DERIVADOS DA FERMENTAÇÃO DE BACTÉRIAS DO ÁCIDO LÁTICO: POTENCIAL TERAPÊUTICO NO TRATAMENTO DE COMPLICAÇÕES MUSCULARES EM DOENÇA INFLAMATÓRIA INTESTINAL

SUMÁRIO

IMPACTO POTENCIAL DESSA PESQUISA

Justificativa e Relevância do Estudo

As doenças inflamatórias intestinais (DII) constituem importante problema de saúde pública, caracterizadas por inflamação crônica, disbiose intestinal e comprometimento da mucosa intestinal, frequentemente associadas a complicações sistêmicas, como sarcopenia, osteoporose, doenças cardiovasculares e diminuição da mobilidade. Essas alterações comprometem a qualidade de vida, o prognóstico e a resposta terapêutica dos pacientes. Com isso, o Artigo 1 ressalta a relação entre inflamação, microbiota intestinal e metabolismo muscular, exibindo a necessidade de abordagens terapêuticas mais amplas. O Artigo 2 resalta essa perspectiva ao demonstrar, em modelo experimental, que o pós-biotico apresenta efeitos promissores na modulação da inflamação, microbiota intestinal e danos sistêmicos, sugerindo maior potencial terapêutico em relação ao probiótico. Assim, o estudo contribui para o avanço científico e para o desenvolvimento de novas estratégias terapêuticas aplicáveis às DII e suas complicações sistêmicas.

Conexão com os ODS da ONU

Este estudo relaciona-se principalmente ao ODS 3 - Saúde e Bem-Estar, ao investigar estratégias terapêuticas inovadoras voltadas às DII e suas complicações sistêmicas, colaborando para a melhoria da qualidade de vida e do manejo de doenças crônicas. A utilização de pós-bióticos como alternativa mais segura e estável aos probióticos amplia as possibilidades de intervenções terapêuticas eficazes e acessíveis. O trabalho também se conecta ao ODS 9 - Indústria, Inovação e Infraestrutura, ao explorar abordagens biotecnológicas baseadas em metabólitos bacterianos bioativos. Além disso, relaciona-se ao ODS 12 - Consumo e Produção Responsáveis, devido ao potencial de padronização, estabilidade e maior segurança microbiológica dos pós-bióticos. Portanto, a pesquisa fortalece estratégias científicas alinhadas à inovação em saúde e ao desenvolvimento sustentável.

Impacto Científico

O impacto científico desta tese está na integração entre evidências teóricas

e experimentais sobre o papel dos pós-bióticos na interface intestino–músculo em DII. O Artigo 1 consolida a sarcopenia como complicação frequente e descreve mecanismos envolvendo inflamação crônica, disbiose intestinal e alterações no metabolismo muscular. Inclusive, destaca o potencial dos pós-bióticos derivados de bactérias lácticas na modulação de vias relacionadas à inflamação e metabolismo energético. Inserindo esses achados, o Artigo 2 corrobora que o pós-biotico promove modulação da microbiota intestinal, redução de danos genotóxicos e melhora de parâmetros hematológicos e bioquímicos. Esses resultados fortalecem o potencial terapêutico dos metabólitos bacterianos e ampliam a compreensão sobre estratégias inovadoras para o manejo das DII e suas complicações sistêmicas.

Impacto Social

O impacto social desta pesquisa está relacionado à ampliação do conhecimento sobre as complicações sistêmicas das DII e suas possibilidades terapêuticas. O Artigo 1 destaca que a inflamação crônica e a disbiose intestinal podem comprometer massa e função muscular, afetando qualidade de vida, autonomia e prognóstico dos pacientes. Já o Artigo 2 demonstra que o pós-biotico melhora parâmetros inflamatórios, hematológicos, genotóxicos e da microbiota intestinal em modelo experimental. Esses achados sustentam a evolução de terapias mais seguras, estáveis e acessíveis, favorecendo maior adesão ao tratamento e redução de complicações associadas às DII. Assim, a tese contribui para o fortalecimento de estratégias terapêuticas inovadoras aplicáveis à saúde pública.

Impacto Tecnológico

O impacto tecnológico desta tese evidencia o potencial dos pós-bióticos como base para o desenvolvimento de produtos biotecnológicos voltados à saúde intestinal e sistêmica. O Artigo 1 destaca compostos bioativos derivados de bactérias lácticas, como ácidos graxos de cadeia curta, peptídeos e exopolissacarídeos, associados a propriedades anti-inflamatórias e moduladoras do metabolismo muscular. O Artigo 2 reforça essa proposta ao demonstrar que o pós-biotico apresenta maior estabilidade e eficácia biológica em comparação ao probiótico. Esses resultados possibilitam o desenvolvimento de formulações mais seguras,

padronizáveis e com maior viabilidade industrial. Desse modo, a tese impulsiona aplicações tecnológicas em alimentos funcionais, suplementos e formulações farmacêuticas direcionadas ao manejo das DII e suas complicações sistêmicas.

Impacto em Inovação

O caráter inovador desta tese está na ampliação do uso dos pós-bióticos para além do controle da inflamação intestinal, incluindo sua atuação na interface intestino–músculo no contexto das DII. O Artigo 1 integra mecanismos que relacionam disbiose, inflamação crônica e alterações no metabolismo muscular, propondo os metabólitos bacterianos como potenciais alvos terapêuticos sistêmicos. O Artigo 2 fortalece essa abordagem ao demonstrar que o pós-biotico demonstra desempenho superior ao probiótico íntegro em diferentes parâmetros biológicos. Esses achados reforçam a transição de terapias baseadas em microrganismos vivos para abordagens centradas em metabólitos bioativos, caracterizados por maior estabilidade, previsibilidade e segurança. Assim, a tese contribui para o desenvolvimento de novas estratégias terapêuticas e tecnológicas voltadas à inovação em saúde.

ARTIGO 1 – ARTIGO REVISÃO: PUBLICADO NA REVISTA FERMENTATION

Pós-bióticos Derivados da Fermentação de Bactérias Láticas: Potencial Terapêutico no Tratamento de Complicações Musculares na Doença Inflamatória Intestinal

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Review

Postbiotics Derived from Lactic Acid Bacteria Fermentation: Therapeutic Potential in the Treatment of Muscular Complications in Inflammatory Bowel Disease

Emili Bruna Toso Bueno [1], Kimberlly de Oliveira Silva [2], Maria Eduarda Ferraz Mendes [2], Lívia Batista de Oliveira [1], Felipe Prado de Menezes [3], Anna Cardoso Imperador [3], Lucimeire Fernandes Correia [1] and Lizziane Kretli Winkelstroter [1,2,3,*]

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Abstract

Inflammatory bowel disease (IBD) is characterized by chronic inflammation in the gastrointestinal tract, which can result in several muscular complications, including sarcopenia, the loss of muscle mass, and impaired muscle function. Recently, postbiotics derived from lactic bacteria, such as *Lactobacillus* and *Bifidobacterium*, have emerged as potential therapeutic modulators for these complications. Postbiotics are bioactive metabolites, such as short-chain fatty acids (SCFAs), antimicrobial peptides, and other compounds produced by microorganisms during fermentation, which have anti-inflammatory, antioxidant, and metabolic regulatory effects. These metabolites are important due to their potential to positively influence muscle health in patients with IBD, mainly by reducing systemic and local inflammation, improving gut microbiota, and modulating muscle metabolism. Studies suggest that these postbiotics may help minimize muscle degradation and promote muscle tissue regeneration, assisting in the prevention or management of IBD-associated sarcopenia. Despite the promising results, challenges remain, such as variability in postbiotic production and the need for further clinical studies to establish clear therapeutic guidelines. This review article explores the mechanisms of action of postbiotics derived from lactic acid bacteria and their potential applications in the treatment of muscle complications in patients with IBD, highlighting future therapeutic perspectives.

Keywords: postbiotics; sarcopenia; short-chain fatty acids; bioavailability; inflammation; gut microbiota; muscle mass

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic, progressive, immune-mediated condition characterized by the dysregulation of both innate and adaptive immune responses. The most well-known forms of IBD are Crohn's disease and ulcerative colitis, whose etiologies are complex and involve a combination of genetic, microbial, and environmental factors [1,2]. IBD is thought to arise as a response to an initial insult to the epithelial barrier

Resumo

A Doença Inflamatória Intestinal (DII) é caracterizada por inflamação crônica no trato gastrointestinal, podendo resultar em várias complicações musculares, incluindo sarcopenia, perda de massa muscular e comprometimento da função muscular. Recentemente, pós-bióticos derivados de bactérias lácticas, como *Lactobacillus* e *Bifidobacterium*, têm se destacado como potenciais moduladores terapêuticos para essas complicações. Pós-bióticos são metabólitos bioativos, como ácidos graxos de cadeia curta, peptídeos antimicrobianos e outros compostos produzidos por microrganismos durante a fermentação, que possuem efeitos anti-inflamatórios, antioxidantes e reguladores do metabolismo. Esses metabólitos são importantes devido ao seu potencial de influenciar positivamente a saúde muscular em pacientes com DII, principalmente ao reduzir a inflamação sistêmica e local, melhorar a microbiota intestinal e modular o metabolismo muscular. Estudos sugerem que esses pós-bióticos podem ajudar a minimizar a degradação muscular e favorecer a regeneração dos tecidos musculares, atuando na prevenção ou no manejo da sarcopenia associada à DII. Apesar dos resultados promissores, ainda existem desafios, como a variabilidade na produção de pós-bióticos e a necessidade de mais estudos clínicos para estabelecer diretrizes terapêuticas claras. Este artigo de revisão explora os mecanismos de ação dos pós-bióticos derivados de bactérias lácticas e suas possíveis aplicações no tratamento das complicações musculares em pacientes com DII, destacando suas perspectivas terapêuticas futuras.

1. Introdução

A doença inflamatória intestinal (DII), é uma doença crônica, progressiva e imunomediada que está associada à uma desregulação de respostas imunes inatas e adaptativas. Dentre elas, são bastante conhecidas a doença de Crohn e a colite ulcerativa, as quais possuem grande complexidade etiológica, uma vez que podem incluir desde fatores genéticos, a microbianos e ambientais [1,2].

Acredita-se que a DII é uma resposta a uma agressão inicial à barreira epitelial não curada, localizada em zonas específicas do tecido intestinal, a qual podem estar associados a fatores, como por exemplo: disbiose mediada pela dieta, exposição a compostos químicos, ou a agentes infecciosos [3].

Nos últimos anos, a taxa de prevalência anual de pacientes portadores de DII tem aumentado significativamente [4]. Em um estudo retrospectivo [5] foi observado que dentre 226 pacientes avaliados, cerca de 54 foram confirmados para DII, sendo estes, 44 para colite ulcerativa (19,46%) e 10 para doença de Crohn (4,42%), com distribuição em diferentes faixas etárias em os ambos sexos.

Existem algumas complicações clínicas musculares provenientes da DII, uma vez que ocorrem distúrbios metabólicos e deficiências nutricionais, que podem impactar a função muscular do indivíduo [4]. Mais de um terço de pacientes adultos com DII apresentam miopenia e pré-sarcopenia [6], uma síndrome associada à má absorção de nutrientes pelo intestino delgado. Isto se dá especialmente pelo processo de inflamação que reduz o tempo de contato entre a superfície da mucosa intestinal e os nutrientes, comprometendo a absorção de aminoácidos entre outros compostos [4,7].

Estudos estimam que a incidência de sarcopenia chegam a alcançar até cerca 60% em pacientes com DII, além da redução na taxa de força muscular. Esta, é gerada não apenas pela baixa biodisponibilidade de nutrientes absorvidos, mas por fatores ocasionados pela própria inflamação intestinal [8].

Os altos níveis de citocinas pró-inflamatórias, reduzem a síntese de proteínas e estimulam a formação de espécies reativas de oxigênio que corroboram para uma disfunção muscular [8].

Dentre os tratamentos mais comumente utilizados no controle da DII, estão especialmente o uso de corticosteróides, imunossupressores, ácido 5-amino salicílico (5-ASA), produtos biológicos, e uma dieta adequada [9]. Contudo, é destacada uma grande influência da microbiota intestinal neste processo terapêutico, uma vez que é consolidado na literatura científica os benefícios do uso de cepas probióticas selecionadas na prevenção e tratamento de colite ulcerativa e Doença de Crohn por exemplo [10].

A microbiota intestinal contém uma ampla variedade de bactérias e microrganismos, cerca de mais de 1000 espécies [10]. O seu desequilíbrio está associado ao aparecimento de diversas doenças metabólicas, tornando-se imprescindível, cada vez mais, um maior cuidado na preservação e reposição deste microbioma. Sendo assim, componentes dietéticos funcionais como prebióticos, probióticos e pós-bióticos, vêm ganhando grande visibilidade neste contexto [11].

Prebióticos são fibras não digeríveis, e contribuem seletivamente para o crescimento e atividade de microrganismos benéficos para o intestino, como bactérias das famílias *Lactobacillus, Bifidobacterium e Bacteroides* [10]. Probióticos são organismos vivos utilizados para manter a homeostase intestinal, modulando o sistema imune, e exercendo diversas funções fisiológicas. E por fim, os pós-bióticos são substâncias bioativas, resultantes da interação entre probióticos e prebióticos, por meio da fermentação [12].

Pós-bióticos apresentam maiores vantagens e benefícios quando comparados aos probióticos. Esse fato se deve a sua maior vida útil, menores dificuldades de resfriamento, armazenamento e transporte, além de não serem capazes de compartilhar genes de resistência à antibióticos e fatores de virulência [12].

Bactérias lácticas, como *Lactobacillus, Bifidobacterium,* são as principais precursoras no desenvolvimento dos pós-bióticos. Muito utilizadas no processo de fermentação, como uma estratégia industrial para a obtenção destes subprodutos, sendo encontrados nas formas de ácidos orgânicos, peptídeos e exopolissacarídeos [13].

Nesse contexto, os pós-bióticos apresentam potencial terapêutico nas DII, por suas propriedades anti-inflamatórias, assim como auxiliam no equilíbrio da microbiota intestinal [14]. Entretanto, existem alguns desafios no manejo destes subprodutos, como a grande variabilidade na produção de pós-bióticos, e a necessidade em investigar sua real eficácia terapêutica. Este artigo de revisão tem como objetivo discorrer sobre seus mecanismos de ação, e sua aplicação no tratamento de complicações musculares por DII.

2. Fisiopatologia das Complicações Musculares na Doença Inflamatória Intestinal

A sarcopenia, caracterizada pela perda progressiva de massa muscular esquelética e força, tem se mostrado uma preocupação crescente em pacientes com Doenças Inflamatórias Intestinais (DII), como a Doença de Crohn e a colite ulcerativa. A prevalência de sarcopenia em pacientes com DII é significativamente maior do que em indivíduos saudáveis. Acredita-se que aproximadamente 51% dos pacientes diagnosticados com DII apresentam sinais de perda muscular [15,16]. Em comparação com a população geral, onde a prevalência de sarcopenia varia entre 5 e 13% em pessoas de 60 a 70 anos, os pacientes com DII, possuem

um risco ampliado de desenvolver essa condição, com dados revelando uma prevalência que pode chegar a 65% em alguns grupos [15].

A inflamação sistêmica e localizada desempenha um papel fundamental na degeneração muscular observada em pacientes com DII. A inflamação crônica no intestino ativa uma resposta inflamatória sistêmica, promovendo a liberação de mediadores inflamatórios que impactam diretamente a integridade muscular. Steell et al. [17] destacaram que a inflamação intestinal, característica da DII, resulta em um aumento da permeabilidade intestinal, facilitando a translocação de endotoxinas para a circulação sistêmica. Esse processo agrava a inflamação sistêmica, levando à ativação de vias catabólicas, como a via do NF-kB, que está diretamente envolvida na degradação muscular.

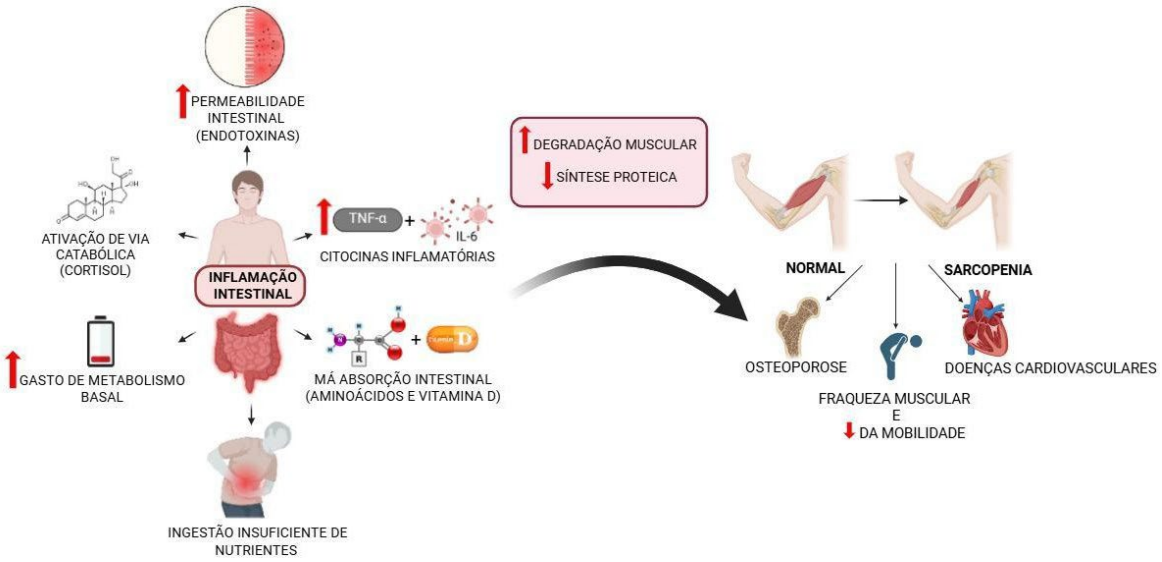

Figura 1. Relação entre doença inflamatória intestinal e sarcopenia.

Além disso, a inflamação crônica resulta em um aumento nos níveis de cortisol, um hormônio catabólico, que é liberado em resposta ao estresse inflamatório. Como discutido por Nishiwaka et al.[4], o aumento do cortisol na circulação favorece a degradação de proteínas musculares e reduz a síntese de proteínas esqueléticas, contribuindo para o desenvolvimento da sarcopenia.

A inflamação local no intestino também aumenta a produção de citocinas como IL-6 e TNF-α, que têm efeito direto no músculo esquelético, promovendo a resistência à síntese proteica e aumentando a degradação muscular [18]. A via proteolítica ubiquitina-proteassoma é uma das principais responsáveis pela degradação da musculatura esquelética em resposta à inflamação, que, por sua vez, é exacerbada pela presença de doenças intestinais crônicas [19]. A perda muscular nos pacientes com DII também é frequentemente associada à resistência à

insulina e o aumento do gasto energético basal, processos que contribuem para o desequilíbrio metabólico que caracteriza essas condições [20].

O aumento do gasto energético basal em pacientes com DII, pode levar a uma catabolização excessiva dos músculos, já que o corpo utiliza a proteína muscular como fonte de energia. Este fenômeno é particularmente preocupante em pacientes desnutridos, que podem ter uma capacidade reduzida de mobilizar reservas de gordura e proteínas para sustentar a função muscular [15].

Somado a isso, a má absorção intestinal, comum em indivíduos com DII, dificulta a obtenção de nutrientes essenciais, como proteínas e aminoácidos, que são fundamentais para a manutenção da massa muscular. A leucina, um aminoácido essencial de cadeia ramificada, tem um papel crucial na ativação da via mTOR, que promove a síntese de proteínas musculares. Em pacientes com DII, a deficiência de leucina é um dos principais fatores que contribui para a perda de massa muscular, uma vez que a ingestão insuficiente desse aminoácido resulta em uma resposta anabólica reduzida nos músculos [20].

Além da leucina, outros nutrientes, como a vitamina D, desempenham um papel importante na saúde muscular e na prevenção da sarcopenia. A vitamina D está envolvida na regulação da função muscular e na promoção da síntese de proteínas musculares, sendo um fator importante na manutenção da massa muscular em pacientes com doenças inflamatórias. Desta forma, a deficiência de vitamina D é comum em pacientes com DII, o que agrava a perda de massa muscular e a fraqueza associada à sarcopenia [15].

A ingestão insuficiente de proteínas também pode estar associada ao quadro clínico desse paciente que apresenta dificuldades para consumir a quantidade adequada devido à dor abdominal, distensão e outros sintomas gastrointestinais. Estudos mostram que aproximadamente 40% dos pacientes idosos com DII não atingem a ingestão diária recomendada de proteínas, o que contribui para a deterioração muscular observada nesses indivíduos [20].

Desta forma, a destruição proteica observada em muitos pacientes com DII compromete ainda mais a capacidade de regeneração muscular, além de estar associada a uma maior taxa de hospitalizações e complicações pós-operatórias [4]. Com a perda de massa muscular e a fragilidade resultante, esses pacientes tornam-se mais vulneráveis a quedas, fraturas e a um risco maior de morte prematura. Portanto, o manejo nutricional desses pacientes deve incluir não apenas a correção das deficiências alimentares, mas também estratégias para melhorar a absorção de nutrientes essenciais.

3. Pós-biótico: Mecanismos de Ação e Benefícios

Os pós-bióticos são compostos bioativos gerados por microrganismos durante processos de fermentação, que podem incluir células inteiras inviáveis, fragmentos celulares, metabólitos ou outras substâncias liberadas. Esses componentes exercem efeitos benéficos à saúde do hospedeiro, de forma semelhante aos probióticos, mas sem a necessidade de que os microrganismos estejam vivos. Assim, os pós-bióticos oferecem benefícios como maior segurança e estabilidade, reduzindo os riscos associados ao consumo de microrganismos viáveis [14, 21–23].

Os pós-bióticos têm sido considerados como intervenção terapêutica para diversas patologias, como para doenças renais, como a hiperoxalúria, doenças oncológicas, como o câncer colorretal, disfunções metabólicas, como a diabetes, doenças inflamatórias, como a artrite reumatoide e a DII e ainda doenças neurodegenerativas [24–28].

Alguns trabalhos ressaltam o benefício dos pós-bióticos. No estudo de Du et al. [29], foi investigada a ação de pós-bióticos derivados das cepas *Lacticaseibacillus rhamnosus*, *Limosilactobacillus reuteri* e *Bifidobacterium animalis* na citotoxicidade e inflamação induzida por sílica em um modelo de macrófagos *in vitro*. Os resultados evidenciaram a atividade anti-inflamatória dos compostos, além de uma redução significativa na toxicidade. Wang et al. [30] também notaram a redução da inflamação além da proliferação e diferenciação das células-tronco intestinais de camundongos após o uso de pós-bióticos. Di Chiano et al. [31] observaram que os pós-bióticos foram capazes de atuar em nível cerebral, protegendo e prevenindo as células microgliais do estresse oxidativo.

Entretanto, os benefícios dos pós-bióticos estão diretamente relacionados ao processo de fermentação. A fermentação realizada por bactérias ácido-láticas (BALs), como *Lactobacillus* e *Bifidobacterium*, é amplamente utilizada para a síntese de pós-bióticos devido à sua capacidade de produzir uma variedade de compostos bioativos benéficos para a saúde humana. Essas bactérias, que são comumente encontradas em alimentos fermentados, como iogurtes e kefir, desempenham um papel crucial na produção de ácidos orgânicos, peptídeos e outras substâncias que podem ter efeitos antimicrobianos, anti-inflamatórios e imunomoduladores [23,32]. Durante o processo de fermentação, essas bactérias metabolizam os nutrientes do substrato, liberando fragmentos celulares e metabólitos que, mesmo após a morte dos microrganismos, continuam a exercer benefícios à saúde do hospedeiro [23,32].

A fermentação realizada por bactérias lácticas é um processo anaeróbio, ou seja, ocorre na ausência de oxigênio, no qual essas bactérias convertem carboidratos, principalmente a glicose, em ácido lático, entre outros produtos. Existem dois tipos principais de fermentação

em bactérias lácticas: a homofermentativa, na qual o produto final é exclusivamente o ácido lático, e a heterofermentativa, em que além do ácido lático, também são produzidos subprodutos como etanol, ácido acético e dióxido de carbono. Além do ácido lático, outras substâncias bioativas podem ser geradas durante a fermentação, como ácidos graxos de cadeia curta (AGCC), vitaminas, exopolissacarídeos (EPS), biossurfactantes e bacteriocinas [33–35].

O processo de fermentação de bactérias lácticas é amplamente aproveitado na indústria alimentícia devido à sua contribuição para o sabor, textura e propriedades funcionais dos alimentos, além de seus potenciais efeitos benéficos à saúde intestinal e ao sistema imunológico [32–36]. Vale ressaltar que a síntese dos pós-bióticos pode variar de acordo com a cepa bacteriana utilizada na sua síntese, além de estarem sujeitos a fatores como os critérios físicos durante a fermentação, os meios de crescimento e os nutrientes fornecidos [32,36].

Os AGCC são produzidos a partir da fermentação bacteriana de polissacarídeos complexos, ou seja, fibras alimentares não digeríveis, sendo os principais representantes o butirato, acetato e propionato [23,36]. Estas substâncias têm se mostrado eficazes em reduzir a inflamação gerada na DII por meio da inibição de histonas e ativação dos receptores acoplados a proteína G. Desta forma apresenta vantagens como: influenciar na proliferação celular, impedir o desenvolvimento de células de caráter maligno, melhorar a vitalidade dos enterócitos e colonócitos, além de promover a manutenção da barreira intestinal [32,36,37].

Estudos mostraram que o butirato possui propriedades de modulação da expressão gênica e efeito imunossupressor, por meio da regulação de citocinas pró-inflamatórias como a IL-1β, IL- 6 e o fator de necrose tumoral (TNF-α). Além disso, foi observado que ele eleva mediadores anti-inflamatórios, como a IL-10, contribuindo para a redução do estresse oxidativo e sendo fonte de energia para mucosa do cólon. Desta forma, foi demonstrado que a disbiose associada a pacientes com DII estava intimamente ligada a redução dos AGCC, principalmente de bactérias que sintetizam o butirato, como as bactérias pertencentes ao filo *Firmicutes* [23,37–39].

Os EPSs são biopolímeros liberados pela parede celular bacteriana responsáveis pela modulação da resposta imunológica por meio da estimulação de células dendríticas e macrófagos. Sabe-se também que eles ativam as células NK e aumentam a proliferação dos linfócitos T, além de reestabelecer a função da barreira intestinal durante a DII por meio da regulação de proteínas de adesão que compõem as junções estreitas [23,32,40].

Zhou et al. [40] demonstraram a capacidade dos EPSs produzidos pelas BALs na regulação da integridade da barreira intestinal durante a DII por meio da ativação de um fator transcricional denominado STAT3. Os efeitos antioxidantes demonstrados pelos EPSs também têm sido bastante atraentes, pois atuam neutralizando e eliminando espécies reativas

de oxigênio (ROS) envolvidas nas reações de estresse oxidativo [32,41].

As enzimas pós-bióticas também desempenham importante função antioxidante, sendo as principais: superóxido dismutase, glutationa peroxidase e NADH peroxidase [14,42]. O estresse oxidativo representa um desequilíbrio entre os processos de oxidação e os antioxidativos, sendo a superóxido dismutase uma das enzimas mais importantes para a regulação da função antioxidante devido sua capacidade de dismutação do radical O_2^-, que faz com que a concentração de cátions livres e os danos causados pelo peróxido de hidrogênio seja reduzido [43,44].

Os ácidos orgânicos e algumas proteínas pós-bióticas são relevantes devido o efeito antimicrobiano. Os principais ácidos orgânicos produzidos são o ácido lático, o ácido propiônico e o ácido 3- fenilláctico, que tem demonstrado ampla aplicação como antimicrobiano, enquanto que em relação as proteínas sintetizadas, podemos citar as bacteriocinas e a S-Layer [21,45].

As bacteriocinas são sintetizadas nos ribossomos das BALs como metabólitos primários e liberadas para o meio extracelular. Elas apresentam ação antimicrobiana por meio da formação de poros na membrana celular de patógenos suscetíveis. Pode exercer efeito bactericida ou bacteriostático e são classificadas em classe I, II ou III, onde as de classe I e II são bacteriocinas resistentes a alterações de pH e calor, enquanto a de classe III não possuem esta mesma resistência [21,32,46].

Os demais compostos que constituem os pós-biótico contribuem para sua eficácia integral devido suas diversas propriedades antioxidantes, antimicrobianas, anti-catabólicas, dentre outras como demonstrado na Tabela 1.

Tabela 1. Caracterização dos principais pós-bióticos gerados a partir de fermentação de bactérias ácido lática

Categoria	Biometabólito	Mecanismo	Propriedades	Funcionalidade	Referências
Ácidos Graxos de Cadeia Curta (AGCC)	Butirato Acetato Propionato	Inibição de histonas e ativação de receptores de superfície acoplados a protína G	Anti-inflamatório, antioxidante, anti-microbiano, anti-catabólico	Manutenção da barreira intestinal, restauração da musculatura, proteção contra patógenos	[36–39].
Carboidratos	Exopolissacarídeos	Estimulação das células dendríticas e macrófagos, neutralização dos ROS e ativação do fator STAT3	Anti-inflamatório e antioxidante	Modulação da resposta imune, Redução do estresse oxidativo e restauração da barreira	[23,32,40,41].
Enzimas	Glutationa Peroxidase Superóxido Dismutase NADH Peroxidase	Dismutação e remoção de radicais superóxido e peróxido de hidrogênio	Antioxidante	Redução do estresse oxidativo	[14,42,47].
Ácidos Orgânicos	Ácido Lático Ácido Propiônico Ácido 3-fenilláctico	Redução do pH	Antimicrobiano	Proteção contra patógenos	[21,45].
Proteínas	S-Layer Bacteriocinas	Inibição da adesão e formação de poros na membrana de microrganismos	Antimicrobiano	Proteção contra patógenos	[21,32,46,48].
Vitaminas	Vitamina B Vitamina K	Cofatores enzimáticos	Mantém a homeostase	Manutenção celular	[21,49].
Biossurfactantes	-	Inibição da adesão de microrganismos	Antimicrobiano	Proteção contra patógenos e inibição da formação de biofilmes	[21].

O uso de pós-bióticos nas indústrias nutracêuticas, farmacêuticas e alimentícias tem se mostrado promissor devido aos seus benefícios para a saúde. No entanto, a produção em larga escala ainda enfrenta desafios [13,14]. De acordo com Thorakkattu et al. [14], a liofilização é uma das formas mais promissoras de comercialização desses compostos, embora esse processo possa afetar sua estabilidade e propriedades antimicrobianas.

Desta forma, a fermentação industrial controlada surge como uma alternativa viável para a produção de pós-bióticos ativos [13]. No entanto, a utilização de biorreatores para fermentação em larga escala ainda enfrenta limitações, como a baixa tolerância a variações de temperatura [50,51]. Além disso, a produção de compostos como os exopolissacarídeos (EPS) pelas bactérias ácido-láticas tem se mostrado inviável comercialmente devido ao baixo rendimento [52].

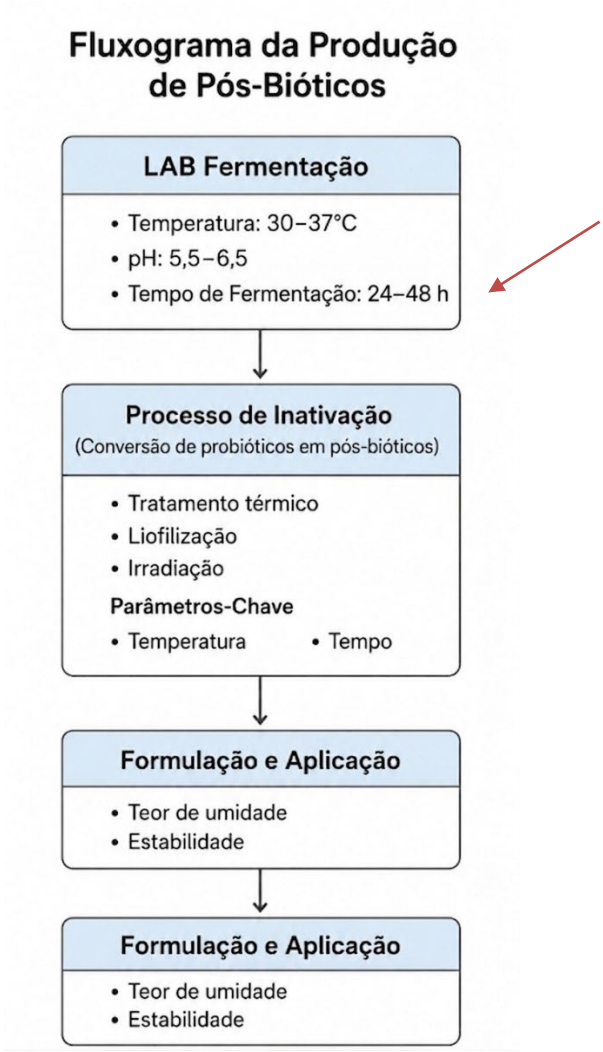

Figura 2. Visão geral abrangente da produção pós-biótica.

4. Aplicação de Pós-biótico Derivados de Bactérias Láticas nas Complicações Musculares

A aplicação de pós-bióticos derivados de bactérias lácticas tem mostrado grande potencial no alívio de complicações musculares, devido às suas propriedades anti-inflamatórias e antioxidantes. Esses compostos bioativos modulam a resposta imunológica e reduzem o estresse oxidativo, favorecendo a recuperação muscular e prevenindo danos adicionais [53–56].

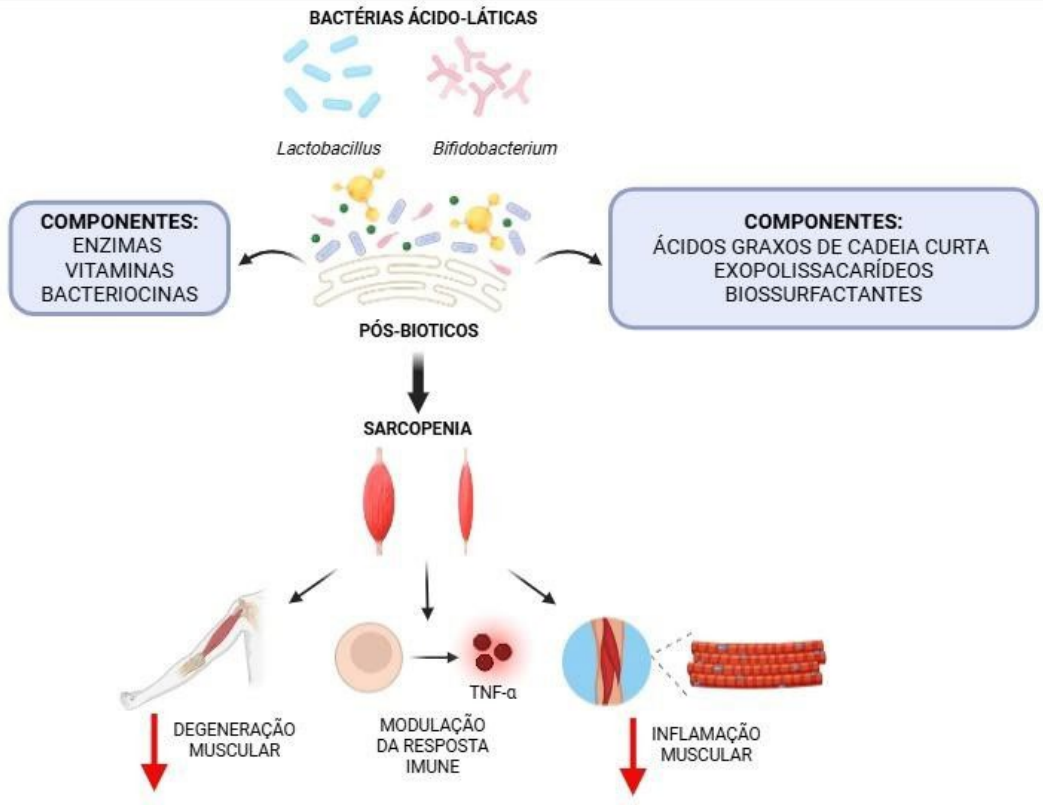

Figura 3. O efeito dos pós-bióticos no manejo de complicações musculares associadas à doença inflamatória intestinal.

Entre os pós-bióticos mais estudados, destacam-se os ácidos graxos de cadeia curta (AGCCs), como o butirato, o acetato e o propionato, que são reconhecidos por suas propriedades anti-inflamatórias e antioxidantes. Esses compostos desempenham um papel importante na neutralização dos danos à musculatura esquelética, auxiliando no reparo e na recuperação muscular. Estudos sugerem que os AGCCs também podem atuar como moduladores do metabolismo muscular, através da ativação dos receptores acoplados à proteína G, como GPR41 e GPR43, que estimulam a secreção de peptídeos intestinais, melhorando a sensibilidade à insulina e aumentando a captação de glicose no músculo esquelético [56–59].

O butirato, especificamente, tem demonstrado benefícios na modulação inflamatória, na preservação da função mitocondrial e na regulação do metabolismo energético [54]. Além disso, o butirato modula vias inflamatórias e o estresse oxidativo, ativando as vias PI3K/AKT/mTOR, e apresenta propriedades antioxidantes, que têm sido associadas à preservação da massa muscular [53,54].

O acetato, por sua vez, ativa a AMPK e a biogênese mitocondrial, enquanto o propionato modula o metabolismo lipídico e da glicose, promovendo proteção da barreira intestinal e melhoria da resposta inflamatória, fatores importantes no controle da sarcopenia [54,57,60].

Estudos adicionais têm avaliado os efeitos de pós-bióticos derivados de *Lactobacillus* em modelos de atrofia muscular. Jeong et al. [56] demonstraram que o pós-biótico gerado por meio do processamento térmico da bactéria *Lactiplantibacillus plantarum* apresentou benefícios na massa e função muscular, com ação anti-inflamatória e anti-catabólica. Em outra pesquisa, o uso de butirato de sódio e ReFerm, derivado de *Lactobacillus plantarum*, resultou em uma redução significativa dos sintomas clínicos e na melhora da qualidade de vida de pacientes com Síndrome do Intestino Irritável [61]. Além disso, frações proteicas pós-bióticas de *Lactobacillus delbrueckii* CIDCA 133 promoveram a cicatrização da mucosa, protegeram a barreira epitelial intestinal e regularam a disbiose em um modelo de camundongo de mucosite induzida por 5-fluorouracil, demonstrando também efeito positivo na redução de citocinas inflamatórias [62].

Outros estudos, como o de Han et al. [63], avaliaram o uso de extrato de casca de melão rico em polifenóis e soro de leite fermentado com *Lentilactobacillus kefiri* (DH5) em camundongos, observando uma redução na atrofia muscular, reparo no comprimento/diâmetro dos miotubos e modulação da microbiota intestinal. Esses efeitos foram atribuídos ao favorecimento dos microrganismos produtores de butirato, ressaltando a importância dessa molécula na manutenção da saúde muscular.

Além desses, as bacteriocinas produzidas por algumas bactérias lácticas inibem patógenos intestinais, promovendo o equilíbrio da microbiota e melhorando a absorção de nutrientes essenciais para o músculo, enquanto os exopolissacarídeos (EPS) atuam como imunomoduladores, reduzindo a inflamação sistêmica associada à sarcopenia e promovendo a manutenção da função muscular [53,64,65]. Esses pós-bióticos, com suas propriedades anti-inflamatórias e antioxidantes, demonstram grande potencial terapêutico

no combate à sarcopenia, oferecendo novas possibilidades para o manejo dessa condição, particularmente em idosos e em situações patológicas associadas à perda muscular.

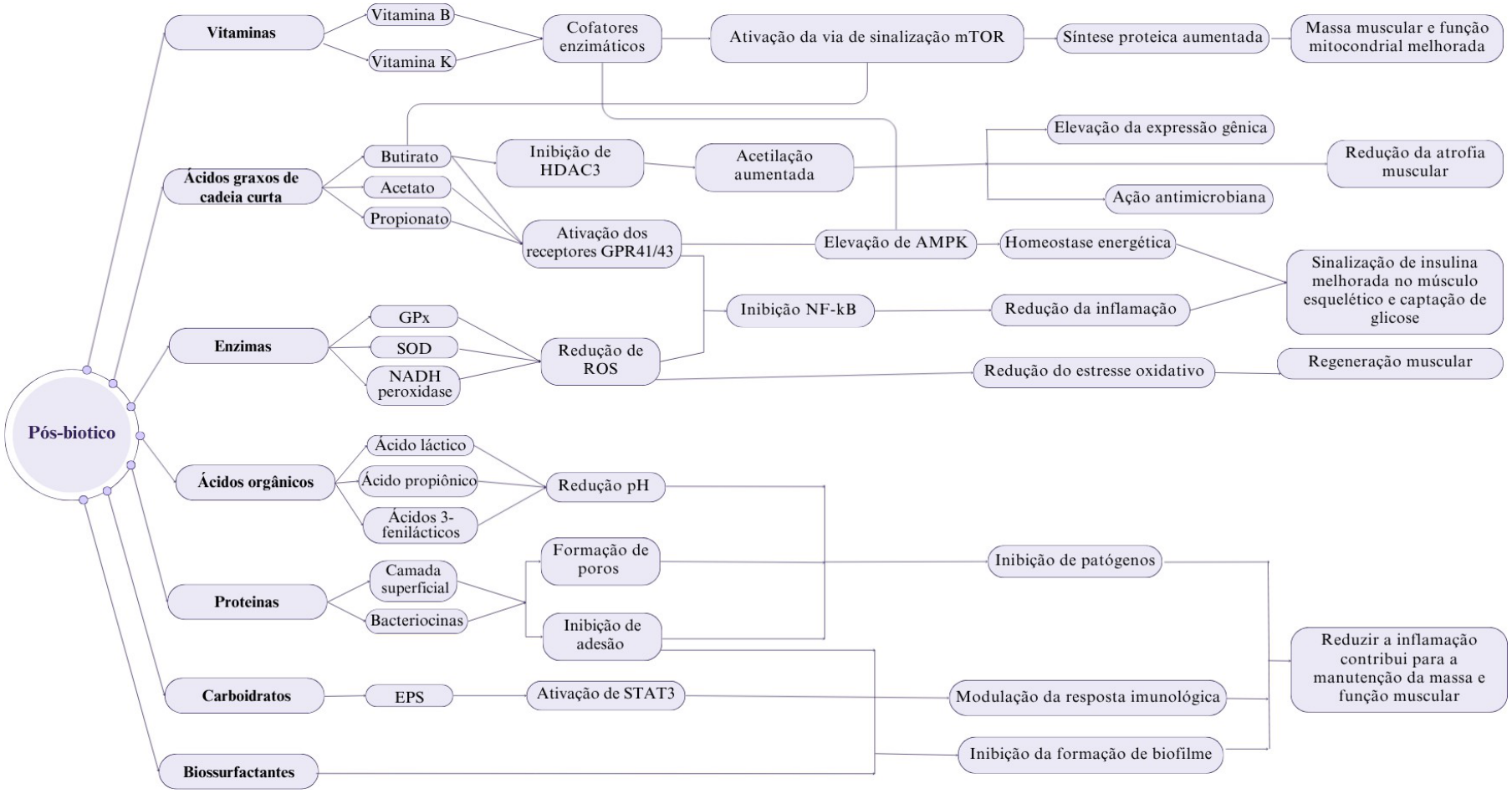

Figura 4. Mecanismos pós-bióticos e interações sinérgicas.

5. Pós-biótico como Terapêutica Adjuvante no Manejo de Complicações Musculares da DII

O manejo das complicações musculares na Doença Inflamatória Intestinal (DII) requer uma abordagem integrada, combinando terapias nutricionais, farmacológicas e estratégias inovadoras, como o uso de pós-biótico [55,66].

A integração dos pós-biótico com terapias nutricionais pode otimizar a absorção e a utilização de nutrientes essenciais à síntese proteica muscular [67,68]. Enquanto que nas terapias farmacológicas, os pós-biótico podem atuar como agentes moduladores complementares ao tratamento convencional da DII. O uso prolongado de corticoides e inibidores do TNF-α, apesar de essencial para o controle da inflamação, pode levar a efeitos adversos como resistência à insulina e atrofia muscular, nesse contexto os pós-bióticos poderiam estar auxiliando nesse processo [69].

A Tabela 2 resume as principais interações entre pós-biótico, terapias nutricionais e farmacológicas, destacando seus benefícios sinérgicos e potenciais limitações.

Tabela 2- Interação entre Pós-biótico, Terapias Nutricionais e Farmacológicas na DII

	Componente Terapêutico	Objetivo	Exemplo	Benefícios Sinérgicos	Potenciais Efeitos Adversos / Limitações	Referências
Terapia Biótica	Pós-bióticos	Redução da inflamação e melhora mitocondrial	AGCCs, EPSs, Peptidoglicanos bacterianos	Redução da inflamação, melhora da função celular	Respostas individuais variáveis, necessidade de padronização	[66,70].
Terapias Nutricionais	Dieta Proteica	Estímulo à síntese proteica	Leucina, whey protein	Recuperação e manutenção da massa muscular	Risco de sobrecarga renal em pacientes com insuficiência renal	[71,72].
	Ômega-3 e Antioxidantes	Redução do estresse oxidativo e inflamação	Suplementação com ômega-3, vitamina E	Diminuição do dano muscular e inflamação crônica	Possíveis interações com anticoagulantes	[73–75].
Terapias Farmacológicas	Anti-inflamatórios	Controle da inflamação intestinal	Mesalazina, corticoides	Redução da atividade inflamatória intestinal	Efeitos adversos como osteoporose e resistência insulínica	[76,77].
	Imunossupressores	Modulação da resposta imune	Azatioprina, infliximabe	Prevenção de crises inflamatórias e proteção muscular	Aumento do risco de infecções e efeitos adversos sistêmicos	[70,78,79].

O avanço das pesquisas na área de administração de pós-biótico pode levar à otimização de formulações e ao desenvolvimento de terapias personalizadas, aumentando sua eficácia no manejo das complicações musculares da DII. A combinação dessas estratégias com intervenções nutricionais e farmacológicas pode representar um grande avanço na abordagem terapêutica para esses pacientes [80,81]. A tabela 3 resume as principais estratégias de administração dos pós-biótico e seus impactos na biodisponibilidade e eficácia terapêutica:

Tabela 3 - Estratégias de Administração de Pós-biótico e seus Impactos na Biodisponibilidade

Forma de Administração	Exemplo de Pós-biótico	Vantagens	Desafios	Biodisponibilidade	Referências
Suplementos Alimentares	Ácidos graxos de cadeia curta, peptídeos bioativos	Controle preciso da dosagem, conveniência	Necessidade de padronização da dose ideal	Média, depende da formulação e da absorção intestinal	[82,83].
Alimentos Funcionais	Pós-bióticos enriquecidos em iogurtes, bebidas fermentadas	Boa aceitação pelo consumidor, consumo diário fácil	Pode haver degradação dos compostos bioativos	Variável, influenciada por processos digestivos	[82,84,85].
Fórmulas Nutricionais	Mistura de metabólitos derivados de *Lactobacillus* e *Bifidobacterium*	Indicado para pacientes com dificuldades alimentares	Custo elevado e menor adesão em indivíduos saudáveis	Alta, devido à formulação otimizada para absorção	[80,82].
Nanotecnologia	Nanoencapsulação de pós-biótico	Aumenta biodisponibilidade e proteção dos compostos	Tecnologia ainda em desenvolvimento, alto custo	Muito alta, proteção contra degradação gástrica	[80,86].

Os pós-bióticos podem ser incorporados a diferentes veículos para garantir sua estabilidade e absorção. Suplementos em cápsulas ou pós solúveis oferecem uma dosagem precisa e são frequentemente utilizados em formulações padronizadas contendo ácidos graxos de cadeia curta (AGCCs), peptídeos antimicrobianos e polissacarídeos bioativos [82]. Esses compostos apresentam alta biodisponibilidade e podem ser formulados para liberação controlada, permitindo uma ação prolongada no trato gastrointestinal [83].

Outra abordagem promissora envolve o uso de alimentos funcionais enriquecidos com pós-biótico, como iogurtes fermentados, bebidas lácteas e barras nutricionais. Além de facilitar a adesão dos pacientes ao tratamento, esses alimentos podem atuar sinergicamente com outros nutrientes essenciais, como proteínas de alta qualidade e antioxidantes [84]. No entanto, a estabilidade dos pós-bióticos nesses produtos precisa ser considerada, visto que variações de pH e temperatura podem comprometer sua atividade biológica [82,85].

A biodisponibilidade dos pós-biótico também pode ser aprimorada por meio de tecnologias como microencapsulação e nanopartículas poliméricas, que protegem os compostos bioativos contra a degradação enzimática e promovem sua liberação direcionada no intestino delgado e cólon. Essas estratégias são fundamentais para garantir que os pós-biótico atinjam o local de ação com a máxima eficácia [80,86].

Além disso, deve-se atentar a dose na aplicação dos pós-bióticos. A definição da dosagem ideal ainda requer estudos clínicos mais robustos, mas evidências preliminares sugerem que concentrações entre 10^8 e 10^{11} UFC/mL (ou seus equivalentes metabólicos) podem ser eficazes na modulação da inflamação e na preservação da massa muscular em pacientes com DII [86]. Dessa forma, a individualização do tratamento, baseada na análise do perfil da microbiota intestinal, pode ser uma abordagem futura para maximizar os benefícios dos pós-bióticos [81,83].

6. Desafios e Limitações no Uso de Pós-biótico para Complicações Musculares na DII

O uso de pós-biótico para manejo de complicações musculares em pacientes com doenças inflamatórias intestinais é emergente, devido ao potencial farmacoterapêutico dos pós-bióticos. Entretanto, deve-se considerar as limitações e contornar desafios para o uso seguro e eficaz [56].

Durante o processo de seleção de BALs para a produção de pós-biótico, é necessário analisar e considerar os fatores que alteram a composição química dos pós-bióticos, pois esses fatores podem afetar seu comportamento e diminuir a taxa de crescimento. Na literatura, a especificidade de bactérias lácticas é amplamente relatada, com destaque para a produção de ácido orgânico independentemente do gênero, mas depende da espécie bacteriana [87].

Outro fator importante a se considerar é o tipo de tecnologia empregada no processo de inativação microbiana. Estudos recentes demonstraram que diferentes tratamentos térmicos (secagem ao ar, secagem por pulverização, liofilização) impactam direta e significativamente a viabilidade, disponibilidade e as propriedades imunomoduladoras dos pós-bióticos. Dessa forma, o processamento térmico de bactérias lácticas para a produção de pós-biótico pode não ser a melhor opção [88]. Em contrapartida, tecnologias como radiação ionizante, campo elétrico, aquecimento de campo magnético e ultrassonicação, podem ser utilizadas para obter pós-biótico estáveis, seguros e com maior biodisponibilidade [89].

A variabilidade individual, devido às diferenças na microbiota intestinal, fatores genéticos, idade e dieta, expõe a necessidade de terapias personalizadas por meio de pesquisas e compreensões extensas [90]. Ademais, as doenças inflamatórias intestinais (DII) podem afetar diretamente o microbioma intestinal do paciente, dificultando a absorção de nutrientes e medicamentos, o que reafirma a necessidade de terapias individuais para selecionar cuidadosamente cepas mais seguras e funcionais, determinar a dose ideal e definir a forma farmacêutica a ser utilizada para administração [14].

Outrossim, o microbioma humano pode interagir de forma inesperada com os metabólitos suplementados, podendo ocasionar disbiose ou biotransformação em estados inativos e até mesmo tóxicos. Além disso, promover a regulação artificial de alguns metabólitos no intestino humano pode alterar a homeostase de feedback metabólico, levando à deficiência na produção endógena. Ou seja, é necessário identificar de forma

sistêmica os compostos bioativos de bactérias lácticas intestinais residentes e sua interação com os pós-bióticos suplementados antes da sua utilização terapêutica [91].

Portanto, é de suma importância analisar os resultados *in vitro* e *in vivo* para estabelecer relação com as características únicas do intestino humano, especialmente o cólon, que possui camadas estratificadas predominantemente na camada externa. Por meio desses estudos clínicos e de avaliações bioquímicas, a exploração dos mecanismos precisos dos pós-bióticos ocorrerá de forma mais aprofundada [92].

A autoridade reguladora dos Estados Unidos, a Food and Drug Administration (FDA), não abordou particularmente sobre pós-biótico e muito provavelmente abordará com base nas regras aplicadas à categoria individual escolhida para produtos em desenvolvimento, pois os pós-biótico podem ter sua produção conduzida sob muitas categorias regulatórias. Sendo assim, a segurança e eficácia do produto terá que cumprir todos os requisitos para aplicação médica e farmacoterapêutica [14].

A autoridade reguladora da Europa, a European Medicines Agency (EMA) [93], aprovou em setembro de 2019 o uso de lisados bacterianos apenas para prevenção de infecções respiratórias recorrentes, exceto a pneumonia. Dessa forma, o uso de pós-biótico sofre restrições que impossibilitam a sua difusão para outras enfermidades.

Pesquisas adicionais são consideradas essenciais para estabelecer a relação entre a eficácia e os efeitos profiláticos dos pós-bióticos. Estudos que integrem múltiplas perspectivas metodológicas, por exemplo ensaios clínicos em larga escala, duplo cego, estudos longitudinais, permitem verificar a eficácia potencial dos pós-bióticos como adjuvantes na recuperação muscular de pacientes com doenças inflamatórias intestinais. Além disso, recomenda-se a realização de pesquisas explorando técnicas aprimoradas e até misturas de cepas bacterianas com diferentes metabólitos bioativos, com a finalidade de acelerar o processo de recuperação muscular ou modificá-lo com base nas necessidades individuais de cada paciente [12].

7. Perspectivas Futuras no Uso de Pós-biótico Derivados de Bactérias Láticas

Os pós-bióticos têm se destacado devido ao seu potencial terapêutico no tratamento de diversas condições, incluindo a sarcopenia associada a doenças inflamatórias intestinais (DII). Com a crescente expectativa de que o mercado de pós-bióticos atinja US$ 91,7 bilhões até 2030, espera-se que surjam formulações inovadoras e tratamentos personalizados, com base em perfis intestinais individuais, para combater a sarcopenia e outras condições inflamatórias. Avanços como a microencapsulação e a

engenharia genética têm potencial para melhorar a estabilidade e a eficácia desses compostos, permitindo tratamentos mais específicos e seguros, além de possibilitar a personalização terapêutica conforme as particularidades de cada paciente [94,95]. A aplicação de pós-bióticos na modulação do microbioma e na regulação da inflamação promete ser uma estratégia eficaz para mitigar o catabolismo muscular, frequentemente exacerbado pela disbiose e inflamação crônica associada às DII [8].

Com relação à sarcopenia, as abordagens envolvendo pós-bióticos, como a suplementação com ácidos graxos de cadeia curta e alimentos fermentados, demonstram grande potencial terapêutico. A modulação do microbioma intestinal por meio de probióticos, prebióticos e pós-biótico pode impactar positivamente processos metabólicos essenciais, como o metabolismo de proteínas e a função mitocondrial, reduzindo a inflamação e favorecendo o aumento da massa muscular [96]. Essa abordagem inovadora não apenas oferece uma alternativa ao tratamento convencional, mas também pode melhorar a qualidade de vida dos pacientes com DII e sarcopenia, abrindo novas perspectivas para a terapia individualizada e a medicina de precisão.

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ARTIGO 2 – ARTIGO EXPERIMENTAL: A SER SUBMETIDO PARA A REVISTA *INTERNATIONAL JOURNAL OF PHARMACEUTICS*

Efeitos de *Pediococcus acidilactici* CE51 e de seus pós-bióticos na integridade intestinal, inflamação e segurança em modelo de enteropatia induzida por indometacina

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RESUMO

A doença inflamatória intestinal é caracterizada por inflamação crônica do trato gastrointestinal, frequentemente associada à disbiose e ao comprometimento da integridade da mucosa. Neste cenário, probióticos e pós-bióticos têm sido investigados como estratégias terapêuticas promissoras. O presente estudo teve como objetivo avaliar os efeitos de *Pediococcus acidilactici* CE51 e de seu pós-biotico sobre parâmetros inflamatórios, estruturais, hematológicos, bioquímicos e microbiológicos em modelo experimental de lesão intestinal induzida por indometacina. Os procedimentos experimentais foram direcionados de acordo com as diretrizes éticas estabelecidas. A toxicidade dos compostos foi primeiramente avaliada em larvas de *Galleria mellonella*. Para o modelo experimental, foram utilizados 45 ratos Wistar, distribuídos em cinco grupos: controle (CMC), indometacina (I), indometacina associada ao probiótico (IP), indometacina associada ao sobrenadante livre de células (ICFS) e indometacina associada à sulfassalazina (IS). Os animais foram submetidos a um período de pré-tratamento de 28 dias, seguido da indução de lesão intestinal por indometacina durante 4 dias. Foram realizadas análises histopatológicas e morfométricas, avaliações hematológicas e bioquímicas, teste do micronúcleo para avaliação de genotoxicidade e caracterização da microbiota intestinal por sequenciamento do gene 16S rRNA. Não foi observada toxicidade aguda nos modelos experimentais, o probiótico não foi capaz de diminuir o dano intestinal, sendo associado a maior frequência de ulcerações, necrose e redução da altura das vilosidades. Entretanto, o sobrenadante livre de células apresentou efeito modulador mais consistente, evidenciado por menor intensidade de lesões teciduais, recuperação dos níveis de plaquetas, aumento da contagem de leucócitos e redução significativa da frequência de micronúcleos. Adicionalmente, o pós-biotico promoveu modulação da microbiota intestinal, com aumento de bactérias potencialmente benéficas, como *Lactobacillus*, em comparação ao grupo inflamatório. Alterações sistêmicas, como menor ganho de peso e hipoproteinemia, foram observadas nos grupos induzidos, sem reversão completa pelos tratamentos. Em conjunto, esses achados indicam que os pós-bióticos derivados de *P. acidilactici* CE51 apresentam maior potencial na modulação da inflamação intestinal e da microbiota quando comparados ao probiótico, destacando-se como uma estratégia promissora para aplicações terapêuticas, embora estudos adicionais ainda sejam necessários para elucidar os mecanismos envolvidos e ampliar sua aplicabilidade clínica.

Palavras-chave: Pós-bióticos; Probióticos; Inflamação intestinal; Microbiota intestinal; *Pediococcus acidilactici*; Indometacina; Disbiose

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ANEXO A - PARECER FINAL DO COMITÊ ASSESSOR DE PESQUISA INSTITUCIONAL (CAPI) E DA COMISSÃO DE ÉTICA EM USO DE ANIMAIS

UNOESTE - Universidade do Oeste Paulista

PRO-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO

PEIC - Programa Especial de Iniciação Científica

Parecer Final

Declaramos para os devidos fins que o Projeto de Pesquisa intitulado **"AVALIAÇÃO DO EFEITO DE POSTBIÓTICOS NA DOENÇA INTESTINAL INFLAMATÓRIA INDUZIDA POR INDOMETACINA EM RATOS"**, cadastrado na Coordenadoria de Pesquisa, Desenvolvimento e Inovação (CPDI) sob o nº **8680** e tendo como participante(s) **LIZZIANE KRETLI WINKELSTROTER ELLER (discente), CAROLINA SANTOS MADIA (discente), DAIANE GALERA VALEJO (discente), GISELE ALBORGHETTI NAI (docente responsável)**, foi avaliado e **Aprovado pelo Comitê Assessor de Pesquisa Institucional (CAPI), Comissão de Ética Uso de Animais (CEUA)** da Universidade do Oeste Paulista - UNOESTE de Presidente Prudente/SP.

Este Projeto de Pesquisa, que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica, encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de Outubro de 2008, do Decreto nº 6.899, de 15 de Julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), tendo sido Aprovado em reunião realizada em 12/06/2024 00:00:00.

MATERIAL ARMAZENADO/DOADO COM ORIGEM EM PESQUISA

Protocolo(s)	Data Aprovação	Armazenado (local)	É doação	Detalhes armazenamento
8591	03/04/2024 00:00:00	Unoeste	SIM	Biotério

Presidente Prudente, quinta-feira, 13 de junho de 2024.

Prof. Dr. Luiz Rodrigo Garcia Jr.
Docente Responsável pela CPDI

Prof. Dr. Felipe Rydygier de Randigo
Coordenador da CEUA - UNOESTE

(CEUA)

ANEXO B – NORMAS DE PUBLICAÇÃO DA PERIÓDICO FERMENTATION

Manuscript Submission Overview

Types of Publications

Full experimental details must be provided so that the results can be reproduced. *Fermentation* requires that authors publish all experimental controls and make full datasets available where possible (see the guidelines on Supplementary Materials and references to unpublished data).

Manuscripts submitted to *Fermentation* should neither be published previously nor be under consideration for publication in another journal. The main article types are listed below and a comprehensive list of article types can be found here—please note that not all article types are available for all disciplines.

- *Article:* These are original research manuscripts. The work should report scientifically sound experiments and provide a substantial amount of new information. The article should include the most recent and relevant references in the field. The structure should include an Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, and Conclusions (optional) sections.
- *Review:* Reviews offer a comprehensive analysis of the existing literature within a field of study, identifying current gaps or problems. They should be critical and constructive and provide recommendations for future research. No new, unpublished data should be presented. The structure can include an Abstract, Keywords, Introduction, Relevant Sections, Discussion, Conclusions, and Future Directions.

  A Scoping Review type can be submitted as a Review. The structure is similar to that of a review. Scoping reviews should strictly follow the PRISMA extension for scoping reviews checklist (https://www.prisma-statement.org/scoping) and submit the checklist as non-published material during submission. Templates for the flow diagram can be downloaded from the PRISMA website and the diagram should be included in the main text. We strongly encourage authors to register their detailed protocols, before data extraction commences, in a public registry such as the Open Science Framework (https://osf.io/) or Inplasy (https://inplasy.com/). Authors must include a statement about following the PRISMA guidelines and registration information (if available) in the Methods section.

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3. Work experience;
4. Current and previous research interests;
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Manuscript Preparation
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  - Front matter: Title, Author list, Affiliations, Abstract, Keywords.
  - Research manuscript sections: Introduction, Materials and Methods, Results, Discussion, Conclusions (optional).
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[Return to top]

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[Return to top]
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[Return to top]

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Requirements for Studies on Vulnerable Groups and Organ Transplants
If a study involves vulnerable groups, the manuscript will undergo an additional review by the editorial office. If requested, the author must provide documentary evidence, including blank consent forms and any related discussion documents from the ethics board or other relevant bodies. Additionally, when studies describe groups by race, ethnicity, gender, disability, disease, etc., an explanation regarding why such categorization was needed must be clearly stated in the article.
Articles describing human organ transplantation studies are subject to all policies for research involving human subjects. Additionally, the authors must specify the institution(s), clinic(s), or department(s) from which the organs or tissues were sourced. MDPI does not accept manuscripts that report data on organs and/or other materials obtained from illegal commercial activity, executed prisoners, or other unethical practices relating to organ donations. Manuscripts addressing this practice, such as editorials or reports on its secondary consequences, may be considered at the discretion of the Editor-in-Chief but require a written appeal to the editorial office before submission. For further resources on organ transplantation, MDPI follows the glossary maintained by the Organ Procurement and Transplantation Network (https://optn.transplant.hrsa.gov/patients/glossary/).
Clinical Trials Registration
Registration
Clinical trials are subject to all policies regarding Research Involving Human Subjects. In addition, MDPI follows the International Committee of Medical Journal Editors (ICMJE) guidelines, which require the registration of clinical trials in a public trial registry at or before the time of first patient enrollment as a condition of consideration for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Therefore, 'clinical trial' not only refers to studies that take place

in a hospital or involve pharmaceuticals but also to all studies which involve participant randomization and group classification in the context of the intervention under assessment.
Authors must preregister clinical trials with an international clinical trial register. Suitable databases include clinicaltrials.gov, the EU Clinical Trials Register, and those listed on the World Health Organisation's International Clinical Trials Registry Platform. The name of the registry, trial registration number, and date of registration should be included in the Institutional Reviewer Board statement or in the Materials and Methods section.
Purely observational studies (e.g., cohort studies, cross-sectional studies, and case–control studies) do not require registration. Editors may consider exceptions to pre-trial registration requirements in some cases. If an exception is granted, the authors must retroactively register the trial and clearly indicate the date and reasons for the retroactive registration in the Materials and Methods section of the publication.
Approval to conduct a study from an independent local, regional, or national review body is not equivalent to prospective clinical trial registration. MDPI reserves the right to decline any paper without trial registration for further peer review.
Randomized Clinical Trial Reporting Guidelines
In addition to clinical trial registration, MDPI requires a completed CONSORT 2025 checklist and flow diagram as a condition of submission when reporting the results of a randomized clinical trial. Checklist templates can be found on the CONSORT website, which also describes several CONSORT checklist extensions for different designs and types of data beyond two-group parallel trials. As a minimum, clinical trial articles should report the content addressed by each item of the checklist.
Ethical Guidelines for the Use of Animals in Research
The editors will require that the benefits potentially derived from any research causing harm to animals are significant in relation to any cost endured by animals, and that procedures followed are unlikely to cause offense to the majority of readers. Authors should particularly ensure that their research complies with the commonly-accepted '3Rs [1]':

- Replacement of animals by alternatives wherever possible,
- Reduction in number of animals used, and
- Refinement of experimental conditions and procedures to minimize the harm to animals.

Authors must include details on housing, husbandry and pain management in their manuscript.
For further guidance authors should refer to the Code of Practice for the Housing and Care of Animals Used in Scientific Procedures [2], American Association for Laboratory Animal Science [3] or European Animal Research Association [4].
If national legislation requires it, studies involving vertebrates or higher invertebrates must only be carried out after obtaining approval from the appropriate ethics committee. As a minimum, the project identification code, date of approval and name of the ethics committee or institutional review board should be stated in Section 'Institutional Review Board Statement'. Research procedures must be carried out in accordance with national and institutional regulations. Statements on animal welfare should confirm that the study complied with all relevant legislation. Clinical studies involving animals and interventions outside of routine care require ethics committee oversight as per the American Veterinary Medical Association. If the study involved client-owned animals, informed client consent must be obtained and certified in the manuscript report of the research. Owners must be fully informed if there are any risks associated with the procedures and that the research will be published. If available, a high standard of veterinary care must be provided. Authors are responsible for correctness of the statements provided in the manuscript.
If ethical approval is not required by national laws, authors must provide an exemption from the ethics committee, if one is available. Where a study has been granted exemption, the name of the ethics committee that provided this should be stated in Section 'Institutional Review Board Statement' with a full explanation on why the ethical approval was not required.
If no animal ethics committee is available to review applications, authors should be aware that the ethics of their research will be evaluated by reviewers and editors. Authors should provide a statement justifying the work from an ethical perspective, using the same utilitarian framework that

is used by ethics committees. Authors may be asked to provide this even if they have received ethical approval.
MDPI endorses the ARRIVE guidelines (arriveguidelines.org/) for reporting experiments using live animals. Authors and reviewers must use the ARRIVE guidelines as a checklist, which can be found at https://arriveguidelines.org/sites/arrive/files/documents/ARRIVE%20Compliance%20Questionnaire.pdf. Editors reserve the right to ask for the checklist and to reject submissions that do not adhere to these guidelines, to reject submissions based on ethical or animal welfare concerns or if the procedure described does not appear to be justified by the value of the work presented.

1. NSW Department of Primary Industries and Animal Research Review Panel. Three Rs. Available online: https://www.dpi.nsw.gov.au/dpi/animals/animal-ethics-infolink/three-rs
2. Home Office. Animals (Scientific Procedures) Act 1986. Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes. Available online: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/388535/CoPanimalsWeb.pdf
3. American Association for Laboratory Animal Science. The Scientific Basis for Regulation of Animal Care and Use. Available online: https://www.aalas.org/about-aalas/position-papers/scientific-basis-for-regulation-of-animal-care-and-use
4. European Animal Research Association. EU regulations on animal research. Available online: https://www.eara.eu/animal-research-law

Research Involving Cell Lines
Methods sections for submissions reporting on research with cell lines should state the origin of any cell lines. For established cell lines the provenance should be stated and references must also be given to either a published paper or to a commercial source. If previously unpublished *de novo* cell lines were used, including those gifted from another laboratory, details of institutional review board or ethics committee approval must be given, and confirmation of written informed consent must be provided if the line is of human origin.
An example of Ethical Statements:
The HCT116 cell line was obtained from XXXX. The $MLH1^{+}$ cell line was provided by XXXXX, Ltd. The DLD-1 cell line was obtained from Dr. XXXX. The DR-GFP and SA-GFP reporter plasmids were obtained from Dr. XXX and the Rad51K133A expression vector was obtained from Dr. XXXX.
Research Involving Plants
Experimental research on plants (either cultivated or wild) including collection of plant material, must comply with institutional, national, or international guidelines. We recommend that authors comply with the Convention on Biological Diversity and the Convention on the Trade in Endangered Species of Wild Fauna and Flora.
For each submitted manuscript supporting genetic information and origin must be provided. For research manuscripts involving rare and non-model plants (other than, e.g., *Arabidopsis thaliana, Nicotiana benthamiana, Oryza sativa*, or many other typical model plants), voucher specimens must be deposited in an accessible herbarium or museum. Vouchers may be requested for review by future investigators to verify the identity of the material used in the study (especially if taxonomic rearrangements occur in the future). They should include details of the populations sampled on the site of collection (GPS coordinates), date of collection, and document the part(s) used in the study where appropriate. For rare, threatened or endangered species this can be waived but it is necessary for the author to describe this in the cover letter.
Editors reserve the rights to reject any submission that does not meet these requirements.
An example of Ethical Statements:
Torenia fournieri plants were used in this study. White-flowered Crown White (CrW) and violet-flowered Crown Violet (CrV) cultivars selected from 'Crown Mix' (XXX Company, City, Country) were kindly provided by Dr. XXX (XXX Institute, City, Country).
Arabidopis mutant lines (SALKxxxx, SAILxxxx,…) were kindly provided by Dr. XXX, institute, city, country).
Dual-Use Research of Concern

MDPI follows the practical framework described in 'Guidance for Editors: Research, Audit and Service Evaluations' and introduced by the Committee on Publication Ethics (COPE). Research that could pose a significant threat, with broad potential consequences to public health or national security, should be clearly indicated in the manuscript, and potential dual-use research of concern should be explained in the cover letter upon submission. Potential areas of concern include, but are not limited to, biosecurity, nuclear and chemical threats, and research with a military purpose or application. For these manuscripts to be considered for peer review, the benefits to the general public or public health must outweigh the risks. The authors have a responsibility to comply with relevant national and international laws.

Sex and Gender in Research

We encourage our authors to follow the 'Sex and Gender Equity in Research – SAGER – guidelines' and to include sex and gender considerations where relevant. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Article titles and/or abstracts should indicate clearly what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the Discussion. We suggest that our authors consult the full guidelines before submission.

Borders and Territories

Potential disputes over borders and territories may have particular relevance for authors in describing their research or in an author or editor correspondence address, and should be respected. Content decisions are an editorial matter and where there is a potential or perceived dispute or complaint, the editorial team will attempt to find a resolution that satisfies parties involved.

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Fermentation is a member of the Committee on Publication Ethics (COPE). We fully adhere to its Code of Conduct and to its Best Practice Guidelines.

The editors of this journal enforce a rigorous peer review process together with strict ethical policies and standards to ensure to add high quality scientific works to the field of scholarly publication. Unfortunately, cases of plagiarism, data falsification, image manipulation, inappropriate authorship credit, and the like, do arise. The editors of *Fermentation* take such publishing ethics issues very seriously and are trained to proceed in such cases with a zero tolerance policy.

Authors wishing to publish their papers in *Fermentation* must abide to the following:

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- Authors should accurately present their research findings and include an objective discussion of the significance of their findings.
- Data and methods used in the research need to be presented in sufficient detail in the paper, so that other researchers can replicate the work.
- Raw data should preferably be publicly deposited by the authors before submission of their manuscript. Authors need to at least have the raw data readily available for presentation to the referees and the editors of the journal, if requested. Authors need to ensure appropriate measures are taken so that raw data is retained in full for a reasonable time after publication.
- Simultaneous submission of manuscripts to more than one journal is not tolerated.
- The journal accepts exact translations of previously published work. All submissions of translations must conform with our policies on translations.
- If errors and inaccuracies are found by the authors after publication of their paper, they need to be promptly communicated to the editors of this journal so that appropriate actions can be taken. Please refer to our policy regarding Updating Published Papers.
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All MDPI submissions are checked for plagiarism using the industry standard software iThenticate. If plagiarism is detected during the peer review process, the manuscript may be rejected. If plagiarism is detected after publication, an investigation will take place and action taken in accordance with our policies.

- Image files must not be manipulated or adjusted in any way that could lead to misinterpretation of the information provided by the original image.

Irregular manipulation includes: 1) introduction, enhancement, moving, or removing features from the original image; 2) grouping of images that should obviously be presented separately (e.g., from different parts of the same gel, or from different gels); or 3) modifying the contrast, brightness or color balance to obscure, eliminate or enhance some information.
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Our in-house editors will investigate any allegations of publication misconduct and may contact the authors' institutions or funders if necessary. If evidence of misconduct is found, appropriate action will be taken to correct or retract the publication. Authors are expected to comply with the best ethical publication practices when publishing with MDPI.
Citation Policy
Authors should ensure that where material is taken from other sources (including their own published writing) the source is clearly cited and that where appropriate permission is obtained.
Authors should not engage in excessive self-citation of their own work.
Authors should not copy references from other publications if they have not read the cited work.
Authors should not preferentially cite their own or their friends', peers', or institution's publications.
Authors should not cite advertisements or advertorial material.
In accordance with COPE guidelines, we expect that "original wording taken directly from publications by other researchers should appear in quotation marks with the appropriate citations." This condition also applies to an author's own work. COPE have produced a discussion document on citation manipulation with recommendations for best practice.
[Return to top]
Reviewer Suggestions
During the submission process, please suggest three potential reviewers with the appropriate expertise to review the manuscript. The editors will not necessarily approach these referees. Please provide detailed contact information (address, homepage, phone, e-mail address). The proposed referees should neither be current collaborators of the co-authors nor have published with any of the co-authors of the manuscript within the last three years. Proposed reviewers should be from different institutions to the authors. You may identify appropriate Editorial Board members of the journal as potential reviewers. You may suggest reviewers from among the authors that you frequently cite in your paper. For detailed information regarding the qualifications and responsibilities of the reviewers, please visit https://www.mdpi.com/reviewers.
[Return to top]
Extensive English Editing
It is the authors' responsibility to submit their work in correct English. The APC includes only minor English editing, conducted by native English speakers. The APC does not include extensive English

editing. If extensive editing is required, your paper could be returned to you at the English editing stage of the publication process. This could delay the publication of your work. You may have your work reviewed by an experienced English-speaking colleague or use a paid language-editing service before submitting your paper for publication. We offer rapid English editing, completed in 1 day, here: Author Services.
[Return to top]
Preprints and Conference Papers
Fermentation accepts submissions that have previously been made available as preprints provided that they have not undergone peer review. A preprint is a draft version of a paper made available online before submission to a journal.
MDPI operates *Preprints*, a preprint server to which submitted papers can be uploaded directly after completing journal submission. Note that *Preprints* operates independently of the journal and posting a preprint does not affect the peer review process. Check the *Preprints* instructions for authors for further information.
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Unpublished conference papers that do not meet the above conditions are recommended to be submitted to the Proceedings Series journals.
[Return to top]
Authorship
MDPI follows the International Committee of Medical Journal Editors (ICMJE) guidelines which state that, in order to qualify for authorship of a manuscript, the following criteria should be observed:

- Make substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work;
- Draft the work or review it critically for important intellectual content;
- Provide final approval of the version to be published;
- Agree to be accountable for all aspects of the work by ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who contributed to the work but do not qualify for authorship should be listed in the acknowledgments. More detailed guidance on authorship is given by the International Committee of Medical Journal Editors (ICMJE).
Any change to the author list should be approved by all authors including any who have been removed from the list. The corresponding author should act as a point of contact between the editor and the other authors and should keep co-authors informed and involve them in major decisions about the publication. We reserve the right to request confirmation that all authors meet the authorship conditions.
For more details about authorship please check MDPI ethics website.
Editorial Independence
Lack of Interference with Editorial Decisions
Editorial independence is of utmost importance and MDPI does not interfere with editorial decisions. All articles published by MDPI are peer reviewed and assessed by our independent editorial boards, and MDPI staff are not involved in decisions to accept manuscripts. When making an editorial decision, we expect the academic editor to make their decision based only upon:

- The suitability of selected reviewers;
- Adequacy of reviewer comments and author response;
- Overall scientific quality of the paper.

In all of our journals, in every aspect of operation, MDPI policies are informed by the mission to make science and research findings open and accessible as widely and rapidly as possible.

Editors and Editorial Staff as Authors

Editorial staff or editors shall not be involved in processing their own academic work. Submissions authored by editorial staff/editors will be assigned to at least two independent outside reviewers. Decisions will be made by other Editorial Board Members who do not have a conflict of interest with the author. Journal staff are not involved in the processing of their own work submitted to any MDPI journals.

Conflicts of Interest

According to The International Committee of Medical Journal Editors, "Authors should avoid entering into agreements with study sponsors, both for-profit and non-profit, that interfere with authors' access to all of the study's data or that interfere with their ability to analyze and interpret the data and to prepare and publish manuscripts independently when and where they choose."

All authors must disclose all relationships or interests that could inappropriately influence or bias their work. Examples of potential conflicts of interest include but are not limited to financial interests (such as membership, employment, consultancies, stocks/shares ownership, honoraria, grants or other funding, paid expert testimonies and patent-licensing arrangements) and non-financial interests (such as personal or professional relationships, affiliations, personal beliefs).

Authors can disclose potential conflicts of interest via the online submission system during the submission process. Declarations regarding conflicts of interest can also be collected via the MDPI disclosure form. The corresponding author must include a summary statement in the manuscript in a separate section "Conflicts of Interest" placed just before the reference list. The statement should reflect all the collected potential conflicts of interest disclosures in the form.

See below for examples of disclosures:

Conflicts of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stocks in Company Y. Author C has been involved as a consultant and expert witness in Company Z. Author D is the inventor of patent X.

If no conflicts exist, the authors should state:

Conflicts of Interest: The authors declare no conflicts of interest.

[Return to top]

Editorial Procedures and Peer Review

Pre-check

Immediately after submission, the journal's Managing Editor will perform the technical pre-check to assess:

- Overall suitability of the manuscript to the journal/section/Special Issue;
- Manuscript adherence to high-quality research and ethical standards;
- Standards of rigor to qualify for further review.

The academic editor (i.e., the Editor-in-Chief in the case of regular submissions, the Guest Editor in the case of Special Issue submissions, or an Editorial Board member in the case of a conflict of interest and of regular submissions if the Editor-in-Chief allows) will be notified of the submission and invited to perform an editorial pre-check. During the editorial pre-check phase, the academic editor will assess the suitability of the submission with respect to the scope of the journal, as well as the overall scientific soundness of the manuscript, including the relevance of the references and the correctness of the applied methodology. Academic editors can decide to reject the manuscript, request revision before peer review, or continue with the peer review process and recommend suitable reviewers.

Peer Review

Once a manuscript passes the initial checks, it will be assigned to at least two independent experts for peer review. A single-blind review is applied, where authors' identities are known to reviewers. Peer review comments are confidential, but will be disclosed if the authors opt for open peer review. In the case of regular submissions, in-house assistant editors will invite experts, including recommendations by an academic editor. These experts may also include *Editorial Board*

Members and Guest Editors of the journal. Potential reviewers suggested by the authors may also be considered. Reviewers should not have published with any of the co-authors during the past three years and should not currently work or collaborate with any of the institutions of the co-authors of the submitted manuscript. For more details about potential conflicts of interest, please check here, https://www.mdpi.com/reviewers#_bookmark9.

Optional Open Peer Review

The journal operates optional open peer review: *Authors are given the option for all review reports and editorial decisions to be published alongside their manuscript. In addition, reviewers can sign their review, i.e., identify themselves in the published review reports.* Authors can alter their choice for open peer review at any time before publication, but once the paper has been published changes will only be made at the discretion of the *Publisher* and *Editor-in-Chief*. We encourage authors to take advantage of this opportunity as proof of the rigorous process employed in publishing their research. To guarantee impartial refereeing, the names of referees will be revealed only if the referees agree to do so, and after a paper has been accepted for publication.

Editorial Decision and Revision

All the articles, reviews and communications published in MDPI journals go through the peer review process and receive at least two reviews. The in-house editor will communicate the decision of the academic editor, which will be one of the following:

- *Reconsider after Major Revision*:
  The acceptance of the manuscript would depend on the revision. The author needs to provide a point by point response or provide a rebuttal if some of the reviewer's comments cannot be revised. A maximum of two rounds of major revision per manuscript is normally provided. Authors will be asked to resubmit the revised paper within a suitable time frame, and the revised version will be returned to the reviewer for further comments.
- *Accept after Minor Revision*:
  In principle, the paper will be accepted after the authors revise based on the reviewers' and the Academic Editor's comments. Authors are given five days for minor revisions; however, extensions are granted on request.
- *Reconsider after Major Revision*:
  The acceptance of the manuscript would depend on the revision. The authors need to provide a point-by-point response or rebuttal if some revisions based on the reviewers' or Academic Editor's comments cannot be made. A maximum of two rounds of major revision per manuscript is normally provided. Authors will be asked to resubmit the revised paper within ten days; however, extensions are granted on request. The revised version of the manuscript will be returned to the reviewers for further comments.
- *Reject and Encourage Resubmission*:
  If additional experiments are needed to support the conclusions, the manuscript will be rejected and the authors will be encouraged to re-submit the paper once further experiments have been conducted.
- *Reject*:
  The article has serious flaws, and/or makes no original significant contribution. No offer of resubmission to the journal is provided.

All reviewer comments should be responded to in a point-by-point fashion. Where the authors disagree with a reviewer, they must provide a clear response.

In the event that the journal's editorial office is unable to maintain communication with the author during the manuscript review or production process, the journal reserves the right to withdraw the manuscript following a designated period of inactivity.

Author Appeals

Authors may appeal a rejection by sending an e-mail to the Editorial Office of the journal. The appeal must provide a detailed justification, including point-by-point responses to the reviewers' and/or Editor's comments using an appeal form. Appeals can only be submitted following a "reject and decline resubmission" decision and should be submitted within three months from the decision date. Failure to meet these criteria will result in the appeal not being considered further.

The *Managing Editor* will forward the manuscript and related information (including the identities of the referees) to a designated *Editorial Board Member*. The Academic Editor being consulted will be asked to provide an advisory recommendation on the manuscript and may recommend acceptance, further peer review, or uphold the original rejection decision. This decision will then be validated by the *Editor-in-Chief*. A reject decision at this stage is final and cannot be reversed.

Production and Publication

Once accepted, the manuscript will undergo professional copy-editing, English editing, proofreading by the authors, final corrections, pagination, and, publication on the www.mdpi.com website.

Typically, it is not permissible for authors to change the main text after acceptance (except for layout, English grammar, etc.). If authors would like to revise the main text, authors should inform the journal editorial office and state their reasons. Then, another round of academic decisions will be made based on the manuscript and the authors' responses.

Please read detailed Editorial Process here.

[Return to top]

ANEXO C

INSTRUÇÕES PARA AUTORES DA REVISTA *INTERNATIONAL JOURNAL OF PHARMACEUTICS* (ARTIGO 2)

About the journal

Aims and scope

The *International Journal of Pharmaceutics* is the third most cited journal in the "Pharmacy & Pharmacology" category out of 366 journals, being the true home for pharmaceutical scientists concerned with the physical, chemical and biological properties of devices and delivery systems for drugs, vaccines and biologicals, including their design, manufacture and evaluation. This includes evaluation of the properties of drugs, excipients such as surfactants and polymers and novel materials. The journal has special sections on pharmaceutical nanotechnology and personalized medicines, and publishes research papers, reviews, commentaries and letters to the editor as well as special issues.

Editorial Policy

The over-riding criteria for publication are originality, high scientific quality and interest to a multidisciplinary audience. Papers not sufficiently substantiated by experimental detail will not be published. Any technical queries will be referred back to the author, although the Editors reserve the right to make alterations in the text without altering the technical content. Manuscripts submitted under multiple authorship are reviewed on the assumption that all listed authors concur with the submission and that a copy of the final manuscript has been approved by all authors and tacitly or explicitly by the responsible authorities in the laboratories where the work was carried out. If accepted, the manuscript shall not be published elsewhere in the same form, in either the same or another language, without the consent of the Editors and Publisher.

Authors must state in a covering letter when submitting papers for publication the novelty embodied in their work or in the approach taken in their research. Routine bioequivalence studies are unlikely to find favour. No paper will be published which does not disclose fully the nature of the formulation used or details of materials which are key to the performance of a product, drug or excipient. Work which is predictable in outcome, for example the inclusion of another drug in a cyclodextrin to yield enhanced dissolution, will not be published unless it provides new insight into fundamental principles.

Journal announcements

International Journal of Pharmaceutics has an open access companion: *International Journal of Pharmaceutics: X*. Both journals share the same aims and scope, editorial team, and rigorous peer review. The difference between the journals is the access model under which the journals will publish your work and the indexation status.

Article types

1. Full Length Manuscripts
2. Reviews and Mini-Reviews

   Suggestions for review articles will be considered by the Review Editor. "Mini-reviews" of a topic are especially welcome.

Peer review

This journal follows a single anonymized review process. Your submission will initially be assessed by our editors to determine suitability for publication in this journal. If your submission is deemed suitable, it will typically be sent to a minimum of two reviewers for an independent expert assessment of the scientific quality. The decision as to whether your article is accepted or rejected will be taken by our editors.

Read more about peer review.

Our editors are not involved in making decisions about papers which:

- they have written themselves.

- have been written by family members or colleagues.
- relate to products or services in which they have an interest.

Any such submissions will be subject to the journal's usual procedures and peer review will be handled independently of the editor involved and their research group. Read more about editor duties.

Authors may submit a formal appeal request to the editorial decision, provided it meets all the requirements and follows the procedure outlined in Elsevier's Appeal Policy. Only one appeal per submission will be considered and the appeal decision will be final.

Special issues and article collections

The peer review process for special issues and article collections follows the same process as outlined above for regular submissions, except, a guest editor may send the submissions out to the reviewers and may recommend a decision to the journal editor. The journal editor oversees the peer review process of all special issues and article collections to ensure the high standards of publishing ethics and responsiveness are respected and is responsible for the final decision regarding acceptance or rejection of articles.

Open access

We refer you to our open access information page to learn about open access options for this journal.

Ethics and policies

Ethics in publishing

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- the article is not under consideration for publication elsewhere.
- the article's publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.
- if accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder.

To verify compliance with our journal publishing policies, we may check your manuscript with our screening tools.

Authorship

All authors should have made substantial contributions to all of the following:

1. The conception and design of the study, or acquisition of data, or analysis and interpretation of data.
2. Drafting the article or revising it critically for important intellectual content.
3. Final approval of the version to be submitted.

Authors should appoint a corresponding author to communicate with the journal during the editorial process. All authors should agree to be accountable for all aspects of the work to ensure that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Changes to authorship

The editors of this journal generally will not consider changes to authorship once a manuscript has been submitted. It is important that authors carefully consider the authorship list and order of authors and provide a definitive author list at submission.

The policy of this journal around authorship changes:

- All authors must be listed in the manuscript and their details entered into the submission system. Changes can only be made prior to acceptance, and only if approved by the journal editor. This includes additions, deletion, or rearrangement of author names.
- Requests to change authorship must be made by the corresponding author using the Authorship Change Request form. The corresponding author must provide the reason for

the request to the journal editor with written confirmation from all authors, including any authors being added or removed, that they agree with the changes. Requests which do not comply with the instructions outlined in the form will not be considered.

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List funding sources in this standard way to facilitate compliance to funder's requirements:

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It is not necessary to include detailed descriptions on the program or type of grants, scholarships and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

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- Definitions of sex and/or gender applied should be explicitly stated to enhance the precision, rigor and reproducibility of the research and to avoid ambiguity or conflation of terms and the constructs to which they refer.

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Units
This journal requires you to use the international system of units (SI) which follows internationally accepted rules and conventions. If other units are mentioned within your article, you should provide the equivalent unit in SI.
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Tables must be submitted as editable text, not as images. Some guidelines:
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- Place any table notes below the table body.
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You are encouraged to publish a description of your research data, methods, or protocols related to your regular article as a co-submission article in *Data in Brief* or *MethodsX*.

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Any references cited within your article should also be present in your reference list and vice versa. Some guidelines:

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- We recommend that you do not include unpublished results and personal communications in your reference list, though you may mention them in the text of your article.
- Any unpublished results and personal communications included in your reference list must follow the standard reference style of the journal. In substitution of the publication date add "unpublished results" or "personal communication."
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Before submission, check that all data provided in your reference list are correct, including any references which have been copied. Providing correct reference data allows us to link to abstracting and indexing services such as Scopus, Crossref and PubMed. Any incorrect surnames, journal or book titles, publication years or pagination within your references may prevent link creation.

We encourage the use of Digital Object Identifiers (DOIs) as reference links as they provide a permanent link to the electronic article referenced.

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This journal does not set strict requirements on reference formatting at submission. Some guidelines:

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- Author names, journal or book titles, chapter or article titles, year of publication, volume numbers, article numbers or pagination must be included, where applicable.
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Van der Geer, J., Handgraaf, T., Lupton, R.A., 2022. The art of writing a scientific article. Heliyon. 19, e00205. https://doi.org/10.1016/j.heliyon.2022.e00205.

Reference to a book:

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