UNIVERSIDADE FEDERAL DE MINAS GERAIS
INSTITUTO DE CIÊNCIAS BIOLÓGICAS
CURSO DE MESTRADO PROFISSIONAL EM MICROBIOLOGIA APLICADA

SAMUEL CENDÓN FERREIRA GUARIENTO

MEMBRANAS DE QUITOSANA CONTENDO METABÓLITOS PRODUZIDOS PELA BACTÉRIA PROBIÓTICA *Lactococcus lactis* subsp. *lactis* NCDO 2118 PARA CICATRIZAÇÃO DE FERIDAS DE QUEIMADURAS E ÚLCERAS DO PÉ DIABÉTICO

BELO HORIZONTE
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Orientador:
Prof. Dr. Vasco Ariston de Carvalho Azevedo
Co-orientadores:
Dr. Túlio Marcos Santos
Dra. Joyce da Cruz Ferraz Dutra

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"MEMBRANAS DE QUITOSANA CONTENDO METABÓLITOS PRODUZIDOS PELA BACTÉRIA PROBIÓTICA *LACTOCOCCUS LACTIS* SUBSP. *LACTIS* NCDO 2118 PARA CICATRIZAÇÃO DE FERIDAS DE QUEIMADURAS E ÚLCERAS DO PÉ DIABÉTICO"

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Belo Horizonte, 03 de setembro de 2025

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RESUMO

As feridas crônicas, como úlceras do pé diabético (UPD) e queimaduras, representam um desafio clínico significativo devido à sua complexidade fisiopatológica e ao alto risco de infecções. Nesse contexto, biomateriais à base de quitosana têm se destacado por suas propriedades bioativas, incluindo biocompatibilidade, atividade antimicrobiana e capacidade de modular a resposta inflamatória. Além disso, os posbióticos – metabólitos bacterianos com efeitos terapêuticos – emergem como uma estratégia promissora para potencializar a cicatrização. Assim, este trabalho propõe o desenvolvimento e caracterização de membranas de quitosana contendo posbióticos produzidos pela bactéria *Lactococcus lactis* subsp. *lactis* NCDO 2118, visando o tratamento de feridas de queimaduras e úlceras do pé diabético (UPD). A abordagem integra duas etapas principais: (1) uma revisão sistemática e metanálise seguindo as diretrizes PRISMA 2020, avaliando o viés metodológico com SYRCLE e MINORS, para determinar a eficácia de curativos à base de quitosana; e (2) a síntese e caracterização inicial de membranas de quitosana contendo metabólitos bioativos (GABA e Hsp65). A metanálise revelou efeito significativo da quitosana na cicatrização (SMD = 2,48; $p < 0,001$), com fatores como liberação sustentada, resistência mecânica e baixo ângulo de contato identificados como preditores-chave de eficácia. As membranas desenvolvidas demonstraram integridade estrutural, flexibilidade, mas sem uma atividade antimicrobiana significativa contra patógenos comuns em feridas crônicas (*Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 700603, *Acinetobacter baumannii* ATCC 19606 e *Proteus mirabilis* ATCC 15290). A combinação dos posbióticos com as propriedades bioativas da quitosana abre novas perspectivas para o desenvolvimento de terapias mais eficazes, seguras e de baixo custo.

Palavras-chave: Quitosana; Posbióticos; *Lactococcus lactis*; Cicatrização de feridas; Queimaduras; Úlcera do pé diabético; Revisão sistemática.

ABSTRACT

Chronic wounds, such as diabetic foot ulcers (DFUs) and burns, represent a significant clinical challenge due to their pathophysiological complexity and high risk of infection. In this context, chitosan-based biomaterials have stood out for their bioactive properties, including biocompatibility, antimicrobial activity, and ability to modulate the inflammatory response. In addition, postbiotics—bacterial metabolites with therapeutic effects—are emerging as a promising strategy to enhance healing. So, this study proposes the development and characterization of chitosan membranes containing postbiotics produced by the bacterium *Lactococcus lactis* subsp. *lactis* NCDO 2118 for the treatment of burn wounds and diabetic foot ulcers (DFU). The approach integrates two main stages: (1) a systematic review and meta-analysis following PRISMA 2020 guidelines, assessing methodological bias using SYRCLE and MINORS tools, to evaluate the efficacy of chitosan-based dressings; and (2) the synthesis and initial characterization of chitosan membranes loaded with bioactive metabolites (GABA and Hsp65). Meta-analysis revealed a significant effect of chitosan on wound healing (SMD = 2.48; $p < 0.001$), with sustained release, mechanical strength, and low contact angle identified as key predictors of therapeutic efficacy. The developed membranes showed structural integrity, flexibility, but without any significative antimicrobial activity against common pathogens in chronic wounds (*Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 700603, *Acinetobacter baumannii* ATCC 19606 e *Proteus mirabilis* ATCC 15290). The combination of postbiotics with chitosan's bioactive properties opens new perspectives for the development of more effective, safe, and low-cost therapies.

Keywords: Chitosan; Postbiotics; *Lactococcus lactis*; Wound healing; Diabetic foot ulcer; Burn; Systematic review; Meta-analysis.

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LISTA DE ABREVIATURAS

AIE – a*ggregation-induced emission* (emissão induzida por agregação)

AGE – *advanced glycation end-product* (produtos finais de glicação avançada)

CHL – Chloramphenicol (Cloranfenicol) DD – do inglês, *degree of deacetylation* (grau de desacetilação)

UPD – Úlcera do Pé Diabético

DAMPs – *damage associated molecular patterns* (padrões moleculares associados a dano)

DM – Diabetes mellitus

GABA – gamma aminobutyric acid (ácido gama-aminobutírico)

GAD – glutamato descarboxilase.

GP IIb-IIIa – glicoproteína IIb/IIIa

HBOT – *hyperbaric oxygen therapy* (oxigenoterapia hiperbárica)

HMW – *high molecular weight* (alto peso molecular)

HPLC – *High Performance Liquid Chromatography* (cromatografia líquida de alta performance)

HSF – *human skin fibroblast* (fibroblastos da pele humana)

HSP – *Heat Shock Protein*

IL-1 – Interleucina-1

IL-2 – Interleucina-2

IL-8 – Interleucina-8

MIC – *minimum inhibitory concentration* (concentração inibitória mínima)

MINORS – *Methodological index for non-randomized studies*

MW – *molecular weight* (peso molecular)

NPWT – *negative pressure wound therapy* (terapia de pressão negativa)

OMS – Organização Mundial da Saúde

L. lactis – *Lactococcus lactis*

LMW – *low molecular weight* (baixo peso molecular)

LPS – lipopolissacarídeos

PCA – *Principal Components Analysis* (Análise de componentes principais)

PDGF – *Platelet-derived growth factor* (fator de crescimento derivado de plaquetas)

PDT – *photodynamic therapy* (terapia fotodinâmica)

RBC – *red blood cells* (glóbulos vermelhos).

ROS – *Reactive Oxygen Species* (espécies reativas de oxigênio)

SIRS – *Systemic inflammatory response syndrome* (Síndrome da resposta inflamatória sistêmica)

SNC – Sistema Nervoso Central

SYRCLE – *SYstematic Review Centre for Laboratory animal Experimentation*

TGF-β – *Transforming growth factor-β* (fator de crescimento transformador β)

T-regs – *T regulatory cells (*Células T reguladoras)

SUMÁRIO

1. INTRODUÇÃO

Feridas crônicas impõem desafios persistentes aos sistemas de saúde globais, devido à dor, à queda na qualidade de vida e ao risco elevado de complicações como infecções e amputações (Dreifke; Jayasuriya; Jayasuriya, 2015; Nussbaum *et al*., 2018). Queimaduras e úlceras do pé diabético (UPD) destacam-se por sua complexidade fisiopatológica (Chang; Nguyen, 2021; McDermott *et al*., 2023; Park *et al*., 2024). Nesses casos, a cicatrização é prejudicada por desregulação inflamatória, colonização bacteriana e dificuldade de regeneração tecidual, o que exige abordagens terapêuticas mais eficazes e inovadoras (Abazari *et al*., 2022).

Nesse contexto, a engenharia de tecidos tem se voltado ao desenvolvimento de biomateriais capazes de atuar além da barreira física, modulando ativamente o microambiente da ferida. Biopolímeros biocompatíveis, especialmente os hidrogéis, destacam-se como plataformas promissoras para curativos de nova geração (Feng *et al*., 2021). Entre eles, a quitosana — biopolímero natural derivado da quitina — apresenta vantagens relevantes, como biocompatibilidade, biodegradabilidade e propriedades bioativas intrínsecas (Blebea *et al*., 2025; Mo; Xiang; Chen, 2021). A quitosana promove hemostasia, possui atividade antimicrobiana, modula a inflamação, apresenta ação antioxidante e estimula a proliferação celular e a formação do tecido de granulação, o que a torna altamente adequada ao tratamento de queimaduras e UPD (Bernkop-Schnürch, 2018; Dong; Zhang; Guo, 2022; Li *et al*., 2025; Zhang *et al*., 2024; Zhao *et al*., 2023).

Embora a quitosana já apresente potencial reconhecido, novas estratégias buscam funcionalizá-la com agentes terapêuticos para superar limitações e ampliar sua eficácia. Uma dessas abordagens é a incorporação de posbióticos — metabólitos, fragmentos celulares ou subprodutos de microrganismos probióticos que exercem efeitos benéficos mesmo na ausência de viabilidade microbiana. Essa estratégia apresenta vantagens em relação aos probióticos vivos, como maior estabilidade, segurança e facilidade de armazenamento e incorporação em matrizes poliméricas (Bazjou *et al*., 2021; Farahani *et al*., 2023; Shokatayeva; Savitskaya; Kistaubayeva, 2021).

Entre as fontes de posbióticos, a bactéria *Lactococcus lactis* subsp. *lactis* NCDO 2118 destaca-se pela produção de metabólitos bioativos com efeitos terapêuticos potenciais. Essa cepa sintetiza, entre outros compostos, o ácido gama-aminobutírico (GABA), com função imunomoduladora (Han *et al*., 2007a; Oliveira, 2020), e a proteína de choque térmico Hsp65, associada à indução de respostas celulares reparadoras (Gusmao-Silva *et al*., 2020). A

integração da quitosana com esses posbióticos pode favorecer o desenvolvimento de curativos tópicos com ação biológica ampliada. No entanto, apesar de existirem estudos isolados sobre a quitosana e, mais recentemente, sobre posbióticos, ainda falta uma avaliação metodológica rigorosa da eficácia de curativos à base de quitosana e, principalmente, a caracterização de sistemas híbridos que combinem quitosana e posbióticos específicos para uso em feridas complexas.

2. JUSTIFICATIVA

O tratamento de feridas crônicas e queimaduras representa um desafio relevante para a saúde pública no Brasil, devido aos altos custos, à morbidade associada e ao impacto direto na qualidade de vida dos pacientes. A cicatrização dessas lesões é comprometida por fatores como infecção, isquemia, inflamação crônica e disfunção celular. Estima-se que, anualmente, cerca de 150 mil brasileiros sofram queimaduras significativas, enquanto aproximadamente 16,8 milhões convivem com diabetes mellitus — muitos deles com UPDs, lesões de difícil cicatrização e alto risco de infecção, amputação e hospitalização prolongada (MINISTÉRIO DA SAUDE, *[S.d.]*; UNIFESP, *[S.d.]*).

Feridas crônicas e queimaduras compartilham um obstáculo central: a interrupção do processo fisiológico de cicatrização, frequentemente agravada por inflamação crônica, isquemia e infecção. Tratamentos convencionais, como curativos passivos e desbridamento, tendem a resultar em recuperação prolongada e em complicações como cicatrizes hipertróficas e contraturas (Costantino *et al*., 2022). Embora biomateriais como alginato e pHEMA tenham representado avanços, esses curativos ainda enfrentam limitações quanto ao custo, à aplicabilidade clínica e à biodegradabilidade (Lee *et al*., 2009; Li *et al*., 2021b).

Nesse contexto, a quitosana destaca-se como biopolímero funcional, por reunir biocompatibilidade, biodegradabilidade, atividade hemostática, ação antimicrobiana e potencial modulador da resposta inflamatória (Feng *et al*., 2021; Zhao *et al*., 2023). Apesar do crescente número de estudos pré-clínicos com curativos de quitosana, ainda falta uma avaliação crítica que relacione suas propriedades físico-químicas à eficácia terapêutica. Muitos desses estudos apresentam viés metodológico, ausência de padronização e resultados conflitantes. Nesse contexto, torna-se necessária uma revisão sistemática com metanálise rigorosa, fundamentada nas diretrizes PRISMA, para identificar evidências consistentes e fatores preditivos de sucesso no uso da quitosana em feridas. Mais do que mapear a literatura, essa análise orienta o desenvolvimento racional de biomateriais.

Com base nos achados da revisão sistemática, este estudo propõe um sistema terapêutico inovador: membranas de quitosana incorporando posbióticos da cepa *Lactococcus lactis* subsp. *lactis* NCDO 2118, como prova de conceito. Essa cepa, produtora de GABA e, em sua forma recombinante, da proteína Hsp65, exerce efeitos imunomoduladores, antinociceptivos e tolerogênicos sem depender da viabilidade bacteriana, favorecendo a segurança e estabilidade do curativo. A combinação quitosana-posbióticos propõe uma abordagem além da ação antimicrobiana, com atuação direta sobre vias inflamatórias e neuroimunológicas envolvidas na cicatrização.

3. OBJETIVOS

3.1. Objetivo geral:

Desenvolver e caracterizar membranas de quitosana contendo posbióticos de *Lactococcus lactis* subsp. *lactis* NCDO 2118 — produtora de GABA e expressando Hsp 65 — para o tratamento de feridas de queimaduras e úlceras do pé diabético, com base em uma avaliação crítica da literatura científica por meio de revisão sistemática e metanálise.

3.2. Objetivos específicos:

3.2.1. Etapa I: Fundamentação Baseada em Evidências

1. Realizar levantamento bibliográfico sobre membranas de quitosana para cicatrização de feridas e sobre a aplicação de posbióticos na formulação de curativos, com foco em potencializar os efeitos terapêuticos.

2. Realizar uma revisão sistemática e metanálise seguindo as diretrizes PRISMA 2020, avaliando o viés metodológico com as ferramentas SYRCLE e MINORS, para avaliar a eficácia de curativos à base de quitosana no tratamento de feridas de queimaduras e UPDs e compara-los aos tratamentos padrões como a gaze comum.

3.2.2. Etapa II: Desenvolvimento e Caracterização do Biomaterial

1. Sintetizar membranas de quitosana contendo posbióticos da cepa *L. lactis* NCDO 2118 nas versões selvagem e recombinante para Hsp 65).

2. Avaliar a integridade estrutural das membranas após desidratação.
3. Avaliar a atividade antimicrobiana das membranas frente a patógenos associados a feridas crônicas (*S. aureus, P. aeruginosa, P. mirabilis, A. baumannii, K. pneumoniae*).

4. REFERENCIAL TEÓRICO

4.1. Cicatrização de feridas: importância para a saúde pública

A pele, maior órgão do corpo humano, representa cerca de 16% da massa corporal total e funciona como uma barreira física contra agressões externas. A pele é dividida em camadas, sendo elas: epiderme, derme e tecido subcutâneo (Chou *et al*., 2013; Sreedevi, 2020). Em estado saudável, a epiderme atua como uma interface impermeável que protege os tecidos internos contra agressões externas (Chou *et al*., 2013). Sua integridade é essencial para a homeostase e proteção contra agentes ambientais (Díaz-García *et al*., 2021). Lesões cutâneas causadas por doenças crônicas, queimaduras, traumas ou cirurgias comprometem essa função, levando a déficits funcionais, morbidade e sofrimento emocional, além de sobrecarregar os sistemas de saúde globalmente (Aragona *et al*., 2017).

A cicatrização eficaz de feridas depende da coordenação sequencial entre diferentes tipos celulares da pele. As feridas classificam-se como agudas (com potencial de cicatrização) ou crônicas (com cicatrização comprometida), conforme sua etiologia e trajetória de reparação. Feridas agudas de menor gravidade são regeneradas pela própria pele por meio de respostas celulares, remodelamento da matriz extracelular e sinalização por fatores de crescimento (Boyce; Lalley, 2018; Tottoli *et al*., 2020). Já as feridas crônicas apresentam reparo lento ou incompleto, geralmente agravado por infecções e perda excessiva de fluidos. Essas lesões comprometem a estrutura e função da pele, afetam milhões de pessoas e impõem custos significativos aos sistemas de saúde (Dreifke; Jayasuriya; Jayasuriya, 2015; Nussbaum *et al*., 2018).

Apesar dos avanços científicos e tecnológicos, ainda existem lacunas no tratamento de feridas cutâneas extensas e crônicas. A principal dificuldade reside na avaliação precisa das lesões e no manejo clínico adequado. Nesse contexto, o desenvolvimento de novos produtos e estratégias terapêuticas segue essencial para melhorar a cicatrização (Mamun *et al*., 2024), especialmente em casos de queimaduras e UPDs.

4.2. Queimaduras

A Organização Mundial da Saúde (OMS) classifica as queimaduras como um problema global de saúde pública, responsável por aproximadamente 180 mil mortes anuais (“World Health Organization - Burns”, 2023). A maioria dos casos ocorre em países de baixa e média renda, especialmente na África e no Sudeste Asiático. Queimaduras não fatais figuram entre as principais causas de morbidade, com consequências como hospitalizações prolongadas, desfiguração física, incapacidades permanentes e estigmatização social. Em crianças, lesões extensas provocam alterações imunológicas e metabólicas significativas, aumentando o risco de infecções e perda de massa magra (Park *et al*., 2024; “World Health Organization - Burns”, 2023).

As queimaduras, causadas por calor, eletricidade, radiação ou agentes químicos, afetam a pele e tecidos subjacentes, configurando um grave problema de saúde pública, especialmente entre crianças e idosos. Sua gravidade é classificada conforme profundidade e extensão da lesão: queimaduras de primeiro grau atingem apenas a epiderme e provocam dor leve e eritema; lesões de segundo grau superficial (2A) envolvem derme parcial, são dolorosas, exsudativas e podem cicatrizar com curativos; lesões de segundo grau profundo (2B) afetam camadas mais internas, são menos dolorosas e geralmente requerem cirurgia; queimaduras de terceiro grau destroem toda a derme, comprometem terminações nervosas e exigem intervenções cirúrgicas; casos de quarto grau atingem músculos ou ossos, apresentando necrose extensa e risco de amputação (Żwierełło *et al*., 2023).

Uma queimadura pode ser dividida em três zonas concêntricas: a zona de coagulação, localizada no centro da lesão, com necrose tecidual irreversível; a zona de estase, caracterizada por isquemia e potencial de recuperação; e a zona de hiperemia, na periferia, com vasodilatação inflamatória e fluxo sanguíneo aumentado (Żwierełło *et al*., 2023). A cicatrização inicia-se com a fase inflamatória, marcada pelo recrutamento de neutrófilos e monócitos, facilitado pela vasodilatação local. Nessa etapa, ocorre a remoção do tecido necrótico e o início de uma cascata de sinalização molecular essencial para a regeneração (Abazari *et al*., 2022; Żwierełło *et al*., 2023).

À medida que a inflamação cede, citocinas e fatores de crescimento ativam queratinócitos e fibroblastos, impulsionando a fase proliferativa, que restaura a vascularização e promove a regeneração tecidual (Abazari *et al*., 2022). Na fase final, de remodelação, há deposição de colágeno e elastina, além da diferenciação de fibroblastos em miofibroblastos, o que contribui para a maturação do tecido (Żwierełło *et al*., 2023). A contração desses miofibroblastos e o

avanço da reepitelização determinam a qualidade da cicatriz (Talbott *et al*., 2022). Cicatrizes anormais, como as hipertróficas e quelóides, são elevadas, avermelhadas, pruriginosas e dolorosas, podendo causar alterações pigmentares e contraturas (Basson; Bayat, 2022).

Pacientes com queimaduras extensas apresentam alto risco de complicações infecciosas devido à disfunção imunológica e à perda da integridade cutânea. A síndrome da resposta inflamatória sistêmica, comum nesses casos, é marcada por liberação excessiva de citocinas e sintomas como febre ou hipotermia, taquicardia e taquipneia (Honoré *et al*., 2025). Simultaneamente, ocorrem prejuízos importantes na resposta imune inata, como a redução da apresentação de antígenos por macrófagos e a menor capacidade dos neutrófilos em eliminar patógenos (Kuznetsova; Andryukov; Besednova, 2022; Yang *et al*., 2021). Além disso, há supressão da proliferação de células T e da produção de interleucina-2 (IL-2), comprometendo a imunidade adaptativa (Keyloun *et al*., 2022; Moins-Teisserenc *et al*., 2021). Esses fatores tornam o organismo mais suscetível a infecções bacterianas, fúngicas, virais e por leveduras, além de favorecer o aumento da virulência microbiana e o risco de falência orgânica (Dobson; Morris; Letson, 2024; Sierawska *et al*., 2022).

4.3. Úlcera do pé diabético (UPD)

A diabetes mellitus (DM) afeta atualmente cerca de 500 milhões de pessoas no mundo, com estimativas apontando para aumento contínuo da prevalência nos próximos anos. Nos Estados Unidos, o impacto econômico anual da doença ultrapassa US$ 300 bilhões, somando custos médicos diretos e perdas por redução de produtividade (Gao *et al*., 2021; Glover *et al*., 2021). A DM é uma doença metabólica caracterizada por hiperglicemia devido à deficiência de insulina ou ao uso ineficaz da insulina. É classificada nos tipos 1 e 2, sendo o tipo 1 representante de 5 a 10% dos casos de diabetes e resulta de uma destruição autoimune mediada pelas células β do pâncreas. Já o tipo 2, abrange indivíduos que apresentam resistência à insulina e geralmente têm deficiência relativa (em vez de absoluta) de insulina (American Diabetes Association, 2009).

Estima-se que entre 20% e 33% dos indivíduos com DM desenvolverão, ao longo da vida, uma ferida crônica, principalmente a UPD, decorrente da interação entre neuropatia periférica, isquemia e disfunção imunológica. Esses fatores comprometem a sensibilidade, a perfusão tecidual e a resposta inflamatória nos membros inferiores. As UPDs apresentam elevadas taxas de recorrência: cerca de 40% dos casos reaparecem em um ano, e 65% em cinco

anos. Atualmente, não há métodos confiáveis para prever sua ocorrência (Chang; Nguyen, 2021; McDermott *et al*., 2023).

Uma parcela expressiva dos pacientes com UPD evolui para amputação de membros inferiores, o que reduz a qualidade de vida e acarreta altos custos médico-hospitalares. Diante desse impacto clínico e econômico, estima-se que o mercado global de tratamentos para UPD crescerá de US$ 7,03 bilhões em 2019 para US$ 11,05 bilhões até 2027, o que evidencia a necessidade de estratégias terapêuticas e ferramentas diagnósticas mais eficazes para o controle da doença (Burgess *et al*., 2021; Glover *et al*., 2021; Perveen *et al*., 2024; Zhu *et al*., 2023). A fisiopatologia da UPD envolve múltiplos mecanismos mediados pela hiperglicemia crônica. Entre suas consequências estão a angiogênese desregulada, inflamação persistente, acúmulo de espécies reativas de oxigênio (ROS) e colonização bacteriana com formação de biofilmes de difícil remoção (Burgess *et al*., 2021). A hiperglicemia também promove aterosclerose, o que compromete a oxigenação e o suprimento de nutrientes no local da lesão, dificultando o processo de cicatrização (Mastrogiacomo *et al*., 2023; Mohsin *et al*., 2024).

Em indivíduos com diabetes, a hiperglicemia induz ainda disfunção endotelial, prejudicando a vasodilatação induzida por pressão — mecanismo crucial na proteção da pele (Dubsky *et al*., 2023; Yang *et al*., 2024). Além disso, interfere nas fases da reepitelização ao inibir a síntese proteica, a migração celular e a proliferação de queratinócitos e fibroblastos, células essenciais para o fechamento da ferida e regeneração do tecido (Shu *et al*., 2022; Song *et al*., 2025).

Outro mecanismo relevante pelo qual a hiperglicemia e a hipóxia tecidual comprometem a cicatrização de feridas é o estresse oxidativo. Indivíduos com diabetes tipo 2 de longa duração apresentam redução da atividade de enzimas antioxidantes, o que favorece o acúmulo de ROS (Chen *et al*., 2025; Deng *et al*., 2021). A hiperglicemia crônica intensifica esse acúmulo por meio de vias metabólicas como a do poliol, hexosamina, ativação da proteína quinase C e formação de produtos finais de glicação avançada (AGEs), resultando em estresse oxidativo e disfunção endotelial. Esse desequilíbrio prejudica a angiogênese, a proliferação celular e a resposta imune, dificultando o reparo tecidual e aumentando o risco de infecções (Deng *et al*., 2021).

Embora as ROS desempenhem papel fisiológico nas fases iniciais da cicatrização, ao mediar a eliminação de patógenos e a sinalização celular (Hunt *et al*., 2024), sua produção excessiva ou prolongada interfere negativamente nas etapas posteriores do processo reparador. Altos níveis de ROS induzem lesões estruturais e metabólicas nos nervos periféricos,

comprometendo sua vascularização. Isso pode gerar disfunção em fibras nervosas sensoriais, motoras e autonômicas, cada uma contribuindo de forma independente para a maior suscetibilidade ao desenvolvimento de úlceras do pé diabético (Yang *et al*., 2022).

De forma integrada, essas alterações fisiopatológicas induzidas pela hiperglicemia descontrolada aumentam a vulnerabilidade da pele a traumas e infecções, comprometendo a progressão das fases reparadoras e dificultando o fechamento eficaz da ferida.

4.4. Biopolímeros biocompatíveis para cicatrização de feridas

Feridas resultantes de queimaduras UPDs representam desafios terapêuticos devido à sua etiologia multifatorial. As abordagens clínicas são divididas em tratamentos convencionais e terapias avançadas. As intervenções convencionais incluem desbridamento, controle glicêmico, manejo da infecção e alívio de pressão no local da lesão. As estratégias avançadas incorporam oxigenoterapia hiperbárica (HBOT), curativos especializados, terapia por pressão negativa (NPWT) e técnicas regenerativas baseadas em fatores de crescimento, plasma rico em plaquetas, células-tronco e produtos derivados de tecidos ou células (Abazari *et al*., 2022; American Diabetes Association Professional Practice Committee, 2025; Chen *et al*., 2021a; Elsharkawi *et al*., 2023; Sharma *et al*., 2021).

A cicatrização da pele envolve eventos celulares e moleculares influenciados por fatores intrínsecos (como idade e comorbidades) e extrínsecos (como infecção e tipo de tratamento). Esse processo pode ser acelerado com o uso de biomateriais que ofereçam suporte físico e bioquímico ao tecido lesado. Para isso, os materiais devem apresentar propriedades como flexibilidade, estabilidade, biodegradabilidade e capacidade de adaptação a diferentes tipos de feridas. Também é essencial que mantenham a umidade local, promovam a hemostasia e absorvam eficientemente o exsudato (Feng *et al*., 2021).

Com os avanços da biologia molecular e da engenharia de tecidos, uma variedade de biomateriais tem sido desenvolvida para aplicações em cicatrização, com destaque para os sistemas à base de hidrogéis. Hidrogéis são redes tridimensionais (3D) formadas por cadeias de polímeros hidrofílicos reticuladas (Yang *et al*., 2023). Sua estrutura confere propriedades viscoelásticas típicas de sólidos, aliadas ao comportamento fluido dos líquidos, o que os torna funcionalmente semelhantes à matriz extracelular natural. Comparados aos curativos convencionais, os hidrogéis oferecem múltiplas vantagens: (1) alta hidrofilicidade, permitindo absorção eficiente do exsudato (Fawzy; Fortunata, 2023); (2) retenção de umidade, que favorece o microambiente cicatricial (Rezvani Ghomi; Niazi; Ramakrishna, 2023); (3)

formação de barreira protetora contra contaminação microbiana (Lagoa; Queiroga; Martins, 2024; Zhang *et al*., 2024); e (4) baixa adesão ao leito da ferida, o que reduz dor e trauma durante as trocas de curativo (Feng *et al*., 2021).

Os hidrogéis podem ser classificados em dois grupos principais: naturais e sintéticos. Os naturais são derivados de polímeros biológicos, como quitosana, alginato de sódio, colágeno e hialuronato de sódio. Entre esses, a quitosana destaca-se como um dos materiais mais amplamente investigados para aplicações biomédicas, devido à sua biocompatibilidade, atividade antimicrobiana e propriedades regenerativas (Feng *et al*., 2021).

4.5. Hidrogel de quitosana: propriedades valiosas como biomaterial para aplicações biomédicas.

A quitosana é um polissacarídeo e copolímero obtido por desacetilação da quitina, presente principalmente no exoesqueleto de crustáceos, insetos e em fungos. Sua estrutura consiste em unidades de N-acetil-D-glucosamina ligadas por ligações β-1,4-glicosídicas, quimicamente identificada como (1→4)-2-amino-2-desoxi-β-D-glucano. A conversão da quitina em quitosana pode ser realizada por métodos químicos — geralmente com solução concentrada de hidróxido de sódio (25–50%) em altas temperaturas (90–120 ºC) — ou por vias enzimáticas, com o uso de desacetilases (**Figura 1**) (Sharifi-Rad *et al*., 2021). Esse biopolímero apresenta alta biocompatibilidade, baixa toxicidade e excelente biodegradabilidade, características que o tornam um dos principais candidatos para formulações de hidrogéis voltados à regeneração tecidual. Essas propriedades têm favorecido seu uso em curativos avançados, especialmente no tratamento de queimaduras e úlceras do pé diabético (Blebea *et al*., 2025; Mo; Xiang; Chen, 2021).

Estruturalmente, a quitosana possui grupos amino e hidroxila que favorecem reações covalentes com diversos polímeros, permitindo a formação de redes tridimensionais estáveis de hidrogel (Guyot; Cerruti; Lerouge, 2021; Li *et al*., 2021a; Zhao *et al*., 2023). Seus grupos amino catiônicos também promovem interações eletrostáticas com ânions e moléculas carregadas negativamente, fundamentais para a formação de hidrogéis físicos (Lv *et al*., 2023). Essas características estruturais tornam os hidrogéis de quitosana altamente versáteis em aplicações biomédicas, incluindo engenharia de tecidos, liberação controlada de fármacos e sistemas de administração direcionada. Além disso, há crescente interesse no desenvolvimento de hidrogéis inteligentes funcionalizados com agentes terapêuticos (Zhao *et al*., 2023).

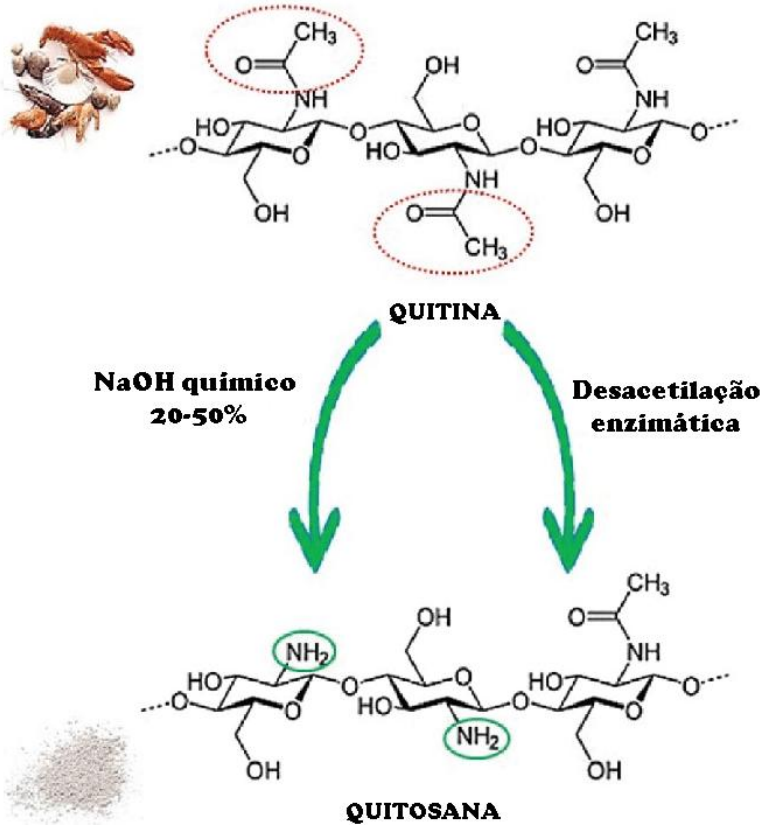

Figura 1. Estrutura química da quitina e da quitosana e processos químicos e enzimáticos de desacetilação para conversão de quitina em quitosana. Em destaque estão os grupamentos acetil da quitina (círculos vermelhos) e amino da quitosana (círculos verdes). Traduzido e modificado de Sharifi-Rad *et al*. (2021).

A quitosana é o único polissacarídeo de ocorrência natural com caráter alcalino, o que a diferencia de outros polímeros de origem vegetal ou marinha, como celulose, dextrano, pectina, ácido algínico, ágar, amido e carragenina, que são neutros ou ácidos. É biocompatível, biodegradável, inodora e não tóxica (Blebea *et al*., 2025). Após aplicação in vivo, a quitosana é degradada lentamente pela ação da lisozima, que a hidrolisa em oligômeros bioativos. Esses fragmentos induzem a ativação de macrófagos, promovendo a liberação de N-acetil-D-glucosaminidase, enzima responsável por converter os oligômeros em unidades menores como N-acetilglucosamina e D-glucosamina (Singh; Ray, 2000). Além disso, a quitosana pode ser degradada por microrganismos presentes no solo, que a utilizam como fonte de carbono e nitrogênio. Em condições ambientais favoráveis, filmes de quitosana se degradam completamente em cerca de 60 dias, dependendo da umidade e da composição da microbiota (Ali *et al*., 2024; Wrońska *et al*., 2023).

A quitosana possui ampla variação de peso molecular (MW), entre 50 Da e 900 kDa, sendo as formas comerciais mais comuns aquelas entre 100 e 800 kDa. Com base nesse parâmetro, é classificada em quitosana de alto peso molecular (HMW) e de baixo peso molecular (LMW), cada uma com propriedades funcionais distintas. A forma HMW apresenta baixa solubilidade em água e biodegradabilidade limitada in vivo, o que pode gerar acúmulo tecidual e potenciais efeitos adversos. No entanto, sua alta viscosidade contribui para maior adesão do hidrogel e resistência mecânica. Já a quitosana LMW é mais solúvel e exibe atividades biológicas mais acentuadas, incluindo efeitos antioxidantes, antibacterianos e antitumorais. Por essas razões, tem sido amplamente explorada em aplicações biomédicas, na indústria alimentícia e em formulações de saúde. As atividades antioxidantes e anti-inflamatórias da quitosana também são moduladas diretamente pelo seu peso molecular (Zhao *et al*., 2023).

As propriedades funcionais da quitosana dependem, principalmente, do peso molecular (MW) e do grau de desacetilação (DD) (Tabassum; Ahmed; Ali, 2021). Derivados da quitina com DD acima de 55% são classificados como quitosana, sendo que, para aplicações industriais, valores superiores a 70% são considerados ideais. Esses dois parâmetros afetam diretamente a solubilidade do polímero, sua capacidade de formar hidrogéis e seu desempenho biológico, incluindo atividade antibacteriana e biodegradabilidade. Tais características são determinantes para a viabilidade da quitosana no desenvolvimento de curativos funcionais (Zhao *et al*., 2023).

4.6. Mecanismos de ação da quitosana

4.6.1. Mecanismos de ação da quitosana em feridas cutâneas

Diante da complexidade fisiopatológica das feridas por queimadura, os hidrogéis de quitosana devem ser projetados para cumprir múltiplas funções terapêuticas simultâneas. Entre os principais objetivos estão: facilitar o desbridamento, prevenir infecções, estimular a angiogênese, absorver exsudatos, aliviar a dor e minimizar a formação de cicatrizes (Yao *et al*., 2021).

A quitosana e seus derivados promovem a cicatrização de feridas cutâneas por meio de múltiplos mecanismos farmacológicos e estruturais. Destacam-se suas propriedades antibacterianas, anti-inflamatórias, hemostáticas e regenerativas, além da excelente

biocompatibilidade e biodegradabilidade, que favorecem seu uso em aplicações biomédicas (Mawazi *et al*., 2024; Tang *et al*., 2023). Sua alta capacidade de absorção e retenção de água contribui para manter um ambiente úmido, condição ideal para a cicatrização. Além disso, os grupos amino (-NH_2) e hidroxila (-OH) presentes ao longo da cadeia polimérica oferecem sítios reativos para modificação química, permitindo o enxerto de moléculas bioativas que potencializam respostas terapêuticas específicas (Feng *et al*., 2021).

A cicatrização de feridas ocorre em quatro fases sequenciais: hemostasia, inflamação, proliferação e remodelação tecidual (Abazari *et al*., 2022; Burgess *et al*., 2021; Feng *et al*., 2021; Zhao *et al*., 2023; Żwierełło *et al*., 2023). Evidências recentes indicam que a quitosana e seus derivados atuam predominantemente nas três primeiras etapas. Durante a hemostasia, favorecem a agregação plaquetária e a formação de coágulo. Na fase inflamatória, exercem efeitos antimicrobianos e anti-inflamatórios, contribuindo para o controle da infecção e modulação da resposta imune. Já na fase proliferativa, estimulam a formação de tecido de granulação e promovem a proliferação de células essenciais à regeneração tecidual, como fibroblastos e queratinócitos (Feng *et al*., 2021; Zhao *et al*., 2023).

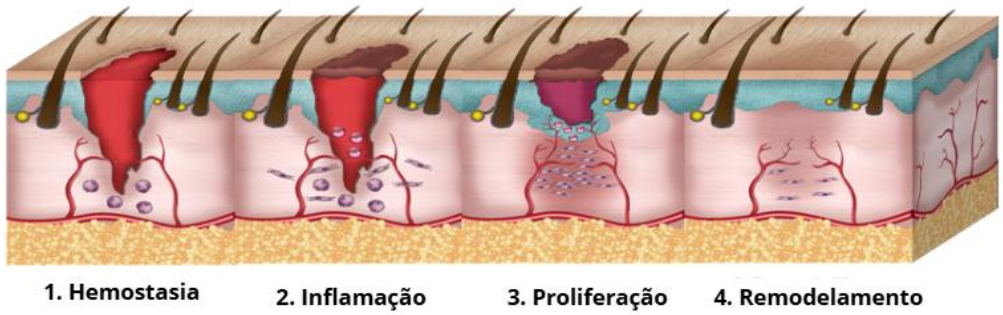

Figura 2. Quatro fases do processo de cicatrização de feridas. Editado e traduzido de Mirhaj *et al*. (2022).

4.6.2. Mecanismos de ação da quitosana: promoção da hemostasia

A quitosana contribui diretamente para a hemostasia ao promover a agregação de plaquetas e eritrócitos (RBCs). Suas cadeias catiônicas interagem eletrostaticamente com as membranas negativamente carregadas das plaquetas ativadas, facilitando sua adesão e agregação. Esse processo estimula a expressão da glicoproteína IIb/IIIa (GP IIb-IIIa), um

receptor essencial para a formação do trombo. A interação entre quitosana e células sanguíneas resulta na formação de uma rede tridimensional que acelera a geração de coágulos de fibrina e estabiliza o tampão hemostático(Zhao *et al*., 2023).

Além de suas ações sobre as plaquetas, a quitosana também favorece a agregação de eritrócitos, etapa fundamental na consolidação do trombo. Os glóbulos vermelhos contribuem para a arquitetura estrutural do coágulo, organizando-se em formas poliédricas compactas que formam uma barreira quase impermeável — essencial para a hemostasia eficaz e para o início da reparação tecidual. A interação eletrostática entre as cargas positivas da quitosana e as membranas negativamente carregadas dos eritrócitos promove sua ligação cruzada em uma malha celular densa. Essa rede aprisiona células adicionais, como plaquetas e eritrócitos, intensificando a formação do coágulo de fibrina e acelerando o fechamento da ferida (Dong; Zhang; Guo, 2022; Fan *et al*., 2023; Huang *et al*., 2024).

4.6.3. Mecanismos de ação da quitosana: atividade antimicrobiana

Durante a cicatrização, o microambiente úmido da ferida favorece a proliferação microbiana (Zhao *et al*., 2023). A quitosana apresenta atividade antimicrobiana de amplo espectro, com eficácia comprovada contra bactérias Gram-positivas e Gram-negativas. Em meio ácido, seus grupos amino ($–NH_2$) são protonados, formando $–NH_3^+$ (**Figura 3**), possibilita interações eletrostáticas com as superfícies bacterianas negativamente carregadas. No caso das Gram-positivas, cuja parede celular contém peptidoglicano e ácidos teicoicos, essas interações promovem desestabilização da membrana, levando à ruptura da parede celular, extravasamento citoplasmático e morte bacteriana (Bernkop-Schnürch, 2018; Kassem; Ayoub; Malaeb, 2019).

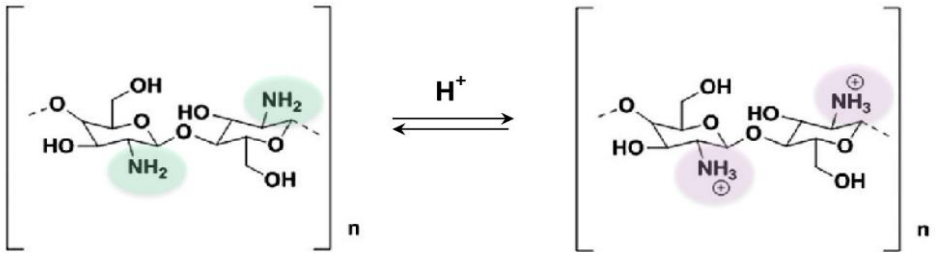

Figura 3. Protonação e desprotonação da quitosana (Yaneva *et al*., 2020).

A quitosana também apresenta atividade antifúngica significativa. Suas cadeias catiônicas interagem com a superfície das células fúngicas, desestabilizando a membrana plasmática e provocando o extravasamento de conteúdos intracelulares. A concentração

inibitória mínima (MIC) contra fungos varia de acordo com diversos fatores, incluindo o peso molecular da quitosana, o grau de desacetilação, o pH do meio e as características específicas da espécie fúngica-alvo (Nasaj *et al*., 2024; Poznanski; Hameed; Orczyk, 2023).

Além de desestabilizar a membrana plasmática, a quitosana atua por meio de mecanismos adicionais que ampliam sua eficácia antimicrobiana. Um deles é a capacidade de quelar íons metálicos essenciais e nutrientes, inibindo o crescimento microbiano e a produção de toxinas (Nasaj *et al*., 2024). Além disso, determinadas moléculas de quitosana podem penetrar nas células microbianas, interferindo na síntese de ácidos nucleicos (DNA e RNA) e proteínas. Esse efeito intracelular reforça sua atividade antimicrobiana, inclusive por meio da inibição da biossíntese proteica em fungos (Ke *et al*., 2021; Nasaj *et al*., 2024; Yan *et al*., 2021).

4.6.4. Mecanismos de ação da quitosana: atividade anti-inflamatória e promoção da proliferação do tecido de granulação

O tecido de granulação é essencial para a cicatrização de feridas, sendo composto por fibroblastos, capilares recém-formados e células inflamatórias. Sua formação envolve a deposição de matriz extracelular e a neovascularização, processos que sustentam a regeneração dérmica e a reepitelização (Chen *et al*., 2021b). A quitosana, especialmente em formas com alto grau de desacetilação e baixo peso molecular, tem demonstrado aumentar significativamente a proliferação de fibroblastos — célula-chave na formação e maturação do tecido de granulação (Li *et al*., 2025).

Estudos in vitro demonstraram que o grau de desacetilação (DD) da quitosana influencia diretamente a adesão e a proliferação de fibroblastos. Formas com DD superior a 85% promovem esses efeitos de maneira mais eficaz do que variantes com DD entre 75% e 85% (Frumento; Țălu, 2025; Li *et al*., 2025). O peso molecular também exerce influência crítica: em um estudo com fibroblastos dérmicos humanos (HSF), sete variantes de quitosana foram avaliadas, revelando que as de baixo peso molecular (LMW) aumentaram significativamente a proliferação celular (Xie *et al*., 2023).

A quitosana também estimula a secreção de fatores de crescimento essenciais para a reparação tecidual, como o fator de crescimento transformador β (TGF-β), o fator de crescimento derivado de plaquetas (PDGF) e a interleucina-1 (IL-1) (Feng *et al*., 2021). O TGF-β promove o recrutamento de macrófagos, intensifica a proliferação de fibroblastos e favorece a deposição de colágeno (Molaei; Hosseinkhani; Saberian, 2025). O PDGF estimula a angiogênese e a proliferação de fibroblastos, além de induzir a síntese de componentes da matriz

extracelular, como glicosaminoglicanos, proteoglicanos e colágeno, fundamentais para o desenvolvimento do tecido de granulação (Ferreira *et al*., 2022). Já a IL-1 contribui para a cicatrização ao potencializar a angiogênese, a atividade dos fibroblastos e a produção de colágeno (Mahmoud *et al*., 2024).

A quitosana também induz a secreção de interleucina-8 (IL-8) por fibroblastos, o que acelera a resposta inflamatória inicial e estimula a angiogênese (Dev; Mohan; Mohan, 2025). Esses efeitos biológicos estão fortemente associados às propriedades físico-químicas da quitosana, especialmente ao seu peso molecular e grau de desacetilação. Formas com alto grau de desacetilação e baixo peso molecular demonstram o maior potencial de estimulação sobre a atividade dos fibroblastos (Li *et al*., 2025; Zhao *et al*., 2023).

4.6.5. Mecanismos de ação da quitosana: propriedade antioxidante

Em concentrações fisiológicas, as espécies reativas de oxigênio (ROS) exercem funções regulatórias importantes, como o recrutamento de linfócitos, a modulação da vasoconstrição e a defesa antimicrobiana (Zhang *et al*., 2024). No entanto, quando em excesso, as ROS desestabilizam o equilíbrio redox, provocando danos teciduais, aumento da suscetibilidade a infecções e prejuízo à cicatrização. Altos níveis de ROS também comprometem a função dos fibroblastos e perturbam a migração e a proliferação dos queratinócitos (Zhang *et al*., 2024).

Devido aos efeitos deletérios do estresse oxidativo, a funcionalidade antioxidante é considerada uma propriedade essencial em curativos, especialmente para o tratamento de feridas crônicas. Nesse contexto, hidrogéis antioxidantes têm ganhado destaque, com formulações à base de quitosana mostrando-se particularmente promissoras. A capacidade antioxidante intrínseca da quitosana é atribuída à alta densidade de grupos amino e hidroxila em sua estrutura, que permite a doação de elétrons ou prótons, promovendo a estabilização de radicais livres e a atenuação do estresse oxidativo (Zhang *et al*., 2024).

4.7. Uso de hidrogéis de quitosana na promoção da cicatrização de queimaduras e úlceras do pé diabético

Nos últimos anos, os hidrogéis e membranas à base de quitosana têm atraído crescente atenção devido às suas propriedades físico-químicas versáteis e ampla aplicabilidade nas áreas biomédica e farmacêutica (Taokaew; Kaewkong; Kriangkrai, 2023; Thirupathi *et al*., 2023). Esse interesse é impulsionado principalmente pelo potencial desses biomateriais em enfrentar desafios clínicos persistentes, como a resistência antimicrobiana e a formação de biofilmes. No

tratamento de queimaduras e UPDs, os hidrogéis de quitosana destacam-se por sua capacidade de manter um ambiente úmido, estimular a formação de tecido de granulação e liberar agentes terapêuticos de forma controlada e sustentada (Carpa *et al*., 2023; Thirupathi *et al*., 2023).

Feridas agudas, como queimaduras leves e cortes superficiais, geralmente cicatrizam rapidamente, embora ainda possam resultar em cicatrizes ou cicatrização retardada. Hidrogéis autorregenerativos à base de quitosana têm demonstrado acelerar esse processo, promovendo a regeneração tecidual e minimizando a formação de cicatrizes. Esses hidrogéis são capazes de se degradar sob demanda e evitam limitações comuns dos curativos tradicionais, como toxicidade e rigidez. Em modelos de feridas superficiais, hidrogéis com degradação responsiva à N-acetilcisteína mostraram acelerar a cicatrização com cicatrização mínima. Já feridas de espessura total, que envolvem a perda completa das camadas cutâneas, apresentam maior complexidade terapêutica. Nesses casos, hidrogéis de quitosana associados à entrega de células-tronco demonstraram potencial para reduzir infecções, estimular a regeneração tecidual e promover uma cicatrização mais eficaz (Zhang *et al*., 2024).

Feridas crônicas são caracterizadas pela incapacidade de cicatrizar dentro de três meses, frequentemente devido à infecção persistente, vascularização insuficiente, inflamação contínua ou formação de biofilmes. Feridas por queimaduras, em particular, apresentam alto risco de infecção, perda excessiva de fluidos e prejuízo na angiogênese. Hidrogéis à base de quitosana oferecem vantagens nesse contexto: são injetáveis, adaptam-se ao formato irregular das feridas, promovem a angiogênese por meio da liberação de agentes bioativos — como hesperidina e Resina Draconis —, e podem ser formulados para não aderir ao leito da ferida, tornando a remoção indolor e evitando lesões secundárias devido à sua capacidade de dissolução sob demanda (Zhang *et al*., 2024).

Em feridas diabéticas, a cicatrização é prejudicada por hiperglicemia crônica, estresse oxidativo elevado e disfunção imunológica. Hidrogéis de quitosana enriquecidos com antioxidantes — como ácido alfa-lipóico ou ácido tânico — auxiliam na neutralização das ROS. Além disso, formulações contendo insulina ou agentes hipoglicemiantes podem contribuir para o controle glicêmico local, promover a angiogênese, modular a inflamação e estimular a proliferação celular, favorecendo a cicatrização completa (Zhang *et al*., 2024).

4.8. Processos de preparação de quitosana para cicatrização de feridas

A preparação de curativos à base de quitosana frequentemente envolve sua forma desidratada, cuja solubilidade em água depende do pH do meio. Isso se deve à presença de

grupos amina livres (-NH_2), que podem ser protonados em meio ácido, formando grupos carregados positivamente (-NH_3^+). A protonação transforma a quitosana em um polieletrólito catiônico, rompendo interações hidrofóbicas e permitindo sua hidratação e dissolução (Sogias; Khutoryanskiy; Williams, 2010). Para esse fim, utiliza-se comumente ácido acético como agente solubilizante.

Curativos ideais para feridas devem apresentar flexibilidade, estabilidade, biodegradabilidade e biocompatibilidade, além de manter um ambiente úmido, promover a hemostasia e absorver eficientemente o exsudato. Hidrogéis à base de quitosana atendem à maioria desses critérios (Che *et al*., 2024). A quitosana destaca-se por sua baixa toxicidade, alta biocompatibilidade e biodegradabilidade, além de ser solúvel em ácidos fracos, o que facilita sua incorporação em formulações biomédicas. Diferentes composições de curativos com quitosana já demonstraram eficácia na promoção da cicatrização em múltiplos estágios do processo e na neutralização de fatores adversos que dificultam o reparo tecidual (Zhang *et al*., 2024). Esses biomateriais atuam predominantemente nas três fases iniciais da cascata de cicatrização.

Hidrogéis à base de quitosana podem ser produzidos por métodos de reticulação física ou química, visando aplicações no tratamento de feridas (Blebea *et al*., 2025; Che *et al*., 2024). Entre as abordagens físicas, destacam-se: (1) interações eletrostáticas, formadas por ligações iônicas entre moléculas aniônicas e grupos amino da quitosana, promovendo gelificação; (2) coordenação de íons metálicos, que resulta na formação de géis estáveis por meio de ligações entre a quitosana e íons metálicos (Bhushan *et al*., 2025; Blebea *et al*., 2025; Pita-López *et al*., 2021); e (3) interações hidrofóbicas, mediadas por forças não polares entre as moléculas de quitosana. Esses métodos dispensam iniciadores ou monômeros potencialmente tóxicos, reduzindo os efeitos adversos da polimerização *in situ* (Blebea *et al*., 2025; Che *et al*., 2024).

Os métodos de reticulação química incluem principalmente a polimerização induzida por iniciadores, na qual agentes químicos promovem a formação de redes covalentes entre os monômeros, conferindo maior resistência mecânica e elasticidade ao hidrogel (Blebea *et al*., 2025; Che *et al*., 2024). Por exemplo, Park *et al*. (2006) empregaram etilenoglicol como agente reticulante, associado a uma técnica de espumação a gás, para desenvolver um hidrogel superporoso de quitosana. Já Fan *et al*. (2016) utilizaram irradiação gama (γ) para sintetizar hidrogéis compostos de quitosana, gelatina e poli(vinil álcool) (CS/Gel/PVA), destinados a aplicações em curativos.

A estrutura química da quitosana permite modificações físicas e químicas, possibilitando a engenharia de hidrogéis multifuncionais — ou “inteligentes” — capazes de liberar compostos bioativos de forma controlada. Esses compostos incluem fármacos, íons metálicos, flavonoides, ácidos fenólicos, óleos essenciais, peptídeos e outros agentes terapêuticos (Che *et al*., 2024; Yao *et al*., 2021). Hidrogéis inteligentes de quitosana respondem a estímulos ambientais, como variações de pH, temperatura e luz, por meio de transições de fase sol-gel. Essa propriedade responsiva tem atraído crescente atenção para aplicações biomédicas. Tais hidrogéis são geralmente classificados em três categorias principais: termossensíveis, fotossensíveis e sensíveis ao pH (Taokaew; Kaewkong; Kriangkrai, 2023).

A aplicação clínica da quitosana exige a otimização criteriosa de suas propriedades físico-químicas, alcançada por meio de métodos de processamento controlados. Para uso na cicatrização de feridas, a quitosana é comumente formulada como hidrogel, utilizando sua dissolução em ácidos orgânicos fracos — como ácido acético a 1% — seguida de neutralização, o que resulta na formação de matrizes sensíveis ao pH (Do Amaral Sobral *et al*., 2022; Mohandas; Rangasamy, 2021). Além disso, a técnica de gelificação iônica, que emprega tripolifosfato de sódio como agente reticulante, permite a produção de nanopartículas de quitosana adequadas para a liberação controlada de fármacos (Gutiérrez-Ruíz *et al*., 2024).

Avanços recentes têm levado ao desenvolvimento de hidrogéis à base de quitosana com estruturas de rede dupla, que demonstram resistência mecânica aprimorada, condutividade elétrica, propriedades antimicrobianas superiores e capacidades anti-incrustantes (Carpa *et al*., 2023). Essas plataformas multifuncionais se destacam como alternativas promissoras em sistemas de liberação controlada de fármacos, engenharia de tecidos, cicatrização de feridas e tecnologias de biossensoriamento (Taokaew; Kaewkong; Kriangkrai, 2023).

Para realização da esterilização destas membranas, foi descrito em Franca *et al* (2020) que a utilização de vapor saturado. É ressaltado na obra que a principal questão em relação à esterilização da formulação quitosana é determinar se os danos causados pela esterilização afetarão ou não o comportamento da formulação. Quando comparada com outros métodos comuns de esterilização, como calor seco, exposição ao óxido de etileno ou glutaraldeído e irradiação gama, a esterilização a vapor demonstrou ser o método de esterilização mais barato, seguro e simples disponível.

4.9. Probióticos, prebióticos, simbióticos e posbióticos incorporados em membranas de quitosana para tratamento de feridas

Probióticos, prebióticos, simbióticos e posbióticos têm emergido como abordagens terapêuticas promissoras no contexto da cicatrização de feridas. Em particular, os probióticos e seus derivados — como sobrenadantes de cultura e formulações contendo múltiplas cepas — têm demonstrado potencial em acelerar a cicatrização devido às suas propriedades antibiofilme, imunomoduladoras, antibacterianas, anti-inflamatórias e angiogênicas (Machado *et al*., 2025). A Organização Mundial da Saúde (OMS) define probióticos como "microrganismos vivos que, quando administrados em quantidades adequadas, conferem um benefício à saúde do hospedeiro" (Hill *et al*., 2014). Kerry *et al*. (2018) observaram que os probióticos também exercem atividades antipatogênicas e angiogênicas.

Além disso, posbióticos — definidos como produtos metabólicos ou componentes celulares liberados por micro-organismos probióticos vivos ou após sua lise — têm ganhado destaque por sua capacidade de modular a resposta imune, controlar infecções e promover a regeneração tecidual. Soltani *et al* (2023) destacam que esses compostos permitem liberação controlada no leito da ferida, amplificando seus efeitos imunomoduladores, anti-inflamatórios e antimicrobianos. Por fim, prebióticos são descritos por Gibson *et al*. (2017) como substratos utilizados seletivamente por microrganismos hospedeiros, conferindo benefícios à saúde.

O uso direto de microrganismos vivos (probióticos) no tratamento de feridas ainda enfrenta limitações significativas, principalmente devido a preocupações com a segurança e o risco potencial de infecções. Em resposta a essas limitações, o conceito de posbióticos tem ganhado destaque crescente. Os posbióticos oferecem muitos dos benefícios terapêuticos dos probióticos, como efeitos anti-inflamatórios, antimicrobianos e imunomoduladores, sem os riscos associados ao uso de bactérias vivas. Além disso, apresentam maior estabilidade química e biológica, além de uma vida útil (*shelf-life*) mais longa, o que os tornam mais adequados para formulações biomédicas, como curativos incorporados a membranas de quitosana.

Cepas probióticas, prebióticos e posbióticos têm se mostrado promissores na promoção da cicatrização quando incorporados a sistemas de quitosana. A combinação do prebiótico frutooligossacarídeo (FOS) com a bactéria probiótica *Lactiplantibacillus plantarum*, utilizada em partículas de quitosana-alginato para tratar feridas por queimaduras infectadas, demonstrou ação antibacteriana e acelerou o processo de cicatrização (Farahani *et al*., 2023). O uso de sobrenadante livre de células de *Bifidobacterium bifidum*, um posbiótico, em associação com quitosana, também melhorou significativamente a reparação tecidual (Bazjou *et al*., 2021).

Além disso, Shokatayeva *et al*. (2021), mostraram que o posbiótico de *Bacillus subtilis* P-2, incorporado em um biocomposto de celulose bacteriana e quitosana, reduziu o tempo de cicatrização em 20% em modelos animais, além de apresentar eficácia contra bactérias Gram-positivos e Gram-negativos.

É importante destacar que a eficácia dos probióticos depende de múltiplos fatores críticos, incluindo a cepa específica utilizada, a dose administrada, o tempo de uso, a forma de liberação, as características individuais do hospedeiro (como composição da microbiota, dieta e estado de saúde), além da qualidade do produto utilizado (McFarland; Evans; Goldstein, 2018).

4.10. O potencial de posbióticos da cepa *L. lactis* subsp. *lactis* NCDO 2118 incorporados em membranas de quitosana para tratamento de feridas

O conceito de posbióticos — compostos bioativos derivados de microrganismos probióticos — tem ganhado destaque como uma estratégia inovadora para modulação imunológica e promoção da regeneração tecidual em feridas. Entre esses compostos, destacam-se o GABA e as proteínas de choque térmico (HSPs), conhecidos por seus efeitos anti-inflamatórios, antioxidantes e citoprotetores. Esses metabólitos podem favorecer o microambiente de cicatrização, reduzindo a inflamação excessiva e promovendo a proliferação celular (Atalay *et al*., 2009; Han *et al*., 2007b).

A cepa *L. lactis* subsp. *lactis* NCDO 2118 é uma produtora natural de GABA por meio da descarboxilação do glutamato, e tem demonstrado efeitos benéficos em modelos animais, como a redução da ansiedade, modulação da microbiota intestinal e regulação da secreção de insulina e glucagon em pacientes diabéticos (Cordeiro *et al*., 2021; Oliveira *et al*., 2017; Saraiva *et al*., 2016). Sua capacidade de biossíntese de GABA pode ser aumentada pela presença de precursores como arginina e malato, o que a torna uma candidata interessante para aplicações terapêuticas além do eixo intestino-cérebro (Laroute *et al*., 2016).

O GABA tem sido destacado como um posbiótico com potencial para a regeneração de feridas, visto que estimula o crescimento de células NIH3T3, uma linhagem fibroblástica responsável por sintetizar componentes da matriz extracelular, como colágeno, fibronectina e proteoglicanos no local da lesão (Han *et al*., 2007a; Oliveira, 2020). Descoberto em 1950 (Froestl, 2011), o GABA é um aminoácido não proteico que atua como neurotransmissor inibitório no sistema nervoso central de mamíferos, regulando a excitabilidade cerebral por meio dos receptores GABA A e GABA B (Sarasa *et al*., 2020; Watanabe *et al*., 2002).

Estudos demonstram que o GABA, quando administrado em alimentos fermentados, pode melhorar o sono e reduzir a ansiedade, provavelmente por meio da modulação da microbiota intestinal (Yu *et al*., 2020). Além disso, conforme Wang *et al*. (2019), o GABA exerce efeitos autócrinos nas células β pancreáticas, estimulando a secreção de insulina, e efeitos parácrinos nas células α, inibindo a liberação de glucagon — aspectos altamente relevantes para pacientes diabéticos.

Conforme demonstrado no trabalho de Yu *et al* (2020), o leite fermentado rico em GABA melhora o sono e reduz a ansiedade, potencialmente por meio da regulação da microbiota intestinal. Também, conforme Wang *et al*. (2019), o GABA exerce efeitos autócrinos nas células β, estimulando a secreção de insulina e exerce efeitos parácrinos nas células α, suprimindo a secreção de glucagon, o tornando de grande relevância para pacientes diabéticos.

Pesquisas recentes têm mostrado que *L. lactis* subsp. *lactis* NCDO 2118, uma bactéria láctica Gram-positivo, anaeróbica facultativa, isolada de ervilhas congeladas (Oliveira *et al*., 2014), possui atividade anti-inflamatória em modelo de colite ulcerativa (Oliveira *et al*., 2017) e atividade de redução da pressão arterial em modelo de hipertensão em ratos (Cordeiro *et al*., 2021; Saraiva *et al*., 2016). Também foi demonstrado que essa cepa apresenta propriedades antinociceptivas, visto que foi capaz de reduzir significativamente a hipersensibilidade visceral induzida pelo estresse devido ao GABA que ela produz (Laroute *et al*., 2022).

O GABA é sintetizado pela cepa *L. lactis* subsp. *lactis* NCDO 2118 por meio da via catalisada pela enzima glutamato descarboxilase (GAD), que converte o glutamato em GABA. Esse processo é altamente dependente do pH do meio, sendo ativado em condições ácidas (pH inferior a 5,1) e durante o início da fase estacionária de crescimento. A presença de substratos como glutamato, arginina e malato influencia a produção de GABA; a arginina, em particular, pode contribuir para o fornecimento de carbamoilfosfato, facilitando a biossíntese de GABA por rotas metabólicas relacionadas ao metabolismo de aminoácidos. Para a bactéria, a função do GABA está associada à resistência ao estresse ácido, uma vez que ele atua como aceptor de prótons na troca com glutamato via o antiportador GadC, auxiliando na manutenção do pH intracelular próximo à neutralidade — condição essencial para a sobrevivência e o metabolismo bacteriano em ambientes ácidos (Laroute *et al*., 2016; Mazzoli *et al*., 2010; Saraiva *et al*., 2016).

Gusmao-Silva *et al* (2020) desenvolveram a bactéria recombinante *L. lactis* NCDO 2118 subsp. *lactis* pXylT:SEC:HSP65 (que também apresenta o nome *L. lactis* NCDO 2118 subsp. *lactis* pxies:sec:HSP65). A proteína de choque térmico Hsp65 é uma molécula ubíqua, superexpressa em tecidos inflamados, com capacidade de induzir mecanismos

imunorregulatórios. Os autores demonstraram que a administração contínua de Hsp65 na mucosa intestinal, mediada pela cepa recombinante, atua como um potente estímulo tolerogênico, promovendo a indução de células T $CD4^{+}LAP^{+}$ reguladoras, capazes de prevenir a artrite induzida por colágeno e por albumina sérica bovina metilada em camundongos. Observou-se inibição dos sinais clínicos e histológicos da artrite, bem como redução dos níveis de citocinas inflamatórias (IL-17 e IFN-γ), dos títulos séricos de anticorpos anticolágeno e do fator reumatoide. A indução de tolerância à Hsp65 e a prevenção da artrite foram associadas ao aumento da produção de IL-10 por células B, sendo dependentes da sinalização de células T LAP^{+}, IL-10 e TLR2. Dessa forma, o tratamento baseado na produção de Hsp65 mostrou-se eficaz na indução de tolerância imunológica e prevenção da artrite, indicando seu potencial como ferramenta terapêutica para doenças autoimunes.

As chaperonas da família HSP 60 desempenham funções essenciais na homeostase celular, atuando tanto na manutenção da conformação proteica quanto como moléculas sinalizadoras em processos imunológicos. Quando liberadas no espaço extracelular, essas proteínas funcionam como padrões moleculares associados a dano (DAMPs), sinalizando eventos como inflamação, hiperplasia ou estresse oxidativo por meio da ativação de receptores do sistema imune inato e adaptativo. Essa dupla função — como chaperona intracelular e mediadora imunológica — destaca o papel central da Hsp65 na interface entre a resposta ao estresse celular e a modulação imunológica (Gusmao-Silva *et al*., 2020).

A *Heat Shock Protein* 65 (Hsp65) é uma chaperona da família HSP60 amplamente distribuída nos diferentes domínios da vida. Sua estrutura altamente conservada permite interações com diversos receptores imunológicos, favorecendo a diferenciação de células T reguladoras durante a ontogênese tímica (Gusmao-Silva *et al*., 2020). Desta maneira, o posbíotico da cepa recombinante *L. lactis* NCDO 2118 subsp. *lactis* pxies:sec:HSP65 em membranas de quitosana pode contribuir para a cicatrização de feridas modulando o processo inflamatório.

5. Etapa I – Revisão Sistemática e Metanálise e revisão da literatura – levantamento bibliográfico

A metodologia, os resultados, a discussão e conclusão da revisão sistemática e metanálise e revisão da literatura com levantamento bibliográfico foram publicados no artigo:

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Systematic review on chitosan dressings for diabetic and burn wound healing: preclinical outcomes and limitations

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Abstract

This systematic review evaluates the effectiveness and physicochemical properties of chitosan-based wound dressings used to treat diabetic and burn wounds, focusing on how different therapeutic combinations influence healing outcomes. Literature from Scopus, Web of Science, Dimensions, and PubMed was selected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The effects of compositional and treatment variables on wound regeneration were analyzed through multivariate (PCA) and bivariate (correlation) statistics. Out of 991 records initially identified, 40 studies met the criteria for inclusion in this review, with a subset evaluated via a meta-analysis. These studies were assessed for their methodological quality and risk of bias using tools such as SYRCLE and MINORS. The results highlighted high variability in the treatment outcomes, with wound regeneration influenced by factors such as tensile strength, drug release profiles, and biocompatibility characteristics. The chitosan-based dressings demonstrated significant potential to enhance wound healing and were generally effective in promoting regeneration compared to that under no treatment or the use of standard gauze. The meta-analysis indicated that while chitosan dressings provide beneficial effects, treatment optimization still faces challenges related to the material composition and variability in the application methods. In conclusion, this review emphasizes the global importance of chitosan-based wound dressings in improving the outcomes for patients with complex wounds.

Keywords: *chitosan, burn wound, diabetic wound, membrane, hydrogel, healing*

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1. Introduction

1.1. Burn wounds

Burn injuries are types of wounds caused by exposure to heat, cold, chemicals, friction, radiation, or electricity [1]. The World Health Organization (WHO) identifies burns as a significant public health issue worldwide, responsible for around one hundred and eighty thousand deaths a year [2]. Most of these cases are found in low- and middle-income countries, with nearly two-thirds in Africa and Southeast Asia. Non-fatal burns are a major cause of morbidity, often resulting in extended hospital stays, physical disfigurement, and long-term disability, which can result in social stigma and rejection within communities due to visible scarring or physical differences. An example of this is that children with major burns have profound changes to their immune system and metabolism, which can lead to various complications, such as infections and loss of lean mass [2, 3].

According to their severity, depth, and size, burn injuries can be classified as superficial (first-degree), which only affect the epidermis, are red, and cause short-lived pain; superficial partial-thickness (second-degree/2A), which are painful and weepy, need dressing, and may scar but do not require surgery; deep partial-thickness (second-degree/2B), which are less painful, are dry, require surgery, and will scar; full-thickness (third-degree), which damage the full dermis and nerves, are not painful, and require protection and usually surgery; and fourth-degree, which extend to the muscle or bone, are blackened, and often lead to loss of the affected part [4].

Right after the injury occurs, a burn wound can be categorized into three distinct zones: the zone of coagulation, located at the center, where the tissue damage is most severe; the zone of stasis or ischemia, which surrounds the central area and has a reduced blood flow but may still be recoverable; and the zone of hyperemia, the outermost area, marked by increased blood flow due to inflammatory vasodilation [4]. The natural process of wound

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healing occurs through a series of dynamic and overlapping stages, beginning with the inflammatory phase. This initial stage is triggered by the recruitment of neutrophils and monocytes to the injury site, facilitated by local vasodilation. During this phase, necrotic tissue is broken down, and a complex signaling cascade essential for tissue repair is initiated. As the inflammation subsides, cytokines and growth factors stimulate the activation of the keratinocytes and fibroblasts, leading to the proliferative phase, which focuses on restoring blood supply and advancing tissue regeneration. The final stage, known as remodeling, involves the deposition of collagen and elastin and the progressive differentiation of fibroblasts into myofibroblasts, contributing to the maturation and strengthening of the repaired tissue [1, 4]. Over time, the interplay between myofibroblast contraction and re-epithelialization plays a crucial role in shaping the quality and flexibility of the healed wound. This dynamic also influences the degree of scar formation, which is marked by the improper organization of collagen fibers [5]. Overall, the intricate healing process is primarily directed towards regenerating the dermis and the epidermis, aiming to restore the skin barrier's closure, flexibility, and functional integrity. However, some wounds may result in abnormal scarring, known as hypertrophic or keloid scars, which are typically raised, red, itchy, painful, and cosmetically disfiguring [4], as well as hyperpigmentation and hypopigmentation of the skin and contractures [6].

Patients with severe burn injuries are also at an increased risk of developing infectious complications. In addition to systemic inflammatory response syndrome (SIRS)—characterized by excessive cytokine release that triggers uncontrolled leukocyte recruitment, fever or hypothermia, tachycardia, and tachypnoea [7]—several aspects of immune function are profoundly impaired. These include reduced macrophage-mediated antigen presentation and a diminished capacity of the neutrophils to eliminate invading pathogens [8, 9]. Furthermore, T-cell proliferation and interleukin-2 (IL-2) production are significantly suppressed [10, 11]. These combined events impair adaptive immune response, making individuals more vulnerable to infections. Patients with severe burn injuries face a significantly higher risk of infectious complications. The disruption of the skin barrier in these patients weakens their immune defenses, leading to increased susceptibility to infections, primarily bacterial but also including yeast, fungal, and viral pathogens; heightened virulence for certain microorganisms; and a greater likelihood of progressing to organ failure [12, 13].

1.2. Diabetic foot ulcers (DFUs)

Currently, it is estimated that nearly 500 million individuals worldwide are affected by diabetes mellitus (DM), with forecasts indicating a substantial rise in prevalence in the coming years. In the United States alone, the annual economic burden of DM surpasses USD 300 billion, encompassing direct medical expenses and losses due to reduced productivity [14, 15]. Alarmingly, it is projected that between one in three and one in five individuals with DM will develop a chronic, non-healing wound during their lifetime, most commonly a diabetic foot ulcer (DFU). These ulcers are characterized by high recurrence rates, with approximately 40% recurring within one year and 65% within five years, and there are currently no reliable methods for predicting their onset [16, 17].

A significant proportion of DFU patients ultimately require lower limb amputation, which severely compromises their quality of life and necessitates expensive medical interventions. Reflecting this burden, the global market for DFU treatments is expected to grow from USD 7.03 billion in 2019 to USD 11.05 billion by 2027, underscoring the urgent need for more effective diagnostic tools and therapeutic strategies to manage this debilitating condition [15, 18–20].

The pathophysiology of DFUs is notably complex, primarily driven by sustained hyperglycemia and its systemic consequences. These include deregulated angiogenesis, a persistently suboptimal inflammatory response, elevated reactive oxygen species (ROS) levels, and chronic bacterial colonization that frequently progresses into difficult-to-eradicate biofilms [20]. Hyperglycemia contributes further to the development of atherosclerosis, impairing the delivery of oxygen and nutrients to the wound site and significantly hindering the healing process [21, 22].

In individuals with DM, hyperglycemia also induces endothelial dysfunction, compromising a key mechanism in skin protection: pressure-induced vasodilation. The endothelial cells play a pivotal role in wound healing, and their impairment negatively impacts the resolution of DFUs [23, 24]. Furthermore, chronic hyperglycemia interferes with the critical phases of re-epithelialization by disrupting protein synthesis, cell migration, and the proliferation of keratinocytes and fibroblasts—cell types essential for effective wound closure and tissue regeneration [25, 26].

Another key mechanism through which hyperglycemia and tissue hypoxia impair wound healing is oxidative damage. People with long-term type 2 diabetes have significant reductions in their antioxidant enzyme activity. Oxidative stress may influence diabetic wound healing through skin injury, neuropathy, ischemic lesions, and topical infections [27, 28]. Hyperglycemia promotes the overproduction of reactive oxygen species (ROS) through multiple biochemical pathways, including the polyol, hexosamine, protein kinase C, and advanced glycation end-product (AGE) pathways [28]. While ROS play an essential role in the early phases of wound healing by facilitating pathogen clearance and cell signaling [29], excessive or prolonged ROS generation has been shown to disrupt the later stages of the repair process. Elevated ROS levels can inflict structural and metabolic damage on the peripheral nerves and compromise their vascular supply. This oxidative stress can result in dysfunction across sensory, motor, and autonomic nerve fibers—each of which independently contributes to an increased susceptibility to diabetic foot ulcers (DFUs) [30].

Collectively, these pathophysiological alterations, driven by uncontrolled hyperglycemia, render the skin more vulnerable to trauma and infection, thereby further delaying or preventing proper wound healing.

Due to their complex and multifactorial nature, both burn and diabetic wounds present significant clinical challenges. The therapeutic strategies are generally classified into standard care and advanced modalities. Standard care typically includes wound debridement, pressure offloading, rigorous blood glucose control, and infection control. Advanced therapies encompass a range of innovative interventions, such as hyperbaric oxygen therapy (HBOT), specialized wound dressings, negative pressure wound therapy (NPWT), and regenerative approaches involving growth factors, platelet-rich plasma, stem cells, and cell- or tissue-based products [1, 31–34].

1.3. Biocompatible hydrogel materials for wound healing

Skin wound healing is a complex physiological process influenced by intrinsic and extrinsic factors. This process can be significantly enhanced by applying the appropriate wound care materials. Such materials should exhibit flexibility, stability, biodegradability, and broad applicability. Additionally, they must maintain a moist wound environment, promote hemostasis, and effectively absorb exudates [35].

With the advancement of molecular biology and tissue engineering, a wide array of innovative biomaterials, particularly hydrogel-based systems, have emerged as promising tools in wound management. Hydrogels are three-dimensional (3D) networks formed by cross-linking hydrophilic polymer chains [36]. They exhibit both the viscoelastic properties of solids and the flow characteristics of liquids, mimicking the structure and functionality of the natural extracellular matrix. Hydrogels offer several distinct advantages over conventional wound dressings: (1) enhanced hydrophilicity, which allows for adequate absorption of wound exudates [37]; (2) moisture retention, which supports the wound healing environment [38]; (3) microbial barrier formation, helping to prevent external contamination [39, 40]; and (4) low adhesion to the wound tissue, minimizing trauma and pain during dressing changes [35].

1.4. Chitosan hydrogel has valuable properties as a biomaterial for biomedical applications

Hydrogels can generally be categorized into two main types: native and synthetic. Native hydrogels are derived from natural polymers such as chitosan, sodium alginate, collagen, and sodium hyaluronate. Among these, chitosan is one of the most extensively studied and promising materials for biomedical applications [35]. Due to its distinctive physical, chemical, and biological properties, chitosan has gained significant attention for developing advanced wound dressings, particularly for diabetic foot ulcers (DFUs) and burn injuries.

Chitosan, chemically identified as (1 → 4)-2-amino-2-deoxy-β-D-glucan, is composed of N-acetyl-D-glucosamine monomers linked by β-1,4-glycosidic bonds and is produced by the deacetylation of chitin, which is primarily extracted from crustacean shells [35]. It is characterized by low toxicity, excellent biodegradability, and high biocompatibility, making it an ideal candidate for hydrogel formation [41, 42].

Structurally, chitosan contains numerous amino and hydroxyl groups that facilitate covalent bonding with various polymers, thereby supporting the creation of stable hydrogel networks [43–45]. Furthermore, the cationic amino groups in chitosan interact electrostatically with negatively charged molecules and anions—interactions fundamental to forming physical chitosan hydrogels [46]. These properties have made chitosan hydrogels widely applicable in tissue engineering, controlled drug release systems, and targeted drug delivery, with growing research interest in smart and drug-loaded hydrogel technologies [45].

Chitosan is the only naturally occurring alkaline polysaccharide, distinguishing it from other neutral or acidic polysaccharides such as cellulose, dextran, pectin, alginic acid, agar, starch, and carrageenan. It is non-toxic, odorless, biocompatible, and biodegradable. Upon its application in vivo, chitosan degrades slowly into harmless amino sugars readily absorbed by the body [42]. Specifically, it is hydrolyzed by lysozymes into oligomers, which then stimulate the macrophages to produce N-acetyl-D-glucosaminidase. This enzyme catalyzes the conversion of oligomers into N-acetylglucosamine, D-glucosamine, and other substituted glucosamines [47]. The biodegradability of chitosan is one of its most advantageous features, as it can also be broken down by soil-dwelling microorganisms or enzymatic activity, such as that of lysozymes [48, 49]. In soil environments, chitosan films typically degrade within approximately 60 days, depending on the moisture levels and microbiota composition, as microbes utilize chitosan as a carbon and nitrogen source [48].

The molecular weight (MW) of chitosan ranges from 50 Da to 900 kDa, with the commercially available forms typically spanning from 100 to 800 kDa. Based on its MW, chitosan is classified into high-molecular-weight (HMW) and low-molecular-weight (LMW) forms, each with distinct performance profiles. HMW chitosan exhibits poor solubility in water and limited biodegradability in vivo, raising concerns about its long-term accumulation and potential adverse effects. However, its high viscosity enhances hydrogels' adhesion and mechanical strength. In contrast, LMW chitosan is more soluble and demonstrates superior biological activities, including antioxidant, antibacterial, and antitumor effects. These properties make LMW chitosan particularly valuable in biomedical, health, and food-related applications. Additionally, chitosan's antioxidant and anti-inflammatory activities are significantly influenced by its molecular weight [45].

The functional properties of chitosan are predominantly determined by two factors: its molecular weight (MW) and degree of deacetylation (DD) [50]. A chitin derivative with more than 55% deacetylation is typically classified as chitosan. For industrial purposes, chitosan with a DD greater than 70% is considered more valuable. These two parameters, MW and DD, critically affect chitosan's solubility, hydrogel-forming capacity, and biological functionalities such as its antibacterial efficacy and biodegradability. These, in turn, influence its suitability and effectiveness in designing and applying wound dressing materials [45].

1.5. Chitosan's mechanisms of action in skin wounds

Given the complex nature of burn wounds, the design of hydrogels intended for their treatment must address several key therapeutic objectives. These include optimizing the wound debridement, minimizing the infection risk, promoting angiogenesis, effectively absorbing wound exudates, alleviating pain, and reducing scar formation [51].

Chitosan and its derivatives have demonstrated numerous beneficial effects on skin wound healing. These benefits include pharmacological activities, such as antibacterial, anti-inflammatory, hemostatic, and skin regenerative properties; excellent biocompatibility and biodegradability, which make them highly suitable for biomedical applications [52, 53]; strong water absorption and retention capacities, essential for maintaining a moist wound environment; and reactive functional groups, namely amino (-NH_2) and hydroxyl (-OH) moieties along the chitosan's molecular chains, which provide chemical sites for grafting other bioactive groups, thereby enhancing specific biological functions [35].

The process of wound healing is typically divided into four sequential phases: hemostasis, inflammation, proliferation, and tissue

remodeling [1, 4, 20, 35, 45]. Current research indicates that chitosan and its derivatives exert their therapeutic effects primarily during the first three phases, specifically by facilitating hemostasis; exerting antimicrobial and anti-inflammatory effects; and promoting granulation tissue formation and cellular proliferation [35, 45].

1.6. Chitosan's mechanisms of action in hemostasis

Chitosan plays a significant role in promoting hemostasis by facilitating both platelet and red blood cell (RBC) aggregation. It enhances the expression of glycoprotein IIb/IIIa (GP IIb-IIIa), a critical receptor involved in platelet adhesion and clot formation. The positively charged chitosan molecules interact electrostatically with the negatively charged surfaces of activated platelets, thereby promoting their adhesion and aggregation. This interaction forms a three-dimensional network structure that accelerates fibrin clot formation [45].

In addition to its effects on the platelets, chitosan also supports the aggregation of red blood cells, which play a vital role in thrombus development. RBCs contribute to the structure of platelet-driven clots by forming tightly packed polyhedral erythrocytes, cells that create a nearly impermeable barrier essential for adequate hemostasis and wound repair. The electrostatic attraction between cationic chitosan and negatively charged RBC membranes facilitates cross-linking of the cells into a mesh-like structure. This network captures platelets and additional RBCs, reinforcing fibrin clot formation and accelerating wound healing [54–56].

1.7. The antimicrobial mechanisms of chitosan

The moist microenvironment of a wound provides favorable conditions for microbial proliferation during the healing process [45]. Chitosan exhibits broad-spectrum antimicrobial activity, being particularly effective against Gram-positive and Gram-negative bacteria. In Gram-positive bacteria, the cell wall primarily comprises acidic polysaccharides, such as peptidoglycan and teichoic acids (e.g., phosphopiridic acid), which confer a net negative surface charge. When chitosan is dissolved in an acidic medium, its amino groups ($-NH_2$) become protonated to form $-NH_3^+$, enabling electrostatic interactions with the negatively charged bacterial surface components. This interaction leads to charge imbalances on the bacterial membranes, causing cell wall disruption, membrane rupture, cytoplasmic leakage, and eventual bacterial death [57, 58].

A similar mechanism is observed in Gram-negative bacteria, where the negatively charged lipopolysaccharide (LPS) components of the outer membranes interact with the protonated amino groups of chitosan. This electrostatic binding disturbs the integrity of the cell envelope, resulting in membrane lysis, leakage of the intracellular contents, and bacterial death [59].

Chitosan also exhibits potent antifungal activity. It can bind to fungal cell surfaces, disrupting the plasma membrane's permeability and causing intracellular material leakage. The minimum inhibitory concentrations (MIC) of chitosan against fungi vary and are influenced by several factors, including its molecular weight and degree of deacetylation (DDA), the solvent's pH, and the fungal species targeted [59, 60].

Beyond membrane disruption, chitosan can chelate essential metal ions and nutrients, inhibiting microbial growth and toxin production [59]. Additionally, some chitosan molecules can penetrate microbial cells, where they interfere with the synthesis of nucleic acids (DNA/RNA) and proteins. This internal mechanism enhances its antimicrobial efficacy further, including its antifungal effects through the inhibition of protein biosynthesis [59, 61, 62].

1.8. Chitosan's mechanisms of action: anti-inflammatory activity and promotion of granulation tissue proliferation

Granulation tissue, which plays a critical role in wound healing, comprises fibroblasts, newly formed capillaries, and various inflammatory cells. It develops on the wound surface through the formation of connective tissue and neovascularization, thereby facilitating tissue regeneration and epidermal repair [63]. Chitosan, particularly in forms with a high degree of deacetylation and a low molecular weight, has significantly enhanced fibroblast proliferation [64].

In vitro studies have demonstrated that the degree of deacetylation greatly influences fibroblast adhesion and proliferation. Chitosan scaffolds with a degree of deacetylation above 85% support fibroblast attachment and growth more effectively than these values for scaffolds with lower deacetylation levels (75–85%) [64, 65]. Additionally, the molecular weight of chitosan also affects cell viability. One study evaluated seven chitosan variants using human skin fibroblasts (HSFs) and found that lower-molecular-weight chitosan significantly enhanced HSF proliferation [66].

Chitosan has also been reported to stimulate the secretion of key cellular growth factors involved in wound repair, including transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and interleukin-1 (IL-1) [35]. TGF-β promotes the migration of macrophages to the injury site, enhancing fibroblast proliferation and collagen deposition [67]. PDGF contributes to skin regeneration by promoting angiogenesis; stimulating fibroblast migration and proliferation; and supporting the synthesis of extracellular matrix components such as glycosaminoglycans, proteoglycans, and collagen, all of which are essential for granulation tissue formation [68]. IL-1 supports wound healing by enhancing angiogenesis, fibroblast proliferation, and collagen synthesis [69].

Furthermore, chitosan has been shown to increase the secretion of interleukin-8 (IL-8) from the fibroblasts, which helps to accelerate the inflammatory response and promote angiogenesis [70]. The biological effects of chitosan on fibroblast proliferation are closely related to its physicochemical properties, particularly its molecular weight and degree of deacetylation. Chitosan with high deacetylation and a low molecular weight demonstrates the most potent stimulatory effects on fibroblast activity [45, 64].

1.9. Chitosan's mechanisms of action: antioxidant properties

At controlled levels, reactive oxygen species (ROS) serve important physiological roles such as lymphocyte recruitment, vasoconstriction regulation, and antimicrobial activity [39]. However, excessive ROS disrupt the redox balance, leading to tissue damage, increased susceptibility to infection, and impaired wound healing. Elevated ROS levels are also associated with compromised fibroblast function, aberrant migration, and keratinocyte proliferation.

Due to these detrimental effects, antioxidant functionality is considered a critical feature for wound dressings, particularly in treating chronic wounds. Recent studies have highlighted the development of antioxidant hydrogels, with chitosan-based hydrogels emerging as promising. Their intrinsic antioxidant capacity is attributed mainly to the high density of amino and hydroxyl groups within chitosan's molecular structure, enabling free radical scavenging and reducing oxidative stress [39].

1.10. Mechanisms that allow chitosan to facilitate healing in burn and diabetic wounds

Acute wounds (e.g., mild burns, cuts) generally heal quickly but can still result in scarring or delayed healing. Chitosan-based self-healing hydrogels enhance healing by promoting tissue regeneration and enabling on-demand degradation and minimal scarring, avoiding the issues with traditional dressings (e.g., toxicity, rigidity). Hydrogels with N-acetylcysteine-responsive degradation accelerate healing with minimal scars for superficial wounds. Full-thickness wounds are difficult to heal due to complete tissue loss. Chitosan scaffolds and hydrogels with stem cell delivery promote healing, reduce infection, and support tissue regeneration [39].

Chronic wounds fail to heal within 3 months due to infection, poor vascularization, inflammation, and biofilm formation. Burn wounds suffer from high infection risks, fluid loss, and impaired vascularization. Chitosan-based hydrogels are injectable and adaptable to the wound's shape; promote angiogenesis using biological agents (e.g., hesperidin, Resina Draconis); can be made non-adhesive and pain-free on removal; and can be dissolved on demand to avoid secondary injury. Diabetic wound healing is delayed by high glucose, oxidative stress, and poor immunity. Chitosan hydrogel preparations release antioxidants (e.g., α-lipoic acid, tannic acid) to reduce ROS levels and include insulin- or glucose-lowering agents to improve metabolism, promote angiogenesis, reduce inflammation, and support cell growth for complete healing [39].

Infection is the most significant factor in delayed secondary healing in chronic open wounds. Infections hinder healing by promoting inflammation and biofilm growth. Chitosan hydrogels can incorporate antimicrobial peptides or agents like usnic acid. Also, photodynamic therapy (PDT) can be used with AIE molecules (e.g., berberine) to kill bacteria and biofilms effectively [39].

1.11. Chitosan preparation processes for wound healing

The ideal wound dressings should exhibit flexibility, stability, biodegradability, and biocompatibility while maintaining a moist wound environment, promoting hemostasis, and facilitating exudate absorption. Chitosan-based hydrogels fulfill most of these criteria [71]. Moreover, various formulations of chitosan-based wound dressings have demonstrated the capacity to enhance wound healing at different stages and counteract adverse factors that impede the repair process [39]. These biomaterials primarily act during the early three phases of the wound healing cascade.

Chitosan is a naturally abundant and renewable biopolymer derived through the deacetylation of chitin, which is found in the exoskeletons of marine arthropods such as shrimp and crabs, as well as in mollusks, insects, and the cell walls of certain plants [72–74].

Both physical and chemical cross-linking methods can be employed to fabricate chitosan-based hydrogels for wound treatment [42, 71]. Physical cross-linking approaches include electrostatic interactions, formed through ionic bonding between anionic molecules and the amino groups of chitosan, resulting in gelation; metal–ion coordination, involving the formation of stable gels through coordination bonds between chitosan and metal ions [42, 75, 76]; and hydrophobic interactions, whereby gelation is achieved through non-polar interactions among chitosan molecules. These methods avoid potentially toxic initiators or monomers, thereby minimizing the side effects of in situ polymerization [42, 71].

One category of chemical cross-linking method is initiator-induced polymerization, where chemical initiators trigger the polymerization of monomers, forming covalently bonded networks that improve the mechanical strength and elasticity of the hydrogel [42, 71]. For instance, Park et al. [77] used ethylene glycol as a cross-linking agent and a gas foaming technique to produce a superporous chitosan hydrogel. Fan et al. [78] applied γ-irradiation to synthesizing CS/Gel/PVA composite hydrogels for wound dressing applications.

Chitosan's structure allows for both physical and chemical modifications, enabling the development of multifunctional or "smart" chitosan-based hydrogels capable of controlled release of bioactive compounds such as drugs, metal ions, flavonoids, phenolic acids, essential oils, peptides, and other therapeutic agents [51, 71]. These hydrogels respond to environmental stimuli (e.g., pH, temperature, light) by undergoing a sol–gel phase transition, which has garnered significant attention in recent years. Smart chitosan hydrogels are typically classified as thermosensitive, photosensitive, or pH-sensitive [79].

The clinical application of chitosan requires careful optimization of its physicochemical properties through controlled processing methods. For wound healing applications, chitosan is most commonly formulated as a hydrogel via dissolution in weak organic acids (e.g., 1% acetic acid), followed by neutralization to form pH-sensitive matrices [80, 81]. The ionic gelation technique using chitosan–sodium tripolyphosphate (CS-TPP) as a cross-linker produces nanoparticles that are ideal for controlled drug delivery [82].

A major challenge in the development of application-specific hydrogels lies in establishing an effective sterilization method that preserves their structural integrity and functional properties [83]. Sterilization of chitosan hydrogel nanoparticles using gamma irradiation indicated possible degradation of the samples; an increase in the average particle size and polydispersity; and a decrease in the zeta potential. Chemical changes were also observed. Conductivity and pH were not affected. The presence of protective sugars (glucose and mannitol at 5%) increased the nanoparticles' resistance to radiation. When using ozone as a sterilization method for chitosan hydrogel nanoparticles, the properties of the samples were not affected. However, ozone sterilization was not as effective as gamma irradiation and appeared to induce some toxicity. The addition of protective sugars caused chemical changes after ozonation. However, for chitosan hydrogel nanoparticles, the steam sterilization method promoted degradation of the samples [83].

In recent years, the research on chitosan-based hydrogels and membranes has significantly expanded due to their versatile physicochemical properties and broad applicability in the biomedical and pharmaceutical fields [79, 84]. Recent advancements include the development of chitosan-based hydrogels with

double-network structures, which exhibit enhanced mechanical strength, electrical conductivity, antimicrobial efficacy, and anti-fouling capabilities [85]. These multifunctional hydrogels are promising for drug delivery systems, tissue engineering, wound healing, and biosensing technologies [79].

The increasing scientific interest in these materials is primarily driven by their potential to address persistent clinical challenges such as antibiotic resistance and biofilm formation [84, 85]. In this context, the present systematic review aims to critically assess the recent scientific literature on the wound healing potential of chitosan-based dressings enriched with various bioactive agents, particularly in treating burn wounds and diabetic ulcers.

2. Materials and methods

2.1. The data selection and screening

This systematic review was based on the guidelines described in the report "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) [86] and reinforced in da Cruz Ferraz Dutra et al. [87] and Dutra et al. [88]. The process of selecting the studies was carried out in three stages: (1) identifying the records in the PubMed, Dimensions, Scopus, and Web of Science databases; (2) screening the documents; and (3) assessing the eligibility and inclusion of the studies.

Records published in PubMed, Dimensions, Scopus, and Web of Science up to 4 Sept. 2023 were included, considering all types of documents, without any distinction based on factors such as their year of publication or language. In order to identify studies of interest, searches in the databases were carried out using terms and keywords related to the topic, including synonymous variations. The terms and keywords included *chitosan, "Chitin-derived polymer", "Chitosan-based material", membrane, dressing, barrier, film, covering, incorporation, integration, inclusion, combination, wound, injury, lesion, trauma, cut, healing, recovery, repair, regeneration, closure, "In vivo", and "In vitro"*. The combination of the words and Boolean operators is detailed in Table S1.

The documents obtained from the PubMed, Dimensions, Scopus, and Web of Science databases were screened following the methodology presented in Dutra et al. [88]. The methodology follows the PRISMA flowchart that goes through the selection, sorting, and inclusion steps. Articles without a DOI and duplicate records were removed. The articles selected after automatic exclusion are given in Tables S2–S4.

The documents were manually reviewed by title and abstract and assessed for eligibility according to the inclusion and exclusion criteria listed in **Table 1**. Since this study's main focus was on using chitosan specifically as a dressing to treat burn wounds and/or diabetic wounds, these were key terms in the inclusion/exclusion criteria.

2.2. The extraction of data from included studies

From the selected documents, after the whole process of screening, assessing eligibility, and inclusion based on the criteria mentioned above, the following information was extracted: (1) the study methodology (hydrogel/membrane); (2) the hydrogel/membrane characterization tests used; (3) the in vitro tests used; (4) the in vivo tests used; and (5) the geographical locations of the authors' affiliations.

Table 1 • Criteria for inclusion or exclusion of studies in the systematic review.

Inclusion criteria
1. The use of a wide range of characterization tests along with in vitro and/or in vivo tests;
2. Language: English.
Exclusion criteria
1. No mention of the words 'Diabetes'/'Diabetic' or 'Burn' in the title and/or abstract;
2. A methodology involving few tests;
3. No use of chitosan;
4. Articles in the format of 'Review', 'Retraction', 'Editorial', 'Note', or 'Published in Proceedings';
5. The inaccessibility of the article or its availability only in a language other than English. 6. A confusing/inconsistent methodology. 7. Redundant content that did not pass the automatic screening.

2.3. The data analysis

In the study selection and screening stages, data extraction and data analysis were carried out by two reviewers, with discrepancies resolved by a third reviewer.

In order to analyze the data, the information collected was grouped by membrane treatment and rate of wound healing in the in vivo tests. Based on the data collected and organized, a risk of bias analysis for non-randomized studies (MINORS), a risk of bias analysis for animal experiments (SYRCLE), and a principal component analysis (PCA) were carried out [89–91]. In the case of the MINORS risk of bias analysis, question number 7 (a less than 5% loss to follow-up), which deals with a loss of patient continuity in trials, was not answered given that it is aimed at human trials, where patients have the option to stop participating at any time. As the tests carried out were characterization tests on membranes/hydrogels, which are inanimate and incapable of fitting into this category, this topic in the MINORS methodology was not addressed.

Principal component analysis is based on an exploratory multivariate analysis that transforms the original variables into a reduced set of statistical components [92, 93]. Here, the values were normalized using the Box–Cox transformation. The interrelationships among the set of studies were assessed using the principal components (PC1 and PC2). Only studies dealing with membrane treatment were considered. The treatment method variables were the cumulative release (%), the contact angle at t1 (°), the maximum membrane extension (%), and the final tensile strength (kPa). Missing data from each article was filled in via linear interpolation to conduct the analysis [94]. The PCA graph was plotted using the Past 4.03 program [88].

For the bivariate analysis, the Shapiro–Wilk test was first carried out to assess the normality of the sample population. A p(normal) value below 0.05 leads to the null hypothesis being rejected, suggesting that the sampled data follows a normal distribution [95, 96]. Spearman's Rho test was applied, as the value obtained rejected the null hypothesis [88].

In the meta-analysis stage, the data were divided into membrane and hydrogel subgroups and analyzed using Review Manager 5.4.1 [87], taking into account the replicate counts, mean values, and standard deviations of the % regeneration in the in vivo diabetic or burn wound experiments. The program was employed to compute the differences in the standard deviation and 95% confidence intervals (CI) through random-effects models. For all included studies, the % regeneration in the in vivo wound experiments was compared by checking it against the negative control values using a membrane or hydrogel based on pure chitosan. The heterogeneity across studies was quantified through the I^2 index, where I^2 values above 50% indicated significant heterogeneity. All of the reported data were standardized to SI (International System of Units) where necessary.

3. Results

3.1. The data selection and screening

In this systematic review, 991 records were obtained from the PubMed, Dimensions, Scopus, and Web of Science databases. After the automatic screening, 448 records were removed as duplicates. After manual evaluation, 503 files were discarded because they did not meet the pre-established criteria. In the end, 40 documents were thoroughly assessed, as shown in the flowchart (**Figure 1**).

3.2. The geographical predominance of the selected studies

Analyzing the geographical distribution of the selected studies provides an overview of the research on wound healing using chitosan-based compounds conducted worldwide. Among the selected studies from 2015 to 2023, 16 countries were identified, with Asian countries predominating and a significant concentration of publications. China leads the way regarding the number of articles, followed by India and Iran, which share second place. In contrast, other continents had a smaller share. The United States, Brazil, South Africa, and Belgium contributed only one selected article each on this subject from each continent (**Figure 2**) (Table S5).

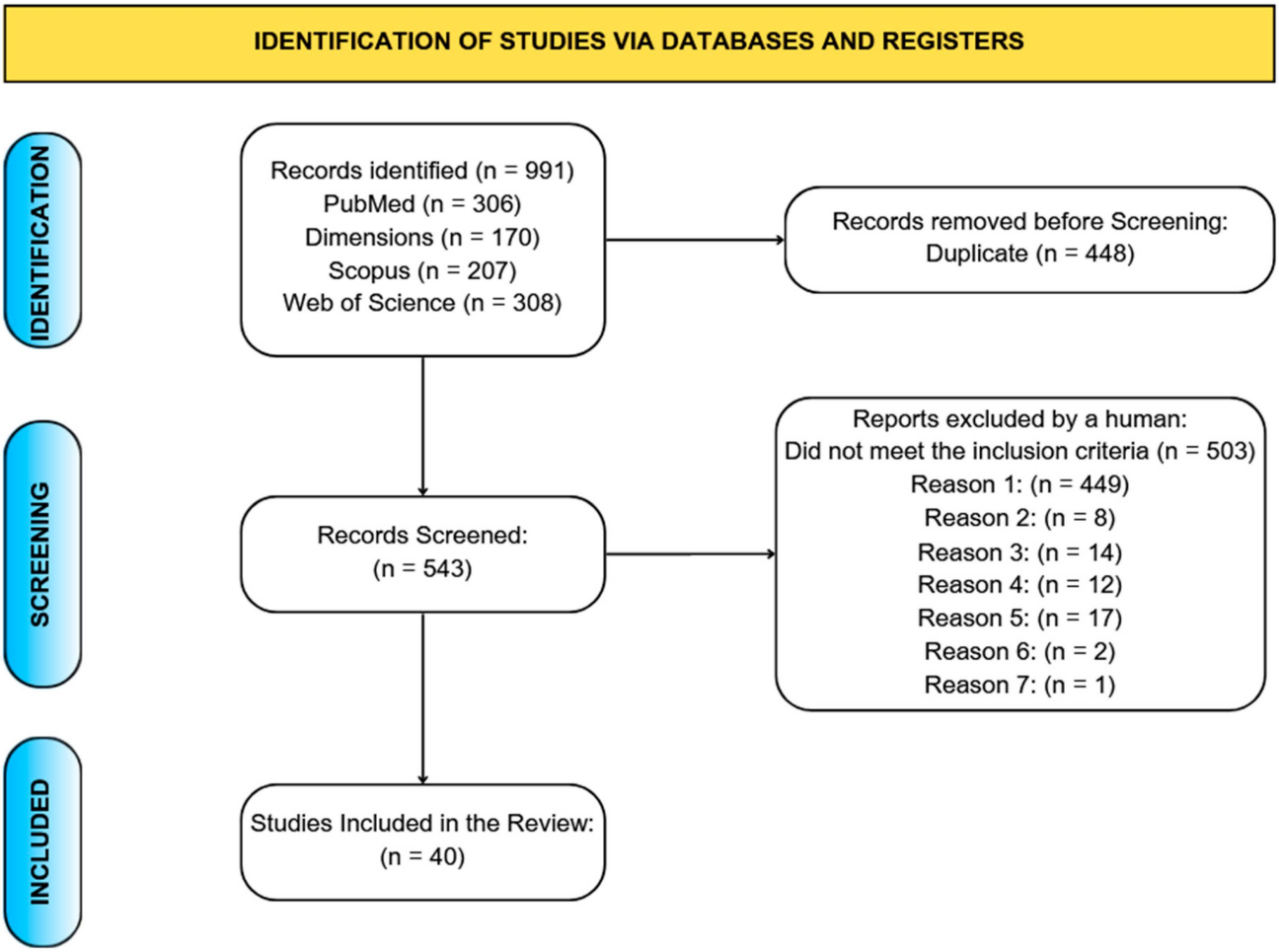

Figure 1 • The PRISMA flowchart describing all of the steps of including the documents in detail, including selection, sorting, and inclusion. Reason 1: Did not mention "Diabetes"/" Diabetic" nor "Burn"; Reason 2: The results did not answer the research question; Reason 3: Did not use chitosan; Reason 4: Was a review, retraction, editorial, note, or proceedings paper; Reason 5: The article was inaccessible or available only in a language that was not English; Reason 6: A confusing/inconsistent methodology was used; Reason 7: Involved repeated content that passed the automatic screening.

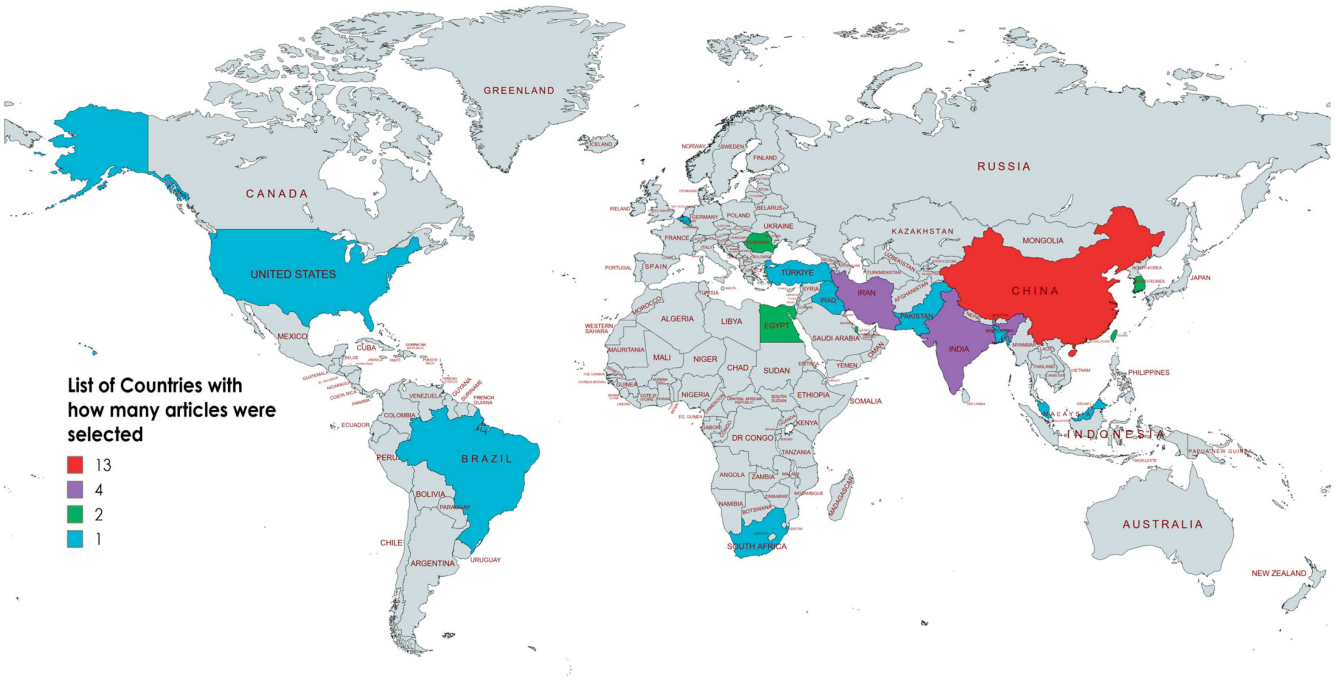

Figure 2 • An illustrative map indicating the countries that published the selected studies about chitosan-based membranes or hydrogels for healing burn or diabetes-related wounds. Created with mapchart.net.

3.3. The analysis of the selected studies for risk of bias

Risk of bias analysis is a systematic assessment used to identify and quantify possible sources of distortion in the results. Bias can be introduced at various stages of the research process, such as the study design, selection of the participants, conduct of the experiments, data collection, or analysis of the results. Analyzing the risk of bias means assessing the methodological quality of the studies and checking for factors that may have compromised the validity and reliability of their conclusions.

The results of analyzing each question for each study that fitted the risk of bias model for animal experiments (SYRCLE) or the non-randomized studies model (MINORS) are elaborated in Tables S6 and S7. In Table S6, one of the main notable points is the uniformity in some of the questions evaluated, such as the second question, in which all but the article with the code 'L002', as indicated in the table, presented a grouping of similar articles from the outset. Other examples are the fifth question, 'Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?', and the sixth question, 'Were animals selected at random for outcome assessment?', the answers to which were negative and verging on negative, respectively, showing that, at least in the writing and editing of the articles, it was not clear that the researchers were double-blinded and that the animals were selected at random. Finally, when assessing the sources of bias, the 'Yes' (Y) classification predominated, suggesting that in general, no potential biases were identified in the studies other than those mentioned above. Thus, analyzing the studies using the SYRCLE tool reveals that many have significant uncertainties, especially in their sequence generation, allocation concealment, blinding, and blinded outcome assessments. These uncertainties represent potential sources of bias that could compromise the validity of the results. It is therefore crucial that future studies adopt a greater degree of clarity to make it explicit whether a method has been carried out using randomization and blinding or not to reduce the risk of bias and increase the reliability.

In Table S7, the results are high and very evenly distributed. The majority of the questions scored values of '2' or '1', with hardly any '0' scores. Considering the exclusion of question 7, the maximum possible score was 22. Based on the scores presented, it is possible to make some observations regarding the methodology of the studies evaluated. The studies generally obtained relatively high scores for criteria such as 'clearly stated objective', 'prospective data collection', 'appropriate outcome criteria', and 'contemporary groups', suggesting that the studies were well planned in terms of the clarity of their objectives; prospective and appropriate data collection; and the definition of outcomes that were aligned with the study's objectives. In addition, the use of contemporary groups for comparison is a solid and robust practice that contributed to the internal validity of these studies.

On the other hand, some criteria showed significant variability in the scores, reflecting inconsistencies between the studies. The 'inclusion of consecutive patients' criterion only received a score of 1, indicating that the studies could not clearly guarantee the inclusion of all consecutive patients, potentially introducing selection bias. 'Unbiased assessment of study outcome' was also a weak point for many studies, with several receiving scores of 1 or 0; this reflected a possible lack of blinding or another mechanism to reduce the assessment bias, which may have impacted the validity of the results. These results show synergy with those in Table S6.

The baseline equivalence of the groups was relatively well maintained, with 77.5 percent of the studies scoring 2, indicating that the groups were comparable at the start of the studies. 'Adequate control group' is another criterion that received consistently good ratings, with 85 percent of the studies scoring well, indicating the presence of a well-designed and relevant control group for comparison with the experimental group. This aspect is essential

to ensure that the differences observed in the outcomes can be attributed to the treatment being studied and not to other factors.

Concerning the total scores, most of the studies scored between 15 and 19 points out of a maximum of 22, which suggests a varied but generally acceptable methodological quality. Thus, although many studies are well-designed in several important respects, some areas need improvement to reduce the risk of bias and increase the validity of the findings. The lack of adequate sample size calculations and inconsistency in the descriptions regarding consecutive patients, where all eligible groups or individuals who are treated in a given period are included sequentially without skipping any patients who meet the inclusion criteria, are critical areas that, if improved, could significantly increase the robustness of the studies. In addition, improving unbiased assessments of the outcomes would help to reduce the detection bias, strengthening the validity of the results further.

3.4. The methodologies used for evaluation of the chitosan membranes in the selected studies

Different methodologies for functional evaluation of the physicochemical properties in the manufacture of the membranes/hydrogels and the combined therapeutic approaches to wound and burn treatment were investigated in the studies to assess the efficacy of various chitosan-based models in wound and burn regeneration. Most of the studies evaluated the effects of the membranes using both in vivo (77.5%) and in vitro (92.5%) experiments (Table S8). There was also a homogeneous distribution of studies that used membranes and hydrogels, at 50% and 52.5%, respectively.

3.5. The assessment of the methodologies used for physicochemical characterization of the chitosan membranes

The methodologies used to characterize the membranes and hydrogels involved a series of specific experiments. The main experiments included mechanical testing; evaluating the membranes' tensile strength and maximum deformation; contact angle analyses; cell viability tests; cumulative release studies; and degradation studies. The distribution of these tests and a comparison of the results can be seen in **Figure 3** and Tables S9–S14, respectively.

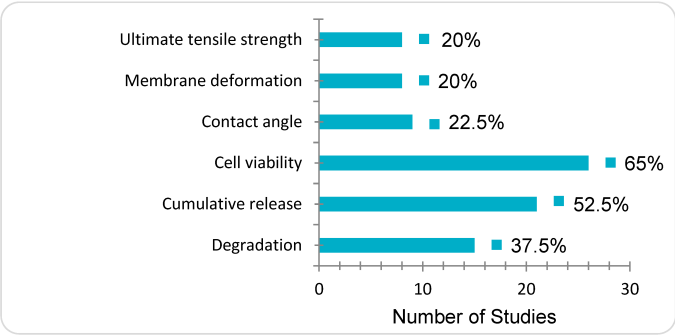

Figure 3 • The number of studies that applied each of the main characterization tests.

Notably, cell viability studies were carried out in the most significant number of articles (65%), followed by cumulative release studies (52.5%), as shown in **Figure 3**. These are the most investigated tests in the characterization of membranes and hydrogels, as they demonstrate, respectively, whether the material will negatively affect the survival of the cells at the wound site and how it will be able to release substances in a controlled manner, a point of interest in the development of membranes as dressings for wound healing, such as chitosan.

Regarding the mechanical tests (of the tensile strength and maximum deformation of the membranes), those best suited were those with a high tensile strength combined with a significant percentage of deformation. Examples include the results of Basit et al. [97], with 9940 kPa and 66.66 ± 3.29%, and Gao et al. [98]'s results, with 1530 ± 275 kPa and 56.80 ± 12.11%. The other results are visualized better in Tables S9 and S10.

Regarding the contact angle, there were variations in the values obtained, characterizing the materials as hydrophobic or hydrophilic. Of these values, the most hydrophobic were the 'Poly(lactic acid) (PLA)/Bovine serum albumin (BSA) loaded chitosan nanoparticles (CNP) nanofiber mats' created by Sun et al. [99], with a value of 130 ± 3°. In contrast, the most hydrophilic value was that for the 'P-CH/HÁ' sample created by Gao et al. [98], with a value of 27.6 ± 6.2°. The other values obtained are available in Table S11.

As for cell viability, 46.15% of the articles did not present percentage values for this analysis, only qualitative data. On the other hand, of the remaining articles, 85.71 percent presented results of increased cell viability or a decrease in cell viability that did not fall within the spectrum of significance. This spectrum is a range of loss in cell viability of up to 30 percent, which is still acceptable. Examples of viability rates that exceeded 100 percent are those from the study by Yu et al. [100] using a PLA/SCS sample, who obtained a value of 123%, and from Abdelbasset et al. [101] using a 'chitosan/CMC/0.3%Mequinol' sample, who obtained values of 127.59 ± 13.95% and 125.64 ± 9.77% on days 3 and 7, respectively. Further details on the other samples can be found in Table S12.

The results were heterogeneous regarding the substance release profiles of the membranes, showing a variety of release percentages at the different times evaluated. Considering that the release time of interest can vary based on the target, the values for different substances present at different positions on the time–release spectrum can be considered significant; this is best visualized by noting that within this table, release values ranging from a maximum of 8 h to 336 h were obtained depending on the site, while the cumulative release ranged from 0 to 100%. An example would be the work by Hajimiri et al. [102], which showed a release of 79.1 ± 6.3% of 'Growth factor rhEGF' from a 'CMCh-based hydrogel' sample within 48 h. Another example in the opposite position would be the work by Sun et al. [99], which showed a release of 87% of the proteins from their 'BSA@CNP nanofiber' sample within 336 h. The other examples and release tests evaluated can be found in Table S12.

Concerning the degradation tests, the data obtained and presented in Table S14 showed heterogeneity and variability. The duration varied from article to article, ranging from two to twenty-eight days. The most commonly used medium was PBS, present in 64.28% of the articles evaluated. In the work by Bryan et al. [103], all of the membranes evaluated showed significant reductions in their mass during the four-week test period, with the 'CE' and 'CEMg' membranes showing an approximately 70% loss in their mass, while the 'C' and 'CMg' membranes showed a 50% loss.

In contrast, in the study by Thangavel et al. [104], only around 11 to 13 percent degradation occurred for all of the hydrogels assessed after 20 days of testing, showing that depending on the polymer assessed and the physicochemical characteristics, there are different degrees of influence on the degradation rates.

3.6. The comparative effect of the membrane characterization variables

The interrelationships between the data groups of the membrane characterization test variables were assessed and then compiled via a principal component analysis (PCA), as shown in **Figure 4**. In addition to the PCA, Spearman's Rho test was carried out.

Figure 4 shows that component 1 appears to be more closely associated with the aspects of membrane strength and extension during the tensile tests and cumulative release. Meanwhile, component 2 shows a stronger correlation with the contact angle, indicating that this component can vary according to the degree of hydrophobicity or hydrophilicity.

After analyzing the level of association between the membrane characterization experiments using Spearman's test, correlations were found that strengthened what was already observed and is shown in **Figure 4**.

3.7. The meta-analysis of the degree of regeneration of diabetic wounds and burns during in vivo experiments using chitosan membranes/hydrogels

In order to set up and carry out the meta-analysis, only studies that carried out in vivo tests and presented the mean, standard deviation, and sample value for the repetitions in each experiment were considered (**Figure 5**).

The results obtained through the meta-analysis confirmed the effectiveness of using membranes/hydrogels in wound treatment compared to that for a negative control, whether this negative control was the use of ordinary gauze or the absence of any treatment in the sample.

During the preparation and assembly of this systematic review, two studies that fell into the hydrogel and membrane groups, one in each, generated a significant increase in the heterogeneity of the analysis ($I^2 > 50\%$), so they were excluded from the analysis and the assembly of the final graph. This aspect of the bias effect mentioned can be visualized by comparing **Figures 6** and **7**. It can be inferred that this effect may have been caused by the aspects of bias highlighted in Tables S6 and S7.

3.8. The effect of incorporating substances into membranes/hydrogels on the degree of regeneration of diabetic wounds/burns during in vivo experiments

Data was collected on the results of the percentage of regeneration in the wound area from studies that clearly presented these values with a margin of error in their structure for collection and analysis. All of the data collected are shown in **Tables 2** and **3**. From these, it is clear that the date on which the lowest final measurement was recorded was day 2, while the date for the highest was day 21. Regarding the values for the percentage of regeneration of the wound area, the lowest value obtained on the final date was 19 ± 6% in Sun et al. [99], while the highest was 100 ± 0% in the work by Razack et al. [105].

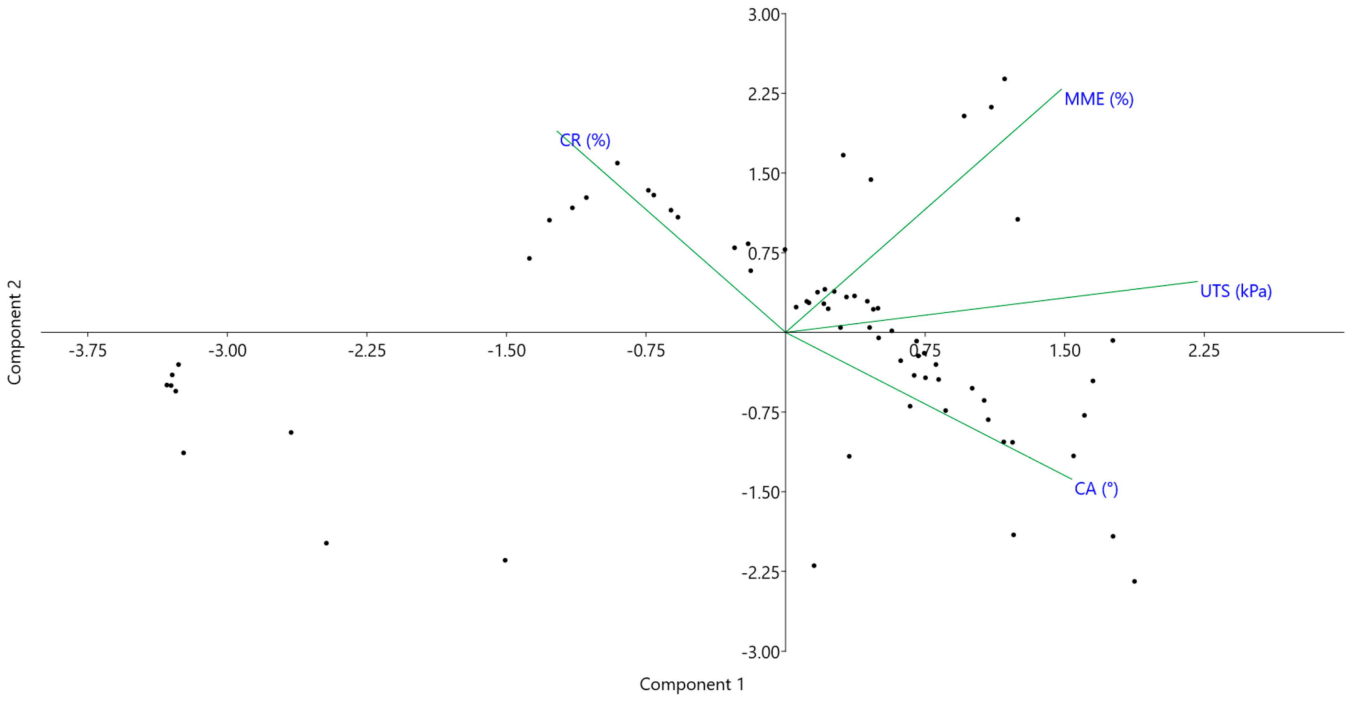

Figure 4 • The principal component analysis (PCA) of the membrane characterization tests. CR: cumulative release; MME: maximum release extension; UTS: ultimate tensile strength; CA: contact angle.

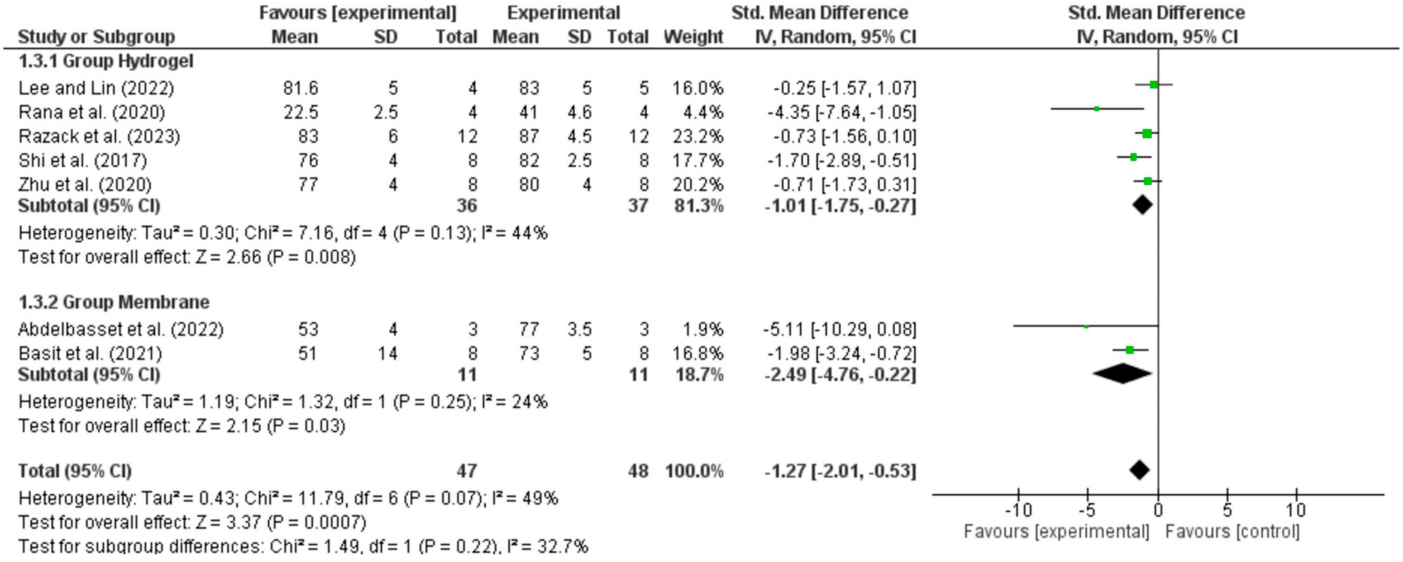

Figure 5 • A summary of the results of the Forest Plot analysis of the degree of regeneration of diabetic wounds/burns during in vivo experiments using pure membranes/hydrogels, utilizing the difference between the standard deviations in the selected studies. [97, 101, 105–109].

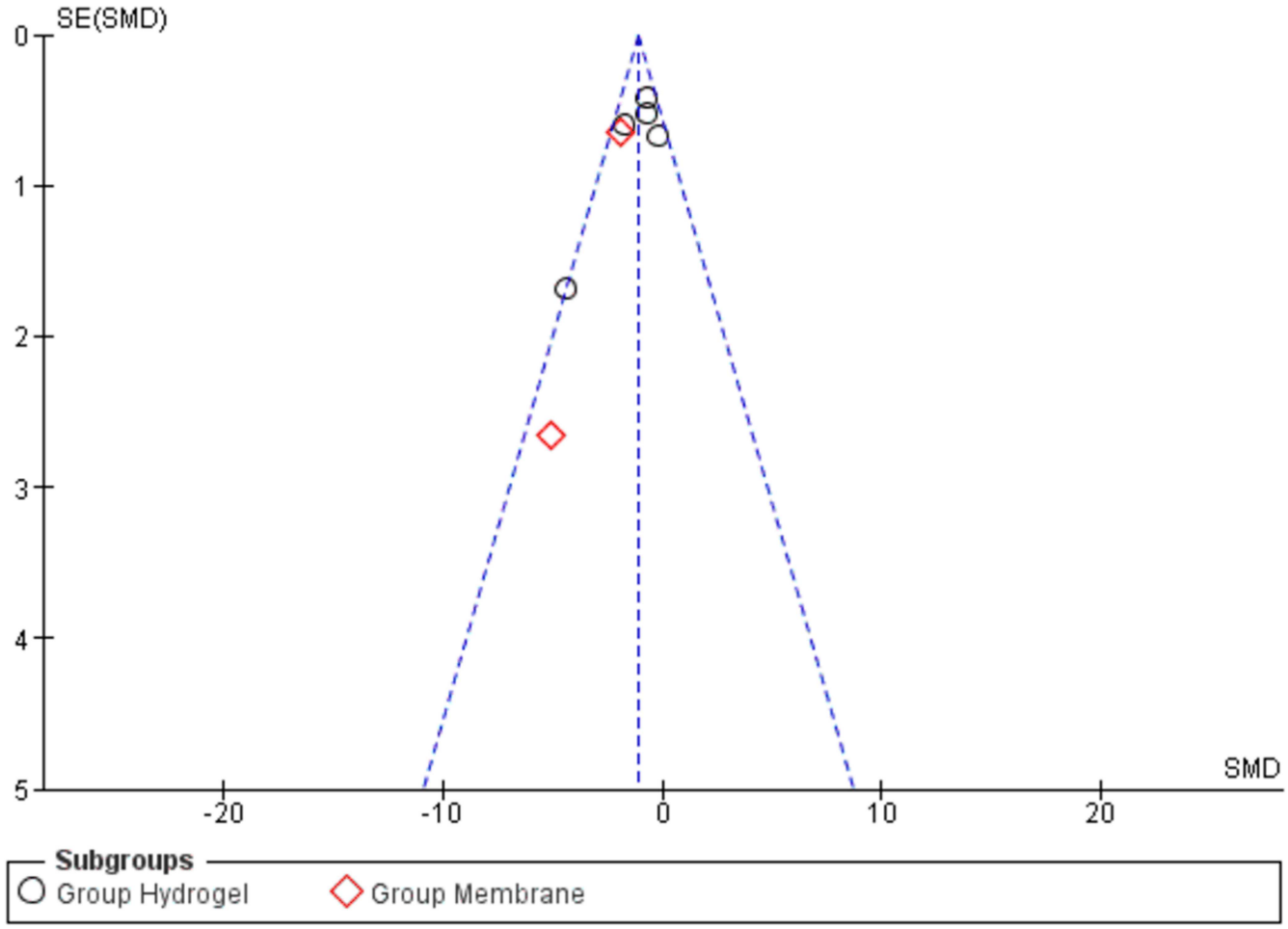

Figure 6 • A funnel plot of the studies included in the meta-analysis.

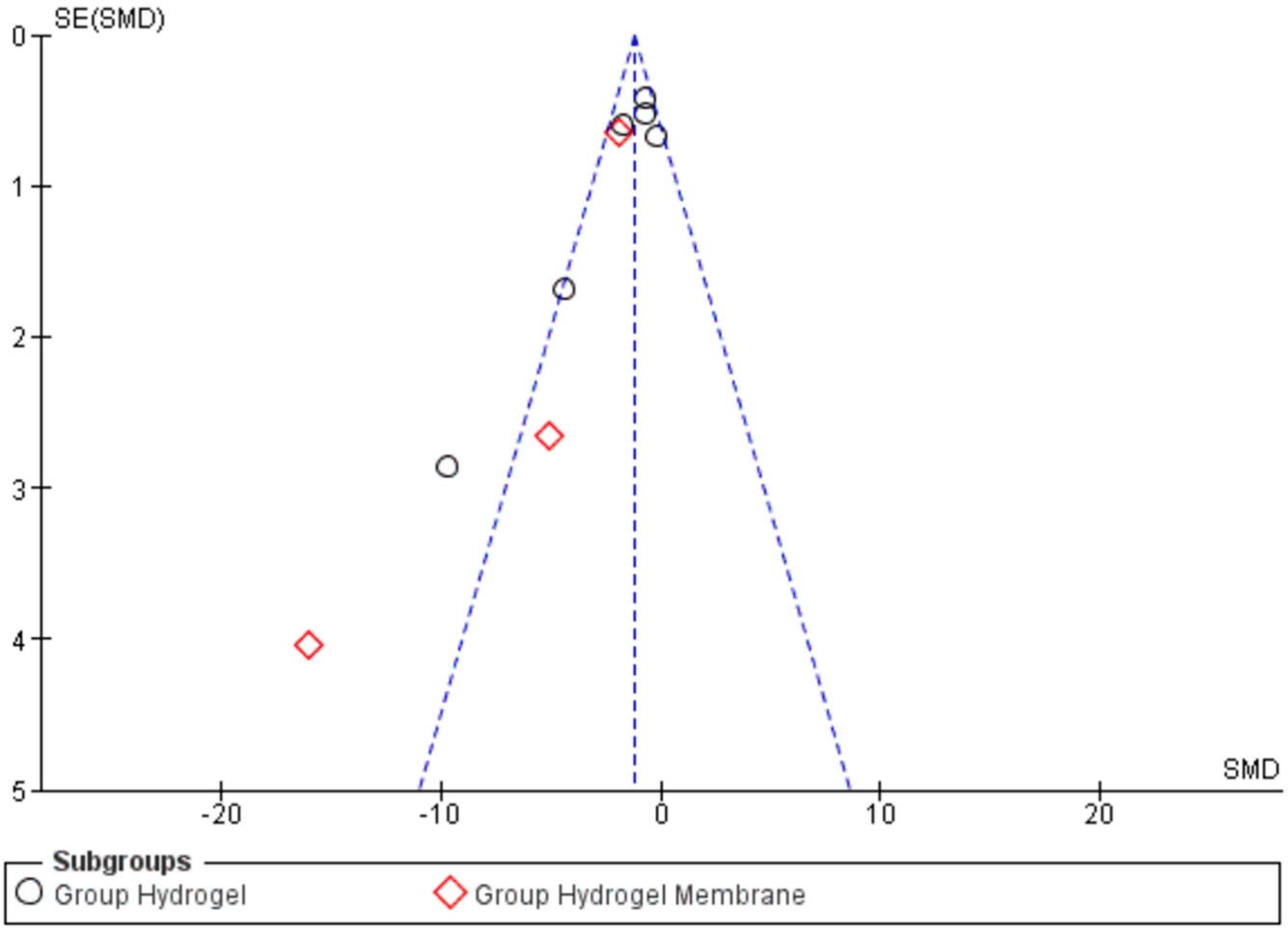

Figure 7 • A funnel plot of the studies initially included in the meta-analysis, with the presence of samples that generated heterogeneity.

Table 2 • The values for the percentage of regeneration of the wound area in the in vivo experiments using chitosan membranes and/or hydrogels.

Membrane/hydrogel	Wound size (mm^2)	Condition	Day of measurement	% of regeneration in the wound region	Reference
Untreated group	113	Diabetes	15	41.5 ± 3.24	[110]
Hydrogel and colloidal silver				60.34 ± 2.23	
Nanoparticles incorporated chitosan (Chitosan/Ca-AlgNps/AgNPs) hydrogel				83.52 ± 4.38	
Synthesized hydrogel mixed with freshly collected blood from the same animal				99.76 ± 1.98	
Normal saline solution (Vehicle)	100	Burn wound	21	28 ± 6	[111]
Chitosan-Alginate and docosahexaenoic acid				80 ± 6	
Chitosan-Alginate and mesenchymal stem cells				67 ± 15	
Chitosan-Alginate, docosahexaenoic acid, and mesenchymal stem cells				93 ± 3	
Untreated group	162.86	Burn wound	18	51 ±14	[97]
Film (Sodium Alginate; Pectin; Glycerol; Tween-80 (0.1% *w*/*w*))				73 ± 5	
Chitosan curcumin nanoparticles				94 ± 10	
Film + chitosan curcumin nanoparticles				100 ± 5	
Gauze	5026.55	Diabetes	15	81.6 ± 5	[106]
Commercial dressing HeraDerm				82 ± 5	
Blank Chitosan				83 ± 5	

Table 2 • *Cont.*

Membrane/hydrogel	Wound size (mm²)	Condition	Day of measurement	% of regeneration in the wound region	Reference
EGF-loaded nanoparticles (ENPs) and the antimicrobials polyhexamethylene biguanide (PHMB), named EnpPCH				89 ± 5	
PFC emulsions (Pes) and the antimicrobials polyhexamethylene biguanide (PHMB), named PePCH				88 ± 5	
PFC emulsions (Pes), EGF-loaded nanoparticles (ENPs), and the antimicrobials polyhexamethylene biguanide (PHMB), named PEENPPCH				93.8 ± 5	
Chitosan/carboxymethyl cellulose (CMC)/0.3% mequinol	225	Diabetes	14	96 ± 2.5	[101]
Chitosan/carboxymethyl cellulose (CMC) scaffolds				77 ± 3.5	
Sterile gauze				53 ± 4	
Gauze	50.27	Diabetes	12	77 ± 4	[112]
Gel-4 (1:2 of Oxidized hyaluronic (OHA) to acid succinyl chitosan (SCS))				80 ± 4	
Insulin-loaded micelles (ILM)-Gel-4				86 ± 4	
Epidermal growth factor (EGF)-Gel-4				90 ± 2.5	
ILM-EGF-GEL-4				95 ± 3	
Normal saline (NS)	153.94	Burn wound	14	71 ± 15	[113]
Silver sulfadiazine (SSD) cream				71 ± 8	
baicalin (BA)/Bletilla striata polysaccharide (BSP)/carboxymethyl chitosan (without silver titanate (ST))				75 ± 8	
baicalin (BA)/Bletilla striata polysaccharide (BSP)/carboxymethyl chitosan (with silver titanate (ST))				78 ± 7	
Gauze dressing	400	Diabetes	16	34 ± 4	[104]
Pure chitosan (CS) hydrogel				68 ± 2	
Chitosan + L-glutamic acid (LG) 1.0% hydrogel				97 ± 3	
Physiological saline	300	Burn wound	21	89.42 ± 1.96	[114]
collagen peptides (COP)				90.88 ± 0.22	
carboxymethyl chitosan (CMC)—collagen peptides (COP)				99.93 ± 0.15	
commercial burn ointment (MEBO)				99.97 ± 0.07	
Blank polylactic acid (PLA)/chitosan nanoparticles (CNPs) nanofiber mats	63.62	Diabetes	7	27 ± 10	[99]
Polylactic acid (PLA)/Epidermal growth factor (EGF)@ chitosan nanoparticles (CNPs) nanofiber mats				19 ± 6	
Vdermlin group (control)	78.54	Diabetes	16	94 ± 2	[115]
VCLD containing 10 mg/mL CMC				84 ± 1	
VCLD containing 30 mg/mLCMC				85 ± 1.3	
VCLD containing 50 mg/mL CMC				86 ± 1	
VCLD containing 50 mg/mL CMC + Dermlin (CLD + DML)				100 ± 0	
Gauze	78.54	Diabetes	14	76 ± 4	[107]
Hydrogel				82 ± 2.5	
Hydrogel loaded with 100 μL PBS containing 150 μg of exosomes				93 ± 1.5	
Amnion gel	490.87	Burn wound	16	51.5 ± 3.5	[108]
Gel consisting of amnion and collagen with a dressing membrane				71.7 ± 3.3	

Table 2 • *Cont.*

Membrane/hydrogel	Wound size (mm²)	Condition	Day of measurement	% of regeneration in the wound region	Reference
Gel consisting of amnion and collagen without a dressing membrane				62.5 ± 4	
Collagen gel				36 ± 4	
No treatment (negative control)				22.5 ± 2.5	
1% silver sulfadiazine (positive control)				41 ± 4.6	
No treatment	28.27	Diabetes	2	83 ± 6	[105]
Nanoemulgel (NEG) (gel only)				87.5 ± 4	
low-level laser therapy (LLLT) (laser only)				87 ± 4.5	
Nanoemulgel (NEG) + low-level laser therapy (LLLT) (combination of gel and laser)				100 ± 0	
Chitosan-Polyvinyl alcohol (CS-PVA)-	314.16	Diabetes	14	64 ± 0.1	[116]
Calcium Peroxide (CPO)-0.5 patches Normal saline solution				51.5 ± 0.6	
No treatment	490.87	Burn wound	14	74 ± 4	[117]
heparin-polyvinylpyrrolidone (HpPVP)				89 ± 4,5	
heparin-polyvinylpyrrolidone/TiO2 (HpPVP/TiO2)				98.5 ± 1.8	
Chitosan film + 50% free all-trans retinoic acid (ATRA) + 50% encapsulated solid lipid particles (SLN) -ATRA.	-	Diabetes	14	90.54 ± 1.5	[118]
Chitosan film + solid lipid particles (SLN) blank				75.6 ± 2.4	
PBS wash	50.27	Diabetes	14	83 ± 1.5	[119]
Experimental dressing, including sterilized gauze				81.4 ± 2.4	
Commercial dressing HeraDerm				90.1 ± 3.6	
CHG				86 ± 3	
EGF-loaded chitosan nanoparticles (CNPE)-loaded chitosan-based composite hydrogel (NPECHG)				92.2 ± 1.8	
SNPECHG				96.5 ± 3.1	
Sterile gauze	400	Diabetes	21	45 ± 3.5	[120]
CS-IHG (Placebo)				52 ± 1.2	
epidermal growth factor (EGF)-CS NPs (Test formulation)				85 ± 2.6	
thermo-responsive injectable hydrogel containing DOX and EGF nanoparticles (C-EGF-D IHG)				98.2 ± 1.8	
PVA-CS	78.54	Diabetes	14	47 ± 2	[121]
PVA-CS-CeNPs				73 ± 3	
PVA-CS-MP				79 ± 2.3	
PVA-CS-CeNPs-MP				90 ± 1.1	
No treatment	225	Diabetes	14	63 ± 4.8	[122]
fumaria officinalis extract-loaded (FOE) 10%—chitosan nanoparticles (CHNPs) /calcium alginate hydrogel				84 ± 5	
fumaria officinalis extract-loaded (FOE) 20%—chitosan nanoparticles (CHNPs) /calcium alginate hydrogel				94 ± 3	
chitosan nanoparticles (CHNPs) /calcium alginate hydrogel				67 ± 4.8	
GranuGEL® hydrogel wound dressing				98 ± 1.8	

The abbreviations that appear throughout the table are those used in each study.

Table 3 • The values for the percentage of regeneration in the wound area during in vivo experiments using chitosan membranes and/or hydrogels at different moments.

Membrane/hydrogel	Condition	Day of measurement		% of regeneration of wound region (t1)	% of regeneration of wound region (t2)	Reference
Untreated group	Diabetes	5	15	5 ± 1.01	41.5 ± 3.24	[110]
Synthesized hydrogel mixed with freshly collected blood from the same animal				40.25 ± 2.41	99.76 ± 1.98	
Untreated group	Burn wound	2	18	13 ± 8	51 ± 14	[97]
Film + chitosan curcumin nanoparticles				53.5 ± 6.1	100 ± 5	
Gauze	Diabetes	12	15	74.9 ± 5	81.6 ± 5	[106]
PFC emulsions (Pes), EGF-loaded nanoparticles (ENPs), and the antimicrobials polyhexamethylene biguanide (PHMB), named PEENPPCH				86.1 ± 5	93.8 ± 5	
Chitosan/carboxymethyl cellulose (CMC)/0.3% mequinol	Diabetes	7	14	60 ± 5	96 ± 2.5	[101]
Sterile gauze				23 ± 3.5	53 ± 4	
Gauze	Diabetes	6	t 12	46 ± 8	77 ± 4	[104, 112]
ILM-EGF-GEL-4				75 ± 7	95 ± 3	
Gauze dressing	Diabetes	8	16	7 ± 2	34 ± 4	[104]
Chitosan + L-glutamic acid (LG) 1.0% hydrogel				49.71 ± 1	97 ± 3	
Gel consisting of amnion and collagen with a dressing membrane	Burn wound	4	16	23.8 ± 3.5	71.7 ± 3.3	[108]
No treatment (negative control)				5.3 ± 2.3	22.5 ± 2.5	
Chitosan-Polyvinyl alcohol (CS-PVA)-Calcium Peroxide (CPO)-0.5 patches	Diabetes	9	14	44.8 ± 0.4	64 ± 0.1	[116]
Normal saline solution				23 ± 0.3	51.5 ± 0.6	
No treatment	Burn wound	7	14	55 ± 3	74 ± 4	[117]
Heparin-polyvinylpyrrolidone/TiO2 (HpPVP/TiO2)				91.5 ± 4.7	98.5 ± 1.8	
Chitosan film + 50% free all-trans retinoic acid (ATRA) + 50% encapsulated solid lipid particles (SLN) -ATRA	Diabetes	10	14	68.39 ± 5.5	90.54 ± 1.5	[118]
Chitosan film + solid lipid particles (SLN) blank				51.9 ± 6.1	75.6 ± 2.4	
Experimental dressing, including sterilized gauze	Diabetes	9	14	51.8 ± 6.8	83 ± 1.5	[119]
SNPECHG				84.8 ± 10	96.5 ± 3.1	
Sterile gauze	Diabetes	14	21	17.7 ± 2.4	45 ± 3.5	[120]
Thermo-responsive injectable hydrogel containing DOX and EGF nanoparticles (C-EGF-D IHG)				65.5 ± 4.8	98.2 ± 1.8	

Table 3 • *Cont.*

Membrane/hydrogel	Condition	Day of measurement		% of regeneration of wound region (t1)	% of regeneration of wound region (t2)	Reference
PVA-CS	Diabetes	7	14	20.3 ± 1.4	47 ± 2	[121]
PVA-CS-CeNPs-MP				65.38 ± 3.8	90 ± 1.1	
No treatment	Diabetes	7	14	36.6 ± 5	63 ± 4.8	[122]
Fumaria officinalis extract-loaded (FOE) 20%- chitosan nanoparticles (CHNPs)/calcium alginate hydrogel.				60 ± 8.7	94 ± 3	

The abbreviations that appear throughout the table are those used in each study.

4. Discussion

4.1. The geographical predominance of the studies

Analyzing the geographical distribution of the selected studies provides an overview of the research into regenerative membranes made from chitosan-based compounds which were analyzed in this review. Out of 16 countries involved, Asia stands out as the main center of scientific production in this area, as demonstrated by its large number of publications, with China as the epicenter of innovation and research in the area, with a total of 13 articles. Significant investments in biomedical research and collaboration between biotechnology industries and academic institutions have contributed to Asia's dominance on the scientific scene [123, 124].

China, India, and Iran are in second place, each contributing four articles. In addition, these countries have a history of significant progress in biomedical sciences and materials, which can be seen in the scientific production of chitosan membranes [123, 124]. The number of articles published in these countries indicates growing interest and skills in manipulating and applying biopolymers for medical purposes.

On the other hand, the other continents participated less intensively. The United States of America presented one article in North America. Despite its global leadership in biomedical research, this low representation indicates the prioritization of other materials or therapeutic methods for treating wounds and tissue regeneration, such as organoids and tissue chips [124–126]. In the South American context, Brazil also contributed one article; this indicates an emerging effort to explore biopolymers, although its scientific production still needs more impetus [127]. Similarly, South Africa represents the African continent with one article, reflecting local initiatives in researching solutions to critical health problems such as diabetic wounds and burns [128].

This geographical distribution of articles highlights the need for greater international collaboration to accelerate the development and application of chitosan-based healing membranes, which are capable of helping with such severe and frequent problems as burns and diabetic wounds. Countries with fewer publications could benefit from leading nations such as China, India, and Iran sharing their knowledge and advanced technologies. In addition, the analysis suggests potential areas for investment in research, especially in under-represented regions where the need for solutions to treat diabetic wounds and burns is critical. Investments in research infrastructure and incentives for collaborative studies could catalyze significant advances [129].

4.2. The analysis of the selected studies for risk of bias

Based on the results in Tables S6 and S7, it is notable that both analyses showed that the studies analyzed had positive scores, indicating a low level of bias in their work, making the data that they provided more reliable for analysis and comparison in this systematic review. Table S7 presents the methodological quality assessment using MINORS. As mentioned in Section 2.3, since item 7 on the adequacy of the follow-up did not apply to the studies included, the maximum achievable score for comparative studies became 22 points rather than the standard 24. To maintain consistency with the original MINORS classification, adjusted thresholds were applied, where studies scoring 16 points or higher were considered low-risk; those scoring between 12 and 15 points were moderate-risk; and studies with 11 points or below were high-risk. These proportional adjustments ensured comparable rigor in the bias assessment despite the omitted item. The analyzed studies provided an average of 17.425 out of 22 points (79.2%), with an average low risk of bias. However, each value must be taken into account in the analysis.

Table S6 presents the results of the risk of bias assessment using the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) tool. This validated instrument evaluates the methodological quality of animal studies through 10 domains addressing specific biases, including selection, performance, detection, attrition, and reporting biases. Each domain was judged as "low-risk", "high-risk", or "unclear risk" based on detailed signaling questions, following the tool's standardized criteria. Considering the results obtained, a positive outcome could be seen since most of the questions were answered with 'Yes', but there was one negative aspect to note: the blinding of the study researchers. After an analysis in triplicate, none of the three researchers noticed the presence of a passage in any of the articles that mentioned that the researchers were blinded to which animal group received which sample, which is a very important factor. As no passages at least suggested this, the answer of 'No' was uniformly assigned (item 5 in Table S6), instead of 'Uncertain.'

4.3. The methodologies used for evaluation of the chitosan membranes in the selected studies

As previously verified in the results, the analysis of the articles in the review showed a variety of approaches to functional assessments of their physicochemical properties during the manufacture of hydrogels and membranes. These methods are essential for recovery from burns and wounds. Rigorous scientific validation prior to the clinical implementation of these technologies was the main objective of the studies, both in vitro (92.5 percent) and in vivo (77.5 percent). To ensure that the physicochemical and biochemical characteristics of membranes and hydrogels can support tissue regeneration in the complex and dynamic environment of the human body, a combined approach of in vitro and in vivo testing is required. Recent studies show that in vitro models can simulate specific wound conditions, making them essential for the initial evaluation of biomaterials [130].

The studies showed that the use of membranes and hydrogels was balanced at 50 percent and 52.5 percent, respectively. It is worth noting that hydrogels are highly hydrated, with a soft and flexible consistency, similar to that of biological tissues, while membranes are more rigid, two-dimensional, solid surface structures. This uniformity in the choice of materials indicates growing awareness of the unique benefits of each type of material. Hydrogels provide a moisturizing environment, which is necessary for cell migration and wound re-epithelialization, as well as favoring gas exchange [131, 132], while chitosan membranes are widely recognized for their antibacterial and hemostatic properties [133].

The studies reviewed extensively examined chitosan-based models for regenerating wounds and burns. According to several studies, chitosan improves healing, re-epithelialization, and granular tissue formation due to its biocompatible, biodegradable, and antimicrobial characteristics. These characteristics are important in preventing infections and promoting fast and efficient wound healing [134, 135].

Based on the data and analysis in Table S8, chitosan-based membranes and hydrogels present several variations and possible combinations with many other substances. Both approaches are therefore practical but involve different mechanisms of action. Therefore, the choice between one over the other should be based on the specific needs of the wound and the patient's clinical condition [109].

The systematic review of these studies suggests that membranes and chitosan hydrogels have significant potential for healing wounds and burns, regardless of the intermediate treatment methodology. The choice of the type of material should be guided by the specific characteristics of the wound, as well as the desired results in the healing process [136]. In addition, there is a need for new, detailed studies to be carried out to optimize these technologies and expand their clinical applications to improving the quality of life of patients with wounds and burns [137].

4.4. The assessment of the methodologies used for physicochemical characterization of the chitosan membranes

Figure 3 shows a 65% predominance of cell viability test in the studies analyzed, indicating this as an aspect of greater importance in the membrane/hydrogel development process, which makes sense since a material that does not allow for epithelial cell viability is unlikely to be helpful or beneficial in any in vivo test [138]. Another aspect shown in **Figure 3** is the more infrequent presence of the two tensile tests ('final tensile strength' and 'maximum membrane extension'), which were only present in the studies dealing with membranes, even though they are relevant to both the hydrogel and membrane classes. However, considering the studies on membranes alone, this type of testing was represented in 40%, which shows its degree of importance in studies involving membranes. Each type of test provides critical and essential information on different aspects of membrane performance and safety [139].

As far as tensile tests were concerned, the data and results in Tables S9 and S10 were taken into account, and it was borne in mind that the tensile strength of a membrane affects its ability to withstand tension during the packaging process and its transport [97]. It is also known that membranes whose functionality and application involves wound healing must be able to provide support for cell proliferation. Based on the literature, it is said that a tensile strength value within the range of 700 to 18,000 kPa is sufficient for a viable dermal cell culture [140, 141]. Thus, based on the best results from each study, 62.5% are within the feasible range defined by the literature.

Based on the results shown in Table S11, there is fluctuation in the contact angles between more hydrophobic values and more hydrophilic values. It is known that a certain degree of humidity is beneficial for wound treatment, as hydration is considered the most important external factor during the optimal healing process, and a hydrated model is considered more efficient than a completely dry model [142–144]. Therefore, an intermediate value is preferred to obtain the benefits of hydration without favoring microorganism growth [145, 146]. Based on this, 38.46 percent of the samples were outside the ideal intermediate range (60° to 120°), 11.54 percent did not report these values, and 50 percent were within the ideal intermediate range [147].

Based on Table S12 regarding the analysis of the effects of the different materials on cell viability, important aspects of cytocompatibility and cell response are revealed. These results highlight the complexity and the need for careful experimental design, considering aspects such as the type of cell of interest, the duration of the tests, and the presence of a varied group of materials for testing to assess the cell viability properly. Concerning the results obtained in the experiments, the membranes showed positive results, either with an increase in cell viability or a loss of viability represented by values that are not considered cytotoxic (70% viability according to the ISO guide "Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity" [148]), which indicates the excellent viability of using chitosan-based membranes and hydrogels. Even with the addition of new compounds, these membranes were still considered acceptable for cellular use.

Regarding the substance release profiles of the membranes, it should be borne in mind that in vitro release studies commonly observe a cumulative release of approximately 70% of the antimicrobial agents over 7 to 14 days, which is considered a practical value for preventing infections. Based on the values tabulated in Table S13, 34.37% of the samples that provided a % release value showed a value above 70%. However, this should not automatically be seen as a negative, as some of the values provided in the table also included negative controls or samples with milder combinations and/or concentrations, not groups that should show

any significant value, for purposes of comparison with another sample that was considered the primary sample in the study. Furthermore, it should be emphasized that this data alone cannot weigh up the antimicrobial effect, as it is only an initial parameter and not a final one.

From the information in Table S14 on the results of the degradation tests of the different hydrogels and membranes, it can be seen that the degradation conditions and the media used vary between the studies, which may influence the comparison of the degradation results. Another aspect to consider when looking at the degradation values obtained is that greater or lesser degradation is not synonymous with a worse or better result, given that in the context of drug loading, degradation over time is a crucial point in the gradual release of the substance of interest. Therefore, the high variability in the results in the table indicates that based on the combinations of materials, it is possible to adapt the degradation of the membrane/hydrogel to the objective of interest, be this a more durable or more easily degradable membrane.

4.5. The comparative effect of the membrane characterization variables

Further analysis of the information in **Figure 4** shows that component 1 seems to be more associated with the strength and maximum deformation of the membranes during the tensile tests, as well as the cumulative release, suggesting that this component may capture variations related to the release of substances from the membranes and their mechanical properties. Component 2 shows a significant correlation with the contact angle, indicating that this component may capture variations related to the surface properties of the membranes, such as their degree of hydrophobicity or hydrophilicity.

When it came to analyzing the level of association between the membrane characterization experiments via the Spearman's test, three correlations were observed: "contact angle" and "cumulative release"; "tensile strength" and "maximum deformation"; and "contact angle" and "maximum deformation". Regarding the relationship between "contact angle" and "cumulative release", the more pronounced negative correlation suggests that a greater contact angle is associated with a lower cumulative substance release by the membranes, following the same pattern. Another correlation observed through the analysis was that between "tensile strength" and "membrane deformation", which showed a positive correlation, implying that membranes with a greater tensile strength also tended to show better extension during the tensile test. A third correlation was that between "contact angle" and "membrane deformation", which showed a moderate positive correlation, suggesting that membranes with a greater contact angle may have a better maximum extension during tensile tests. Finally, the fourth correlation observed in the figure is that between "cumulative release" and "membrane deformation", which shows a slight to moderate negative correlation, suggesting that more significant tensile extension may be slightly associated with a lower cumulative release.

4.6. The meta-analysis of the degree of regeneration of diabetic wounds/burns in in vivo experiments using membranes/hydrogels

The results obtained through the meta-analysis confirmed the efficacy of using membranes/hydrogels in treating wounds compared to that of a negative control, whether this negative control was the use of ordinary gauze or the absence of any treatment in the sample.

Moderate heterogeneity was observed in the studies analyzed in the hydrogel group (I^2 = 44%), and moderate to low heterogeneity was seen in the studies in the membrane group (I^2 = 24%). The overall heterogeneity was 49%. In addition, a highly significant effect is visible ($Z = 3.37$, $p = 0.0007$), suggesting that the differences observed are unlikely to occur by chance. Another aspect to consider is the value of the degrees of freedom (df = 6), indicating the greater robustness and security of the statistical test carried out.

Based on the information in **Figures 6** and **7**, it becomes clear how these studies generated heterogeneity in their respective groups. It was found that parameters relating to the proper treatment of incomplete result data and random housing of the animals during the experiment were uncertain, as analyzed in Table S6. However, there is no guarantee that these factors directly affected the results to the point of generating such heterogeneity in the meta-analysis, and these issues are only assumptions and inferences based on parallel data from other analyses.

Although the wound sizes varied across the studies, interfering directly with the time taken to close the wounds, this variability did not compromise the analysis, as comparisons were made exclusively between the treated (membrane) and untreated (control) groups within each study, not between different studies or membrane types.

4.7. The effect of incorporating substances into membranes/hydrogels on the degree of regeneration of diabetic wounds/burns in in vivo during experiments

From the data obtained and shown in **Table 2**, it is clear that most of the values showed results with % regeneration values higher than those for the controls or simplified groups that did not incorporate other substances. Of this group of articles, only 14.28% showed values with a less than 10% difference between the control/simplified group and the sample with the best result. Only 4.76% showed the value of the control/simplified group to be better than that for the best sample with incorporation. These findings demonstrate chitosan's remarkable capacity for functional integration with diverse materials and therapeutic modalities, significantly enhancing wound regeneration outcomes. Multiple studies have reported superior regeneration rates using innovative chitosan-based combinations. For instance, Choudary et al. [110] achieved enhanced healing using a chitosan hydrogel incorporating autologous whole blood, while Razack et al. [105] reported synergistic effects by combining a chitosan nanoemulgel with low-level laser therapy. These representative examples underscore chitosan's versatility as a platform for combinatorial wound healing strategies, with various formulations consistently demonstrating accelerated tissue regeneration across experimental models.

Added to this is the factor of the time taken to obtain this result. In 71.42% of the articles analyzed, the final time range was between 12 and 16 days, varying between 2 and 21 days. The temporal analysis reveals significant differences in healing efficiency, as demonstrated in **Table 3**. The most effective chitosan-based membranes/hydrogels achieved results comparable to those for the control groups at earlier time points, indicating accelerated wound regeneration. This enhancement is particularly evident

in the work by Razack et al. [105], where by day 15, untreated wounds reached similar regeneration percentages (41.5 ± 3.24%) to those observed with chitosan-blood hydrogels as early as by day 5 (40.25 ± 2.41%). This acceleration pattern was corroborated further by Yang et al. [122], where the Fumaria officinalis-extract-loaded chitosan nanoparticles/calcium alginate hydrogel (20% FOE-CHNPs) combination attained 60 ± 8.7% regeneration by day 7, matching the 63 ± 4.8% healing observed in the untreated controls at day 14. These examples of consistent findings across independent studies demonstrate that functionalized chitosan formulations improve regeneration quality and significantly reduce healing times.

Another aspect to highlight is the heterogeneity of the groups, which show the wide variety of substances and combinations of incorporation that can applied to achieving satisfactory results. Thus, providing various options for researchers or entrepreneurs who want to work with this type of substance, they can choose the materials that are easiest to access or cheapest in their regions without significantly affecting their results.

5. Conclusions

Based on the results obtained, it can be said that there have been significant advances in the use of chitosan membranes to regenerate wounds caused by burns or diabetes, but there is still room for innovation to provide even more efficient results and improve the quality of life of patients suffering from these conditions. This room for innovation is because various combinations can be incorporated into chitosan-based membranes, so there is always the possibility of new groupings capable of surpassing the limits currently achieved. Another aspect that supports their innovation potential is the current concentration of the research in China, which opens opportunities for new countries to enter this field of study. The motivation for such expansion lies in the potential for collaborative partnerships that could combine diverse expertise and local resources, such as unexplored materials from regional fauna and flora, to develop more effective solutions for the stigmatized and clinically challenging problem of burns and diabetes-related wounds. Some examples of this variety can be observed in the work by Rathinamoorthy and Sasikala [149], mixing chitosan with *Leptospermum scoparium* honey (Manuka Honey), leading to a wound contraction percentage higher than that achieved using a commercial dressing. Another example is in the work by Kurek et al. [150] using *Opuntia ficus* (prickly pear) fruit pulp, peel, powdered extracts, and aqueous extracts, which showed results reflective of antioxidant activity.

By fostering international cooperation, researchers could leverage their complementary strengths to achieve more satisfactory outcomes in tissue regeneration and wound healing. In addition, it is possible to conclude that the use of chitosan membranes/hydrogels in wound treatment is, in fact, more efficient than a negative control, whether ordinary gauze or no treatment at all. In addition, it can also be concluded that chitosan membranes/hydrogels showed better results when a wide range of substances were incorporated into them than those in control groups or groups without incorporation. In addition, the characterization aspects for chitosan membranes/hydrogels are essential to understanding the capacity and functions of these products. Thus, the conclusion is that the current results in the literature are promising, and future studies should deepen and improve the scenario for chitosan membranes and hydrogels aimed towards diabetes-related and burn wounds further.

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Author contributions

Conceptualization, S.C.F.G. and J.d.C.F.D.; methodology, S.C.F.G.; software, J.d.C.F.D.; validation, S.C.F.G.; M.L.S.P. and J.d.C.F.D.; formal analysis, S.C.F.G.; investigation, S.C.F.G., L.I.R., L.B.B.B., L.D.F., R.J.d.O., M.A.C. and M.L.S.P.; resources, T.M.S. and V.A.d.C.A.; data curation, S.C.F.G.; writing—original draft preparation, S.C.F.G.; writing—review and editing, J.d.C.F.D., M.F.P., T.M.S. and V.A.d.C.A.; visualization, S.C.F.G.; supervision, V.A.d.C.A.; project administration, V.A.d.C.A.; funding acquisition, T.M.S. and V.A.d.C.A. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The authors ensured compliance with the Materials Today Data Availability guidelines and have appropriately referenced all of the datasets utilized.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Supplementary materials

The Supplementary materials (Table S1. Keywords used to search each database, Table S2. Articles without DOI separated using automated screening of PubMed, Dimensions, Scopus, and Web of Science repositories,

Table S3. Duplicate articles removed using auto-mated screening of PubMed, Dimensions, Scopus, and Web of Sci-ence repositories, Table S4. Articles selected from PubMed, Dimensions, Scopus, and Web of Science repositories after automatic exclusion, Table S5. Number of articles selected by year of publication, Table S6. Results of the risk of bias test for animal experiments (SYRCLE) of the studies that carried out this analysis, Table S7. Results of the risk of bias test for non-randomized studies (MI-NORS) of the studies that performed this analysis, Table S8. General characteristics of the selected studies, Table S9. The highest ultimate tensile strength values are presented in the studies conducting this analysis, Table S10. Maximum membrane length values are presented in this analysis's studies, Table S11. Contact angle values at t1 in the studies performed in this analysis, Table S12. Cell viability parameters in the studies that carried out this analysis, Table S13. Cumulative release values (%) of substances in the studies that carried out this analysis, Table S14. Results of the degradation tests in the studies that carried out this analysis) are available at https://doi.org/10.20935/AcadMatSci7810.

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6. ETAPA II – SÍNTESE E CARACTERIZAÇÃO INICIAL DAS PROPRIEDADES DE MEMBRANAS DE QUITOSANA CONTENDO POSBIÓTICOS DA BACTÉRIA *LACTOCOCCUS LACTIS* SUBSP. *LACTIS* NCDO 2118

A Etapa II deste trabalho foi projetada não como um experimento isolado, mas como uma prova de conceito direcionada por evidências, cujo objetivo é desenvolver um curativo funcional que integre os benefícios da quitosana com os efeitos imunomoduladores de posbióticos derivados de *L. lactis* subsp. *lactis* NCDO 2118.

Esta abordagem inovadora parte do pressuposto de que o sucesso no tratamento de feridas crônicas depende menos da ação antimicrobiana direta e mais da modulação do microambiente inflamatório, um dos principais obstáculos à cicatrização. A escolha por posbióticos — produtos ou subprodutos metabólicos liberados por bactérias probióticas — em vez de microrganismos vivos, aumenta a segurança, estabilidade e *shelf-life* do produto, tornando-o mais adequado para aplicações clínicas (Soltani *et al*., 2023).

6.1. Materiais e métodos

6.1.1. Quitosana e outros reagentes

Foi utilizada quitosana de baixo peso molecular (LMW) — 50,000-190,000 Da — adquirida da Merck (Sigma-Aldrich). Os meios de cultura e demais reagentes foram adquiridos das empresas Kasvi, BD Difco, Merck (Sigma-Aldrich) e Thermo Fisher Scientific.

6.1.2. Microrganismos, meios e condições do pré-inóculo

Duas cepas de *L. lactis* subsp. *lactis* foram utilizadas:

- NCDO 2118 (selvagem), produtora de GABA;

- NCDO 2118 pXies:sec:HSP65, recombinante com expressão da proteína Hsp 65 (Gusmao-Silva *et al*., 2020).

Os pré-inóculos foram cultivados em meio MRS suplementado com 1,25% de glicose (NCDO 2118) ou 10 μg/mL de cloranfenicol (NCDO 2118 HSP65), incubados a 30 °C por 16–18 h sem agitação.

6.1.3. Fermentação e preparo dos posbióticos

A cepa *L. lactis* subsp. *lactis* NCDO 2118 foi cultivada em meio MRS suplementado com 1% de glutamato e 1,25% de glicose, com pH ajustado para 4,6, visando à produção de GABA. A cepa recombinante expressando HSP 65 foi cultivada em meio M17 suplementado com 1% de xilose, para induzir a expressão da proteína. Ambas foram fermentadas por 48 h a 30 °C, sem agitação, conforme protocolo descrito por Dhakal, Bajpai e Baek (2012). Após centrifugação (7000 rpm, 10 min, 25 °C), os sobrenadantes foram filtrados em membrana de 0,22 μm para remoção celular. A esterilidade foi verificada por inoculação em ágar MRS e incubação por 48 h a 30 °C

6.1.4. Síntese das membranas de quitosana contendo os posbióticos de NCDO 2118

As membranas foram sintetizadas por método de *casting*, utilizando 2% (p/v) de quitosana em solução de ácido acético 1%. O agente solubilizador foi substituído por diferentes soluções, conforme **Tabela 1**, para avaliar o impacto da composição na integridade e atividade das membranas. A mistura foi agitada por 24 h, vazada em placas de Petri e secaram em uma estufa de circulação de ar forçado a 30 °C. As membranas foram desgrudadas com bisturi.

Tabela 1. Lista de agentes solubilizadores utilizados para síntese das membranas de quitosana.

Agente Solubilizador
Posbiótico de NCDO 2118
Posbiótico de NCDO 2118 pXies:sec:HSP65
Água deionizada
Meio MRS
Meio M17
Água deionizado com GABA (42,6 g/L)
Água deionizada com Ácido Glutâmico (1%)

A membrana com adição de GABA (comercialmente adquirido) na concentração 42,6 g/L advém do estudo de Laroute *et al* (2021) que obteve a produção de 413 mM de GABA (equivalente a ~42.6 g/L, considerando a massa molar do GABA ≈ 103 g/mol) em condições otimizadas. Já a membrana com adição de ácido glutâmico 1% advém da concentração utilizada na metodologia deste estudo que segue a metodologia de Oliveira *et al* (2020).

6.1.5. Avaliação do potencial antimicrobiano das membranas de quitosana contendo posbióticos de NCDO 2118

A atividade antimicrobiana das membranas foi avaliada segundo protocolo Br-CAST (BrCAST, *[S.d.]*). Seis cepas patogênicas foram testadas: *Enterococcus faecium* ATCC BAA 2127, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 700603, *Acinetobacter baumannii* ATCC 19606 e *Proteus mirabilis* ATCC 15290, cedidas gentilmente pela Professora Simone Odília Antunes Fernandes, docente da Universidade Federal de Minas Gerais, Faculdade de Farmácia, Departamento de Análises Clínicas e Toxicológicas. Os microrganismos foram cultivados em meios sólidos (MacConkey e Mueller-Hinton) e ressuspendidos em soro fisiológico estéril, com ajuste de turbidez ao padrão 0,5 da escala de McFarland (OD625 entre 0,080 e 0,130). As suspensões foram espalhadas com swab estéril em placas de Petri, onde foram posicionadas amostras circulares (0,5 cm de diâmetro) das membranas. As placas foram incubadas a 35 ± 1 °C por 18–

24 h. Ao final, os halos de inibição do crescimento bacteriano foram medidos em milímetros (mm).

6.2. Resultados

6.2.1. Síntese das membranas de quitosana contendo posbióticos da bactéria *Lactococcus lactis* subsp. *lactis* NCDO 2118

Após a síntese e o processo de secagem, as membranas foram removidas com auxílio de bisturi, podendo ser observadas na **Figura 4**. As formulações contendo posbióticos de *L. lactis* subsp. *lactis* NCDO 2118 apresentaram integridade estrutural, flexibilidade e coesão, indicando que a substituição do agente solubilizador pelos sobrenadantes fermentativos não comprometeu a formação da matriz de quitosana. Esses resultados sugerem compatibilidade entre o biopolímero e os metabólitos microbianos.

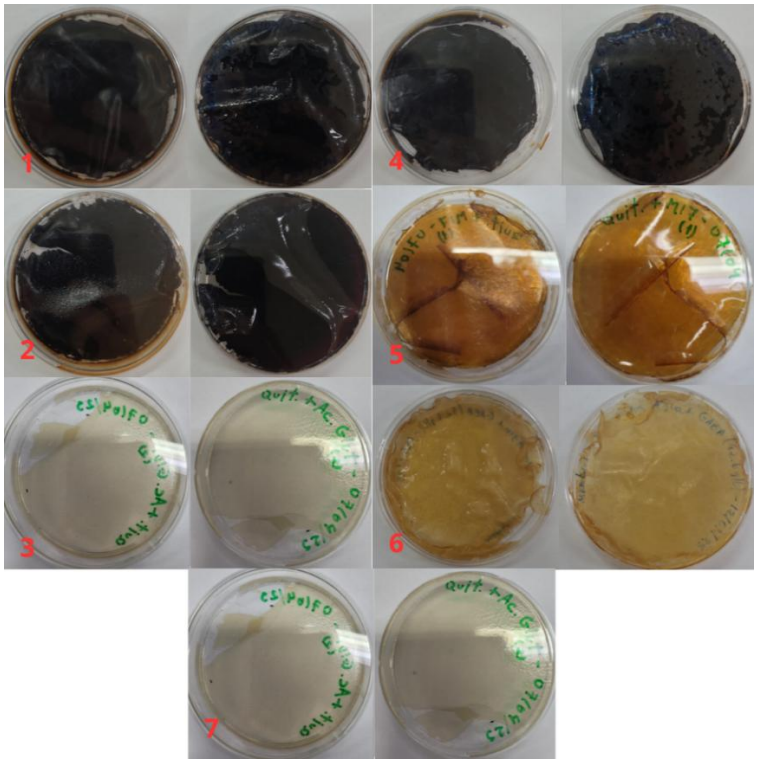

Figura 4. Membranas de quitosana que foram sintetizadas contendo posbióticos de NDCO 2118 e os seus respectivos controles. (1) Posbiótico de NCDO 2118; (2) Posbiótico de NCDO 2118 expressando HSP65; (3) Água; (4) Meio de cultura MRS; (5) Meio de cultura M17; (6) GABA; (7) Ácido glutâmico. Vistas de cima da membrana (imagem à esquerda) e de baixo (imagem à direita).

6.2.2. Atividade antimicrobiana das membranas de quitosana contendo posbióticos da bactéria *Lactococcus lactis* subsp. *lactis* NCDO 2118

A atividade antimicrobiana das membranas contendo posbióticos de *L. lactis* subsp. *lactis* NCDO 2118 foi avaliada contra cinco cepas bacterianas patogênicas. As culturas bacterianas apresentaram crescimento adequado. Observou-se halo de inibição apenas para as membranas com o posbiótico da cepa selvagem (NCDO 2118), frente a *Pseudomonas aeruginosa* ATCC 27853 (9 mm) e *Acinetobacter baumannii* ATCC 19606 (4 mm). As demais combinações não apresentaram inibição. A leitura de resultado na placa de cultura foi observada após 18 ± 2h, porém em 24h os resultados descritos na **Tabela 2** não se alteraram.

Apesar da formação de halo, os diâmetros foram inferiores aos observados para o controle positivo (ciprofloxacino 5 µg), que gerou halos entre 16 e 31 mm (**Tabela 3**).

Tabela 2. Atividade antimicrobiana das membranas de quitosana contendo posbióticos da bactéria *Lactococcus lactis* subsp. *lactis* NCDO 2118

	Bactérias patogênicas (halo de inibição em mm)				
Agentes solubilizadores de quitosana	*Proteus mirabilis 15290*	*Pseudomonas aeruginosa 27853*	*Staphylococcus aureus 29213*	*Acinetobacter baumannii 19606*	*Klebsiella pneumoniae 700603*
NCDO 2118	-	9	-	4	-
NCDO 2118 HSP65	-	-	-	-	-
Água*	-	13	-	-	-
Meio de cultura MRS*	-	-	-	4	-
Meio de cultura M17*	-	-	-	-	-
GABA*	-	-	-	-	-
Ácido glutâmico*	-	-	-	-	-
Antibiótico Ciprofloxacino	25	23	26	16	31

5µg[#]					

[*] Controles negativos.

[#] Controle positivo.

6.3. Discussão

A Etapa II deste trabalho demonstrou que é possível incorporar posbióticos de *L. lactis* NCDO 2118 em membranas de quitosana sem comprometer a integridade estrutural do curativo. Esse resultado é essencial, pois confirma a viabilidade técnica da proposta terapêutica de incorporar posbióticos em membranas de quitosana, como já evidenciado em Bazjou *et al.* (2021) e Shokatayeva *et al.* (2021) que realizaram tal fato, sendo desta vez, o posbiótico originário de *L. lactis* NCDO 2118 selvagem e recombinante (HSP65).

No entanto, a atividade antimicrobiana foi não significativa, de espectro restrito e não atribuível aos posbióticos, mas sim à própria quitosana — como evidenciado pelos halos nos controles com água e meio MRS. Este fato é reforçado por outros trabalhos da literatura como de Kong *et al*. (2010) e Mawazi *et al*. (2024) que tratam sobre a capacidade antimicrobiana natural da quitosana. Isso mostra que o principal potencial da membrana produzida não é a eliminação direta de patógenos, mas sim a modulação do microambiente da ferida.

A ausência de atividade antimicrobiana tanto com a cepa recombinante produtora de Hsp65 quanto com o GABA purificado sugere que a atividade observada não é mediada pela produção de GABA. Adicionalmente, a Hsp65 em sua forma solúvel não parece exercer um efeito antibacteriano direto. Esses resultados indicam que o potencial terapêutico da cepa probiótica reside predominantemente em sua ação imunomoduladora — previamente demonstrada para a linhagem *L. lactis* NCDO 2118 — e não em uma atividade antimicrobiana direta.

Essa conclusão é coerente com os achados da Etapa I, que destacaram que fatores como liberação sustentada e propriedades mecânicas são mais relevantes que a atividade antimicrobiana direta.

Além disso, o uso de posbióticos — em vez de bactérias vivas — aumenta a segurança, estabilidade e *shelf-life* do produto, tornando-o mais adequado para aplicações clínicas.

7. CONCLUSÕES

Na Etapa I:

- O teste de viés MINORS indicou que os estudos analisados apresentavam baixo risco de presença de viés na análise feita em cada estudo.
- O teste de viés SYRCLE indicou que não havia pontos que indicariam viés na maioria dos estudos com experimentos em animais. Porém, todos apresentaram ausência ou falta de clareza a respeito do cegamento dos pesquisadores em relação ao tratamento aplicado em cada grupo testado e em relação à seleção aleatória dos animais para avaliação dos resultados. Assim, indica-se um possível viés comum a todos ou uma falha na escrita dos trabalhos que não tornaram a realização dessas etapas claras no texto.
- A metanálise confirmou que curativos de quitosana são significativamente mais eficazes que métodos convencionais.
- A PCA identificou propriedades mecânicas e liberação sustentada como preditores-chave de eficácia.

Na Etapa II:

- Foi demonstrado que posbióticos de *L. lactis* NCDO 2118 podem ser incorporados em membranas de quitosana sem comprometer sua integridade.
- A atividade antimicrobiana foi mínima e atribuível à quitosana, não aos posbióticos.

Portanto, este trabalho apresenta uma prova de conceito para um curativo funcional baseado em evidências, cujo potencial deve ser explorado em ensaios *in vitro* e *in vivo* focados em imunomodulação, angiogênese e reepitelização, e não apenas em atividade antimicrobiana.

8. PERSPECTIVAS FUTURAS

Como perspectivas futuras para este trabalho, deverão ser realizados os seguintes experimentos:

- Avaliar a resistência mecânica das membranas após a incorporação dos sobrenadantes, visando garantir sua estabilidade e funcionalidade em aplicações práticas.
- Realizar estudos *in vitro* utilizando cultivos de fibroblastos humanos para verificar a biocompatibilidade e eficácia da junção entre os sobrenadantes e a estrutura de quitosana, assegurando sua possível aplicação em terapias de reparo tecidual.
- Testar em modelos animais (ratos) a eficácia no tratamento de feridas utilizando as membranas de quitosana contendo os posbióticos de NCDO 2118.

- Avaliar o impacto da inibição da produção de GABA nos posbióticos de NCDO 2118, permitindo elucidar o papel específico desse neurotransmissor no processo de cicatrização.

Esses estudos futuros servirão para validar e otimizar a proposta terapêutica, abrindo caminho para possíveis aplicações clínicas das membranas de quitosana contendo posbióticos da bactéria *Lactococcus lactis* subsp. *lactis* NCDO 2118 selvagem e recombinante expressando Hsp65.

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10. PRODUÇÃO ACADÊMICA

10.1. Artigo publicado

- Guariento, S. C. F.; Rodrigues, L. I.; Basilio, L. B. B.; Freitas, L. D.; Oliveira, R. J. de; Cardoso, M. A.; Pereira, M. L. S.; Passos, M. F.; Santos, T. M.; Dutra, da J. C. F.; Azevedo, V. A. de C. Systematic review on chitosan dressings for diabetic and burn wound healing: preclinical outcomes and limitations. **Academia Materials Science**, 2(3). DOI: 10.20935/AcadMatSci7810

10.2. Pôster apresentado em evento

- Guariento, S. C. F. Avaliação pré-clínica e caraterização de curativos à base de quitosana para feridas de diabetes e queimaduras: uma revisão sistemática. In: **XI SIMPÓSIO DE MICROBIOLOGIA DA UFMG**, 2024, Belo Horizonte, MG, Brasil.

11. APÊNDICE

Supplementary materials

Table S1. Keywords used to search each database.

Database	Keywords
PubMed Dimensions Scopus Web of Science	(chitosan OR "Chitin-derived polymer" OR "Chitosan-based material") AND (membrane OR dressing OR barrier OR film OR covering) AND (incorporation OR integration OR inclusion OR combination) AND (wound OR injury OR lesion OR trauma OR cut) AND (healing OR recovery OR repair OR regeneration OR closure) AND ("In vivo" OR "In vitro")

Table S2 Articles without DOI separated using automated screening of PubMed, Dimensions, Scopus, and Web of Science repositories.

Item	Year	Document Type	Language	Repository
1	2021	Article	English	Scopus
2	2017	Conference paper	English	Scopus
3	2017	Conference paper	English	Scopus
4	2017	Conference paper	English	Scopus
5	2011	Book Chapter	English	Scopus
6	2010	Article	English	Scopus
7	2010	Article	Chinese	Web of Science
8	2021	Article	English	Web of Science
9	2015	Article	English	Web of Science
10	2019	Article	English	Web of Science
11	2018	Review	English	Web of Science
12	2012	Review	English	Web of Science

Table S3. Duplicate articles removed using automated screening of PubMed, Dimensions, Scopus, and Web of Science repositories.

Item	Year	DOI	Document Type	Language	Repository
1	2020	10.3390/pharmaceutics12060484	Article	English	Web of Science
2	2019	10.1016/j.msec.2019.01.073	Article	English	Web of Science
3	2021	10.1016/j.ijbiomac.2020.11.119	Article	English	Web of Science
4	2017	10.1002/jbm.b.33394	Article	English	Web of Science
5	2019	10.1021/acsabm.9b00727	Article	English	Web of Science
6	2023	10.3390/pharmaceutics15041122	Article	English	Web of Science
7	2016	10.1097/01.asw.0000490362.64517.d7	Article	English	Web of Science
8	2019	10.2147/dddt.s219224	Article	English	Web of Science
9	2020	10.3233/bme-201076	Article	English	Web of Science
10	2022	10.1080/21655979.2022.2031415	Article	English	Web of Science
11	2018	10.1016/j.ijbiomac.2018.02.073	Article	English	Web of Science
12	2021	10.1016/j.ijpharm.2021.121132	Article	English	Web of Science
13	2012	10.1007/s00289-012-0761-7	Article	English	Web of Science
14	2016	10.1021/acsami.5b11160	Article	English	Web of Science
15	2023	10.1016/j.ijpharm.2023.122648	Article	English	Web of Science
16	2010	10.1016/j.ijpharm.2010.03.024	Article	English	Web of Science
17	2017	10.1016/j.carbpol.2016.09.051	Article	English	Web of Science
18	2023	10.1016/j.ijbiomac.2023.126056	Article	English	Web of Science
19	2020	10.1016/j.ijbiomac.2020.02.140	Article	English	Web of Science

20	2018	10.1016/j.ijbiomac.2018.08.057	Article	English	Web of Science
21	2018	10.1177/0883911517724809	Article	English	Web of Science
22	2023	10.1007/s11696-022-02553-x	Article	English	Web of Science
23	2023	10.1016/j.eurpolymj.2022.111758	Article	English	Web of Science
24	2019	10.3390/ijms20163890	Article	English	Web of Science
25	2021	10.1016/j.apmt.2021.101186	Article	English	Web of Science
26	2020	10.1016/j.ijbiomac.2020.03.114	Article	English	Web of Science
27	2020	10.1016/j.ijbiomac.2020.03.161	Article	English	Web of Science
28	2023	10.1021/acsomega.3c00999	Article	English	Web of Science
29	2021	10.1016/j.ijbiomac.2020.10.142	Article	English	Web of Science
30	2023	10.1177/08853282221131130	Article	English	Web of Science
31	2022	10.1007/s10570-022-04753-w	Article	English	Web of Science
32	2013	10.1080/09205063.2012.701549	Article	English	Web of Science
33	2023	10.1016/j.actbio.2023.01.021	Article	English	Web of Science
34	2021	10.3390/polym13172959	Review	English	Web of Science
35	2017	10.1039/c7py00038c	Article	English	Web of Science
36	2022	10.3389/fbioe.2022.1026876	Article	English	Web of Science
37	2022	10.1007/s13738-021-02374-x	Article	English	Web of Science
38	2020	10.3390/pharmaceutics12010056	Article	English	Web of Science
39	2019	10.1088/1748-605x/ab026c	Article	English	Web of Science
40	2022	10.3390/membranes12020121	Article	English	Web of Science
41	2020	10.3390/ma13122819	Article	English	Web of Science

42	2021	10.1016/j.ijbiomac.2021.04.156	Article	English	Web of Science
43	2022	10.1039/d2bm00224h	Article	English	Web of Science
44	2017	10.1016/j.msec.2017.08.052	Article	English	Web of Science
45	2016	10.1021/acsami.6b00739	Article	English	Web of Science
46	2023	10.1016/j.ijbiomac.2023.124529	Article	English	Web of Science
47	2023	10.1016/j.ijbiomac.2023.124427	Article	English	Web of Science
48	2020	10.1016/j.ijpharm.2020.120001	Article	English	Web of Science
49	2022	10.1016/j.actbio.2022.08.075	Article	English	Web of Science
50	2012	10.1021/am300292v	Article	English	Web of Science
51	2021	10.1016/j.cej.2021.130302	Article	English	Web of Science
52	2020	10.1016/j.carbpol.2020.116106	Article	English	Web of Science
53	2017	10.1002/jbm.b.33675	Article	English	Web of Science
54	2023	10.1016/j.ijbiomac.2022.12.291	Article	English	Web of Science
55	2022	10.1007/s10924-021-02239-7	Article	English	Web of Science
56	2022	10.1016/j.jiec.2021.12.027	Article	English	Web of Science
57	2021	10.1016/j.ijbiomac.2021.04.119	Article	English	Web of Science
58	2020	10.1016/j.colsurfb.2019.110749	Article	English	Web of Science
59	2022	10.3390/pharmaceutics14030537	Article	English	Web of Science
60	2018	10.1680/jbibn.17.00036	Article	English	Web of Science
61	2013	10.1007/s10934-012-9655-1	Article	English	Web of Science
62	2021	10.3390/pharmaceutics13122152	Article	English	Web of Science
63	2020	10.1016/j.apmt.2020.100756	Article	English	Web of Science

64	2022	10.1016/j.ijbiomac.2021.12.125	Article	English	Web of Science
65	2012	10.3969/j.issn.1673-5374.2012.29.002	Article	English	Web of Science
66	2023	10.1016/j.inoche.2023.110885	Article	English	Web of Science
67	2021	10.3390/polym13162716	Article	English	Web of Science
68	2020	10.1016/j.ijbiomac.2020.06.181	Article	English	Web of Science
69	2023	10.1111/iwj.13947	Article	English	Web of Science
70	2020	10.1016/j.ijbiomac.2020.09.212	Article	English	Web of Science
71	2017	10.1016/j.carbpol.2016.11.056	Article	English	Web of Science
72	2015	10.1080/00405000.2014.906100	Article	English	Web of Science
73	2023	10.1016/j.ijbiomac.2022.11.130	Article	English	Web of Science
74	2017	10.3390/molecules22091513	Article	English	Web of Science
75	2022	10.1016/j.ijpharm.2022.121508	Article	English	Web of Science
76	2014	10.1177/0883911514554146	Article	English	Web of Science
77	2021	10.1002/adfm.202105932	Article	English	Web of Science
78	2019	10.1021/acsami.8b18931	Article	English	Web of Science
79	2017	10.1016/j.msec.2017.05.116	Article	English	Web of Science
80	2021	10.1177/08839115211053921	Article	English	Web of Science
81	2023	10.1002/jbm.a.37475	Article	English	Web of Science
82	2018	10.1016/j.phymed.2017.09.024	Review	English	Web of Science
83	2021	10.1166/jbn.2021.3079	Article	English	Web of Science
84	2018	10.1016/j.ijbiomac.2017.10.056	Article	English	Web of Science
85	2022	10.1021/acsomega.2c03222	Article	English	Web of Science

86	2021	10.1016/j.ijbiomac.2021.02.133	Article	English	Web of Science
87	2014	10.1155/2014/153808	Review	English	Web of Science
88	2021	10.1016/j.ijbiomac.2021.09.118	Article	English	Web of Science
89	2017	10.1038/s41598-017-10882-1	Article	English	Web of Science
90	2013	10.1016/j.carbpol.2013.06.022	Article	English	Web of Science
91	1998	10.1080/02844319850158462	Article	English	Web of Science
92	2018	10.1016/j.ijbiomac.2018.04.010	Article	English	Web of Science
93	2022	10.1016/j.apsusc.2021.151825	Article	English	Web of Science
94	2022	10.1039/d2bm00836j	Article	English	Web of Science
95	2017	10.1016/j.msec.2017.03.199	Article	English	Web of Science
96	2023	10.1002/slct.202300722	Article	English	Web of Science
97	2021	10.3390/antibiotics10050524	Article	English	Web of Science
98	2022	10.3389/fbioe.2022.1006584	Article	English	Web of Science
99	2017	10.1016/j.msec.2017.02.076	Article	English	Web of Science
100	2022	10.3390/md20100615	Article	English	Web of Science
101	2023	10.3390/pharmaceutics15051560	Review	English	Web of Science
102	2022	10.1016/j.colsurfb.2022.112479	Article	English	Web of Science
103	2021	10.1016/j.actbio.2021.07.018	Article	English	Web of Science
104	2022	10.3390/nano12193426	Article	English	Web of Science
105	2021	10.1557/s43579-021-00124-x	Article	English	Web of Science
106	2019	10.1016/j.msec.2019.109873	Article	English	Web of Science
107	2017	10.1002/jbm.a.36097	Article	English	Web of Science

108	2020	10.1002/bip.23354	Article	English	Web of Science
109	2022	10.1021/acsnano.2c05557	Article	English	Web of Science
110	2019	10.3390/ma12142223	Article	English	Web of Science
111	2023	10.1016/j.jiec.2023.06.027	Article	English	Web of Science
112	2020	10.1021/acsbiomaterials.0c00923	Article	English	Web of Science
113	2016	10.1016/j.ijbiomac.2016.09.083	Article	English	Web of Science
114	2012	10.3791/3527	Article	English	Web of Science
115	2021	10.3390/polym13111869	Article	English	Web of Science
116	2023	10.3389/fbioe.2023.1096532	Article	English	Web of Science
117	2022	10.1016/j.actbio.2022.06.018	Article	English	Web of Science
118	2017	10.1021/acsbiomaterials.7b00681	Article	English	Web of Science
119	2019	10.1016/j.actbio.2019.10.012	Article	English	Web of Science
120	2021	10.1515/ntrev-2021-0046	Review	English	Web of Science
121	2022	10.1016/j.polymer.2022.124902	Article	English	Web of Science
122	2021	10.1007/s10989-020-10082-y	Article	English	Web of Science
123	2015	10.1155/2015/108571	Article	English	Web of Science
124	2019	10.1088/2053-1591/ab5533	Article	English	Web of Science
125	2020	10.1016/j.msec.2020.111273	Article	English	Web of Science
126	2021	10.1016/j.colsurfa.2021.126722	Article	English	Web of Science
127	2021	10.1016/j.ijbiomac.2021.02.124	Article	English	Web of Science
128	2019	10.1021/acsami.9b09123	Article	English	Web of Science
129	2021	10.1039/d0tb02160a	Article	English	Web of Science

130	2023	10.3389/fmats.2023.1144752	Article	English	Web of Science
131	2018	10.1016/j.colsurfb.2018.07.028	Article	English	Web of Science
132	2018	10.1039/c8ra06274a	Article	English	Web of Science
133	2019	10.1016/j.jconrel.2019.10.050	Article	English	Web of Science
134	2019	10.2147/ijn.s214359	Article	English	Web of Science
135	2020	10.1002/jbm.a.36980	Article	English	Web of Science
136	2023	10.3390/ijms241311037	Article	English	Web of Science
137	2023	10.3390/pharmaceutics15020705	Article	English	Web of Science
138	2020	10.1016/j.actbio.2019.10.046	Article	English	Web of Science
139	2022	10.1016/j.burns.2021.12.009	Article	English	Web of Science
140	2017	10.1177/0883911517690758	Article	English	Web of Science
141	2021	10.1002/ptr.7242	Review	English	Web of Science
142	2011	10.1002/lsm.21076	Article	English	Web of Science
143	2011	10.1007/s13233-011-0812-1	Article	English	Web of Science
144	2023	10.1002/adma.202301664	Article	English	Web of Science
145	2023	10.1208/s12249-023-02584-x	Article	English	Web of Science
146	2018	10.1016/j.apmt.2018.07.006	Article	English	Web of Science
147	2020	10.1016/j.ijpx.2020.100047	Article	English	Web of Science
148	2022	10.3390/ijms23179517	Article	English	Web of Science
149	2014	10.1111/wrr.12171	Article	English	Web of Science
150	2016	10.1016/j.actbio.2016.09.035	Article	English	Web of Science
151	2017	10.1016/j.actbio.2017.08.001	Article	English	Web of Science

152	2020	10.1016/j.bioactmat.2020.05.008	Article	English	Web of Science
153	2016	10.1016/j.ijpharm.2016.08.053	Article	English	Web of Science
154	2018	10.1186/s12951-018-0348-z	Article	English	Web of Science
155	2023	10.1021/acsomega.2c053512931acsomeg	Article	English	Web of Science
156	1998	10.1080/02844319850158462			PubMed
157	2009	10.1002/lsm.20774			PubMed
158	2010	10.1016/j.ijpharm.2010.03.024			PubMed
159	2011	10.1002/lsm.21076			PubMed
160	2012	10.1021/am300292v			PubMed
161	2012	10.3969/j.issn.1673-5374.2012.29.002			PubMed
162	2012	10.3791/3527			PubMed
163	2013	10.1016/j.biomaterials.2012.11.062			PubMed
164	2013	10.1080/09205063.2012.701549			PubMed
165	2013	10.1016/j.carbpol.2013.06.022			PubMed
166	2014	10.1111/wrr.12171			PubMed
167	2017	10.1002/jbm.b.33394			PubMed
168	2015	10.1155/2015/108571			PubMed
169	2016	10.1021/acsami.5b11160			PubMed
170	2016	10.1021/acsami.6b00739			PubMed
171	2017	10.1002/jbm.b.33675			PubMed
172	2016	10.1016/j.ijpharm.2016.08.053			PubMed
173	2016	10.1007/s10561-016-9585-2			PubMed

174	2016	10.1016/j.actbio.2016.09.035			PubMed
175	2016	10.1016/j.ijbiomac.2016.09.083			PubMed
176	2017	10.1016/j.carbpol.2016.09.051			PubMed
177	2017	10.1016/j.carbpol.2016.11.056			PubMed
178	2017	10.1016/j.msec.2017.02.076			PubMed
179	2017	10.1002/jbm.a.36097			PubMed
180	2017	10.1016/j.msec.2017.03.199			PubMed
181	2017	10.1016/j.msec.2017.05.116			PubMed
182	2017	10.1016/j.actbio.2017.08.001			PubMed
183	2017	10.1038/s41598-017-10882-1			PubMed
184	2017	10.1016/j.msec.2017.08.052			PubMed
185	2017	10.3390/molecules22091513			PubMed
186	2018	10.1016/j.ijbiomac.2017.10.056			PubMed
187	2017	10.1021/acsbiomaterials.7b00681			PubMed
188	2018	10.1016/j.phymed.2017.09.024			PubMed
189	2018	10.1016/j.ijbiomac.2018.02.073			PubMed
190	2018	10.1016/j.jphotobiol.2018.02.018			PubMed
191	2018	10.1186/s12951-018-0348-z			PubMed
192	2018	10.1016/j.ijbiomac.2018.08.057			PubMed
193	2018	10.1039/c8ra06274a			PubMed
194	2019	10.1088/1748-605x/ab026c			PubMed
195	2019	10.1021/acsami.8b18931			PubMed

196	2019	10.1016/j.msec.2019.01.073			PubMed
197	2019	10.1016/j.jmbbm.2019.03.013			PubMed
198	2019	10.1089/ten.tea.2019.0021			PubMed
199	2019	10.3390/ma12142223			PubMed
200	2019	10.3390/ijms20163890			PubMed
201	2019	10.1021/acsami.9b09123			PubMed
202	2019	10.1016/j.ijbiomac.2019.08.158			PubMed
203	2019	10.1016/j.msec.2019.109873			PubMed
204	2019	10.2147/dddt.s219224			PubMed
205	2019	10.1016/j.carbpol.2019.115302			PubMed
206	2019	10.1016/j.actbio.2019.10.012			PubMed
207	2020	10.1016/j.actbio.2019.10.046			PubMed
208	2019	10.1021/acsabm.9b00727			PubMed
209	2019	10.2147/ijn.s214359			PubMed
210	2020	10.1016/j.colsurfb.2019.110749			PubMed
211	2020	10.3390/pharmaceutics12010056			PubMed
212	2020	10.1016/j.ijbiomac.2020.02.140			PubMed
213	2020	10.3233/bme-201076			PubMed
214	2020	10.1016/j.ijbiomac.2020.03.114			PubMed
215	2020	10.1016/j.ijbiomac.2020.03.161			PubMed
216	2020	10.1016/j.ijpx.2020.100047			PubMed
217	2020	10.1002/jbm.a.36980			PubMed

218	2020	10.1016/j.carbpol.2020.116106			PubMed
219	2020	10.1002/bip.23354			PubMed
220	2020	10.3390/pharmaceutics12060484			PubMed
221	2020	10.1039/d0ra03704d			PubMed
222	2020	10.1016/j.ijbiomac.2020.06.181			PubMed
223	2020	10.3390/ma13122819			PubMed
224	2020	10.1016/j.bioactmat.2020.05.008			PubMed
225	2020	10.1080/03639045.2020.1811305			PubMed
226	2020	10.1016/j.msec.2020.111273			PubMed
227	2020	10.1016/j.ijbiomac.2020.09.212			PubMed
228	2020	10.1016/j.ijpharm.2020.120001			PubMed
229	2021	10.1016/j.ijbiomac.2020.10.142			PubMed
230	2021	10.1016/j.ijbiomac.2020.11.119			PubMed
231	2021	10.1039/d0tb02160a			PubMed
232	2020	10.1021/acsbiomaterials.0c00923			PubMed
233	2021	10.1016/j.ijbiomac.2021.02.124			PubMed
234	2021	10.1016/j.ijbiomac.2021.02.133			PubMed
235	2021	10.1016/j.ijbiomac.2021.04.119			PubMed
236	2021	10.1016/j.ijbiomac.2021.04.156			PubMed
237	2021	10.3390/antibiotics10050524			PubMed
238	2021	10.1166/jbn.2021.3079			PubMed
239	2021	10.3390/polym13111869			PubMed

240	2021	10.1016/j.actbio.2021.07.018			PubMed
241	2021	10.1002/ptr.7242			PubMed
242	2021	10.3390/polym13162716			PubMed
243	2021	10.3390/polym13172959			PubMed
244	2021	10.1016/j.ijbiomac.2021.09.118			PubMed
245	2021	10.1016/j.ijpharm.2021.121132			PubMed
246	2021	10.3390/pharmaceutics13122152			PubMed
247	2022	10.1016/j.burns.2021.12.009			PubMed
248	2022	10.1016/j.ijbiomac.2021.12.125			PubMed
249	2022	10.1016/j.ijpharm.2022.121508			PubMed
250	2022	10.1080/21655979.2022.2031415			PubMed
251	2022	10.3390/membranes12020121			PubMed
252	2022	10.3390/pharmaceutics14030537			PubMed
253	2022	10.1016/j.colsurfb.2022.112479			PubMed
254	2022	10.1016/j.ijbiomac.2022.04.025			PubMed
255	2022	10.1039/d2bm00224h			PubMed
256	2022	10.1016/j.actbio.2022.06.018			PubMed
257	2022	10.1021/acsnano.2c05557			PubMed
258	2022	10.1080/10717544.2022.2112995			PubMed
259	2022	10.1021/acsomega.2c03222			PubMed
260	2022	10.3390/ijms23179517			PubMed
261	2022	10.1016/j.actbio.2022.08.075			PubMed

262	2022	10.3389/fbioe.2022.1006584			PubMed
263	2023	10.1177/08853282221131130			PubMed
264	2022	10.3390/nano12193426			PubMed
265	2022	10.3390/md20100615			PubMed
266	2022	10.3389/fbioe.2022.1026876			PubMed
267	2023	10.1016/j.ijbiomac.2022.11.130			PubMed
268	2022	10.1039/d2bm00836j			PubMed
269	2023	10.1002/jbm.a.37475			PubMed
270	2023	10.1016/j.ijbiomac.2022.12.291			PubMed
271	2023	10.1016/j.actbio.2023.01.021			PubMed
272	2023	10.1016/j.ijpharm.2023.122648			PubMed
273	2023	10.1021/acsomega.2c05351			PubMed
274	2023	10.3390/pharmaceutics15020705			PubMed
275	2023	10.1111/iwj.13947			PubMed
276	2023	10.3389/fbioe.2023.1096532			PubMed
277	2023	10.1016/j.ijbiomac.2023.124427			PubMed
278	2023	10.1016/j.ijbiomac.2023.124529			PubMed
279	2023	10.3390/pharmaceutics15041122			PubMed
280	2023	10.1002/adma.202301664			PubMed
281	2023	10.1021/acsomega.3c00999			PubMed
282	2023	10.1208/s12249-023-02584-x			PubMed
283	2023	10.3390/ijms241311037			PubMed

284	2023	10.1016/j.ijbiomac.2023.126056			PubMed
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287	2020	10.3233/bme-201076			Dimensions
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298	2020	10.1016/j.ijbiomac.2020.03.161			Dimensions
299	2021	10.1016/j.ijbiomac.2021.04.119			Dimensions
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312	2020	10.3390/pharmaceutics12010056			Dimensions
313	2022	10.1002/jbm.a.37475			Dimensions
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317	2019	10.1016/j.carbpol.2019.115302			Dimensions
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327	2018	10.1016/j.ijbiomac.2018.02.073			Dimensions

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329	2020	10.1080/03639045.2020.1811305			Dimensions
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333	2019	10.3390/ijms20163890			Dimensions
334	2022	10.1039/d2bm00836j			Dimensions
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338	2021	10.1016/j.actbio.2021.07.018			Dimensions
339	2020	10.1016/j.carbpol.2020.116106			Dimensions
340	2012	10.1080/09205063.2012.701549			Dimensions
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342	2020	10.1016/j.ijbiomac.2020.02.140			Dimensions
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344	2023	10.1021/acsomega.2c05351			Dimensions
345	2022	10.3390/nano12193426			Dimensions
346	2020	10.1016/j.ijbiomac.2020.03.114			Dimensions
347	2022	10.1016/j.colsurfb.2022.112479			Dimensions
348	2017	10.1016/j.msec.2017.08.052			Dimensions
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354	2016	10.1002/jbm.b.33675			Dimensions
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356	2017	10.3390/molecules22091513			Dimensions
357	2012	10.1021/am300292v			Dimensions
358	2016	10.1016/j.carbpol.2016.11.056			Dimensions
359	2023	10.1016/j.joim.2023.07.002			Dimensions
360	2020	10.1016/j.ijbiomac.2020.06.181			Dimensions
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362	2020	10.1016/j.msec.2020.111273			Dimensions
363	2016	10.1007/s10561-016-9585-2			Dimensions
364	2023	10.3389/fbioe.2023.1096532			Dimensions
365	2023	10.3390/ijms241311037			Dimensions
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367	2022	10.1016/j.ijbiomac.2022.04.025			Dimensions
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369	2019	10.1021/acsami.8b18931			Dimensions
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372	2021	10.1016/j.ijbiomac.2021.02.124			Dimensions
373	2020	10.1016/j.ijbiomac.2020.10.142			Dimensions
374	2019	10.1088/1748-605x/ab026c			Dimensions
375	2017	10.1016/j.msec.2017.03.199			Dimensions
376	2012	10.3969/j.issn.1673-5374.2012.29.002			Dimensions
377	2017	10.1016/j.msec.2017.02.076			Dimensions
378	2017	10.1016/j.phymed.2017.09.024			Dimensions
379	2017	10.1016/j.ijbiomac.2017.10.056			Dimensions
380	2017	10.1038/s41598-017-10882-1			Dimensions
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388	2019	10.1016/j.msec.2019.109873			Dimensions
389	2019	10.3390/ma12142223			Dimensions
390	2021	10.1016/j.burns.2021.12.009			Dimensions
391	2012	10.3791/3527			Dimensions
392	2015	10.1155/2015/108571			Dimensions
393	2020	10.1021/acsbiomaterials.0c00923			Dimensions

394	2023	10.1002/adma.202301664			Dimensions
395	2019	10.1016/j.actbio.2019.10.012			Dimensions
396	2023	10.1208/s12249-023-02584-x			Dimensions
397	2017	10.1021/acsbiomaterials.7b00681			Dimensions
398	2019	10.1016/j.jmbbm.2019.03.013			Dimensions
399	2019	10.2147/ijn.s214359			Dimensions
400	2009	10.1002/lsm.20774			Dimensions
401	2022	10.3390/ijms23179517			Dimensions
402	2020	10.1002/jbm.a.36980			Dimensions
403	2011	10.1002/lsm.21076			Dimensions
404	2020	10.1016/j.bioactmat.2020.05.008			Dimensions
405	2018	10.12968/jowc.2018.27.6.394			Dimensions
406	2017	10.1016/j.actbio.2017.08.001			Dimensions
407	2019	10.1016/j.actbio.2019.10.046			Dimensions
408	2020	10.1016/j.ijpx.2020.100047			Dimensions
409	2012	10.1016/j.biomaterials.2012.11.062			Dimensions
410	2018	10.1039/c8ra06274a			Dimensions
411	2016	10.1016/j.ijpharm.2016.08.053			Dimensions
412	2016	10.1016/j.actbio.2016.09.035			Dimensions
413	2019	10.1089/ten.tea.2019.0021			Dimensions
414	2018	10.1186/s12951-018-0348-z			Dimensions
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422	2017	10.1039/c7py00038c			Dimensions
423	2021	10.1007/s13738-021-02374-x			Dimensions
424	2012	10.1007/s10934-012-9655-1			Dimensions
425	2020	10.1016/j.apmt.2020.100756			Dimensions
426	2018	10.1680/jbibn.17.00036			Dimensions
427	2022	10.1016/j.jiec.2021.12.027			Dimensions
428	2021	10.1002/adfm.202105932			Dimensions
429	2021	10.1016/j.cej.2021.130302			Dimensions
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431	2023	10.1016/j.inoche.2023.110885			Dimensions
432	2021	10.1177/08839115211053921			Dimensions
433	2023	10.1016/j.eurpolymj.2022.111758			Dimensions
434	2023	10.1002/slct.202300722			Dimensions
435	2014	10.1177/0883911514554146			Dimensions
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441	2023	10.3389/fmats.2023.1144752			Dimensions
442	2017	10.1177/0883911517690758			Dimensions
443	2019	10.1088/2053-1591/ab5533			Dimensions
444	2011	10.1007/s13233-011-0812-1			Dimensions
445	2018	10.1016/j.apmt.2018.07.006			Dimensions
446	2023	10.1021/acsomega.2c05351	Article	English	Web of Science
447	2023	10.1049/mna2.12171	Article	English	Web of Science
448	2016	10.3109/03639045.2015.1075030			PubMed
449	2021	10.21203/rs.3.rs-1043996/v1			Dimensions

Table S4 Articles selected from the PubMed, Dimensions, Scopus, and Web of Science repositories **after automatic exclusion**.

Item	Year	DOI	Document Type	Language	Repository
1	2021	10.1016/j.ijbiomac.2021.02.133	Article	English	Scopus/Web of Science/PubMed/Dimensions
2	2023	10.1177/08853282221131130	Article	English	Scopus/Web of Science/PubMed/Dimensions
3	2020	10.1016/j.ijpharm.2020.120001	Article	English	Scopus/Web of Science/PubMed/Dimensions
4	2021	10.1016/j.apmt.2021.101186	Article	English	Scopus/Web of Science/Dimensions
5	2022	10.1016/j.ijbiomac.2021.12.125	Article	English	Scopus/Web of Science/PubMed/Dimensions
6	2023	10.1016/j.ijbiomac.2023.124213	Article	English	Scopus
7	2021	10.1016/j.ijpharm.2021.121132	Article	English	Scopus/Web of Science/PubMed/Dimensions
8	2023	10.3390/pharmaceutics15041122	Article	English	Scopus/Web of Science/PubMed/Dimensions
9	2022	10.1021/acsomega.2c03222	Article	English	Scopus/Web of Science/PubMed/Dimensions
10	2023	10.1016/j.ijpharm.2023.122648	Article	English	Scopus/Web of Science/PubMed/Dimensions
11	2022	10.1016/j.actbio.2022.06.018	Article	English	Scopus/Web of Science/PubMed/Dimensions
12	2022	10.1016/j.colsurfb.2022.112479	Article	English	Scopus/Web of Science/PubMed/Dimensions
13	2023	10.1088/1748-605x/acce88	Article	English	Scopus
14	2022	10.3390/md20100615	Article	English	Scopus/Web of Science/PubMed/Dimensions

15	2021	10.3390/polym13162716	Article	English	Scopus/Web of Science/PubMed/Dimensions
16	2023	10.1016/j.ijbiomac.2022.11.130	Article	English	Scopus/Web of Science/PubMed/Dimensions
17	2023	10.1016/j.eurpolymj.2022.111758	Article	English	Scopus/Web of Science/Dimensions
18	2021	10.3390/ijms222111437	Review	English	Scopus
19	2021	10.3390/polym13172959	Review	English	Scopus/Web of Science/PubMed/Dimensions
20	2023	10.3390/pharmaceutics15020705	Article	English	Scopus/Web of Science/PubMed/Dimensions
21	2023	10.1002/slct.202300722	Article	English	Scopus/Web of Science/Dimensions
22	2022	10.1007/s13738-021-02374-x	Article	English	Scopus/Web of Science/Dimensions
23	2022	10.3390/pharmaceutics14030537	Article	English	Scopus/Web of Science/PubMed/Dimensions
24	2021	10.1186/s13036-021-00268-3	Article	English	Scopus
25	2023	10.1016/j.ijbiomac.2022.12.291	Article	English	Scopus/Web of Science/PubMed/Dimensions
26	2023	10.1002/jbm.a.37475	Article	English	Scopus/Web of Science/PubMed/Dimensions
27	2023	10.1208/s12249-023-02584-x	Article	English	Scopus/Web of Science/PubMed/Dimensions
28	2023	10.3390/ijms241311037	Article	English	Scopus/Web of Science/PubMed/Dimensions
29	2021	10.1177/08839115211053921	Article	English	Scopus/Web of Science/Dimensions
30	2020	10.1016/j.ijbiomac.2020.08.190	Article	English	Scopus
31	2023	10.1016/j.jiec.2023.06.027	Article	English	Scopus/Web of Science/Dimensions
32	2023	10.1002/adma.202301664	Article	English	Scopus/Web of Science/PubMed/Dimensions
33	2023	10.1111/iwj.13947	Article	English	Scopus/Web of Science/PubMed/Dimensions

34	2020	10.1016/j.ijbiomac.2020.09.212	Article	English	Scopus/Web of Science/PubMed/Dimensions
35	2022	10.1089/ten.tea.2021.0068	Article	English	Scopus
36	2022	10.1016/j.ijpharm.2022.121508	Article	English	Scopus/Web of Science/PubMed/Dimensions
37	2021	10.3390/polym13111869	Article	English	Scopus/Web of Science/PubMed/Dimensions
38	2021	10.1007/s10989-020-10082-y	Article	English	Scopus/Web of Science/Dimensions
39	2021	10.1016/j.ijbiomac.2021.02.124	Article	English	Scopus/Web of Science/PubMed/Dimensions
40	2021	10.1016/j.ijbiomac.2021.04.119	Article	English	Scopus/Web of Science/PubMed/Dimensions
41	2023	10.1016/s1773-2247(23)00270-8	Editorial	English	Scopus
42	2022	10.1016/j.ijbiomac.2022.04.025	Article	English	Scopus/PubMed/Dimensions
43	2022	10.1021/acsomega.2c05351	Article	English	Scopus/Web of Science/PubMed/Dimensions
44	2022	10.3390/nano12193426	Article	English	Scopus/Web of Science/PubMed/Dimensions
45	2023	10.1021/acsomega.3c00999	Article	English	Scopus/Web of Science/PubMed/Dimensions
46	2021	10.3390/pharmaceutics13122152	Article	English	Scopus/Web of Science/PubMed/Dimensions
47	2022	10.1016/j.polymer.2022.124902	Article	English	Scopus/Web of Science/Dimensions
48	2021	10.1016/j.ijbiomac.2021.09.118	Article	English	Scopus/Web of Science/PubMed/Dimensions
49	2021	10.1016/j.ijbiomac.2020.10.142	Article	English	Scopus/Web of Science/PubMed/Dimensions
50	2021	10.1039/d0tb02160a	Article	English	Scopus/Web of Science/PubMed/Dimensions
51	2021	10.3390/cells10113189	Review	English	Scopus

52	2022	10.1016/j.nano.2021.102495	Article	English	Scopus
53	2022	10.3390/ijms23179517	Article	English	Scopus/Web of Science/PubMed/Dimensions
54	2022	10.1039/d2bm00224h	Article	English	Scopus/Web of Science/PubMed/Dimensions
55	2023	10.1016/j.biomaterials.2023.122184	Article	English	Scopus
56	2022	10.1016/j.burns.2021.12.009	Article	English	Scopus/Web of Science/PubMed/Dimensions
57	2021	10.1016/j.ijbiomac.2021.04.156	Article	English	Scopus/Web of Science/PubMed/Dimensions
58	2021	10.1016/j.jcis.2021.02.107	Article	English	Scopus
59	2021	10.1515/ntrev-2021-0046	Review	English	Scopus/Web of Science/Dimensions
60	2022	10.3389/fbioe.2022.1026876	Article	English	Scopus/Web of Science/PubMed/Dimensions
61	2021	10.3389/fonc.2021.685784	Article	English	Scopus
62	2021	10.1016/j.colsurfa.2021.126722	Article	English	Scopus/Web of Science
63	2022	10.1007/s10570-022-04753-w	Article	English	Scopus/Web of Science/Dimensions
64	2023	10.3389/fbioe.2023.1096532	Article	English	Scopus/Web of Science/PubMed/Dimensions
65	2021	10.1016/j.actbio.2021.07.018	Article	English	Scopus/Web of Science/PubMed/Dimensions
66	2021	10.1557/s43579-021-00124-x	Note	English	Scopus/Web of Science
67	2021	10.1016/j.ijbiomac.2020.11.119	Article	English	Scopus/Web of Science/PubMed/Dimensions
68	2020	10.1016/j.ijpx.2020.100047	Article	English	Scopus/Web of Science/PubMed/Dimensions
69	2022	10.1080/21655979.2022.2031415	Article	English	Scopus/Web of Science/PubMed/Dimensions
70	2023	10.3390/pharmaceutics15051560	Review	English	Scopus/Web of Science

71	2023	10.1016/j.inoche.2023.110885	Article	English	Scopus/Web of Science/Dimensions
72	2023	10.1016/j.ijbiomac.2023.124529	Article	English	Scopus/Web of Science/PubMed/Dimensions
73	2022	10.1016/j.actbio.2022.08.075	Article	English	Scopus/Web of Science/PubMed/Dimensions
74	2023	10.1016/j.ijbiomac.2023.124427	Article	English	Scopus/Web of Science/PubMed/Dimensions
75	2022	10.3389/fbioe.2022.1006584	Article	English	Scopus/Web of Science/PubMed/Dimensions
76	2022	10.1007/s10924-021-02239-7	Article	English	Scopus/Web of Science/Dimensions
77	2021	10.1002/adhm.202001384	Review	English	Scopus
78	2021	10.1007/s42600-021-00187-8	Article	English	Scopus/Dimensions
79	2022	10.1016/j.jiec.2021.12.027	Article	English	Scopus/Web of Science/Dimensions
80	2020	10.1016/j.msec.2020.111273	Article	English	Scopus/Web of Science/PubMed/Dimensions
81	2022	10.1016/j.apsusc.2021.151825	Article	English	Scopus/Web of Science/Dimensions
82	2022	10.3390/membranes12020121	Article	English	Scopus/Web of Science/PubMed/Dimensions
83	2020	10.1016/j.bioactmat.2020.05.008	Article	English	Scopus/Web of Science/PubMed/Dimensions
84	2021	10.1016/j.ijbiomac.2020.11.014	Article	English	Scopus
85	2022	10.1039/d2bm00836j	Article	English	Scopus/Web of Science/PubMed/Dimensions
86	2023	10.1016/j.ijbiomac.2023.124911	Article	English	Scopus
87	2023	10.1016/j.actbio.2023.01.021	Article	English	Scopus/Web of Science/PubMed/Dimensions
88	2023	10.1016/j.joim.2023.07.002	Article	English	Scopus/PubMed/Dimensions
89	2021	10.1002/adfm.202105932	Article	English	Scopus/Web of Science/Dimensions
90	2023	10.3389/fmats.2023.1144752	Article	English	Scopus/Web of Science/Dimensions
91	2021	10.1016/j.bioactmat.2021.02.033	Article	English	Scopus

92	2021	10.3390/antibiotics10050524	Article	English	Scopus/Web of Science/PubMed/Dimensions
93	2021	10.1016/j.cej.2021.130302	Article	English	Scopus/Web of Science/Dimensions
94	2023	10.1016/j.ijbiomac.2023.126056	Article	English	Scopus/Web of Science/PubMed/Dimensions
95	2022	10.47750/pnr.2022.13.04.026	Article	English	Scopus
96	2023	10.1007/s11696-022-02553-x	Article	English	Scopus/Web of Science/Dimensions
97	2022	10.1021/acsnano.2c05557	Article	English	Scopus/Web of Science/PubMed/Dimensions
98	2021	10.1002/ptr.7242	Review	English	Scopus/Web of Science/PubMed/Dimensions
99	2021	10.1166/jbn.2021.3079	Article	English	Scopus/Web of Science/PubMed/Dimensions
100	2017	10.1016/j.carbpol.2016.11.056	Article	English	Scopus/Web of Science/PubMed/Dimensions
101	2019	10.1016/j.jmbbm.2019.03.013	Article	English	Scopus/PubMed/Dimensions
102	2015	10.1155/2015/108571	Article	English	Scopus/Web of Science/PubMed/Dimensions
103	2012	10.1021/am300292v	Retracted	English	Scopus/Web of Science/PubMed/Dimensions
104	2020	10.3390/ma13122819	Article	English	Scopus/Web of Science/PubMed/Dimensions
105	2018	10.1016/j.ijbiomac.2017.10.056	Article	English	Scopus/Web of Science/PubMed/Dimensions
106	2020	10.1016/j.ijbiomac.2020.03.114	Article	English	Scopus/Web of Science/PubMed/Dimensions
107	2019	10.1016/j.msec.2019.109873	Article	English	Scopus/Web of Science/PubMed/Dimensions
108	2014	10.1155/2014/153808	Review	English	Scopus/Web of Science
109	2017	10.1177/0883911517690758	Article	English	Scopus/Web of Science/Dimensions

110	2013	10.1080/09205063.2012.701549	Article	English	Scopus/Web of Science/PubMed/Dimensions
111	2017	10.3390/molecules22091513	Article	English	Scopus/Web of Science/PubMed/Dimensions
112	2020	10.1016/j.ijbiomac.2020.02.140	Article	English	Scopus/Web of Science/PubMed/Dimensions
113	2019	10.1159/000493210	Article	English	Scopus
114	2018	10.1016/j.colsurfb.2018.07.028	Article	English	Scopus/Web of Science
115	2020	10.1021/acsbiomaterials.0c00923	Article	English	Scopus/Web of Science/PubMed/Dimensions
116	2018	10.1039/c8ra06274a	Article	English	Scopus/Web of Science/PubMed/Dimensions
117	2018	10.1186/s12951-018-0348-z	Article	English	Scopus/Web of Science/PubMed/Dimensions
118	2015	10.1080/00405000.2014.906100	Article	English	Scopus/Web of Science/Dimensions
119	2020	10.1016/j.apmt.2020.100756	Article	English	Scopus/Web of Science/Dimensions
120	2018	10.1177/0883911517724809	Article	English	Scopus/Web of Science/Dimensions
121	2017	10.1016/j.msec.2017.03.199	Article	English	Scopus/Web of Science/PubMed/Dimensions
122	2020	10.1080/03639045.2020.1811305	Article	English	Scopus/PubMed/Dimensions
123	2017	10.1002/jbm.b.33675	Article	English	Scopus/Web of Science/PubMed/Dimensions
124	2017	10.3969/j.issn.2095-4344.2017.09.018	Article	Chinese	Scopus
125	2013	10.1016/j.biomaterials.2012.11.062	Article	English	Scopus/PubMed/Dimensions
126	2014	10.1177/0883911514554146	Article	English	Scopus/Web of Science/Dimensions
127	2020	10.1002/jbm.a.36980	Article	English	Scopus/Web of Science/PubMed/Dimensions
128	2020	10.1002/bip.23354	Article	English	Scopus/Web of Science/PubMed/Dimensions

129	2020	10.1016/j.actbio.2019.10.046	Article	English	Scopus/Web of Science/PubMed/Dimensions
130	2019	10.1021/acsabm.9b00727	Article	English	Scopus/Web of Science/PubMed/Dimensions
131	2017	10.1038/s41598-017-10882-1	Article	English	Scopus/Web of Science/PubMed/Dimensions
132	2016	10.1021/acsami.5b11160	Article	English	Scopus/Web of Science/PubMed/Dimensions
133	2019	10.3390/ijms20163890	Article	English	Scopus/Web of Science/PubMed/Dimensions
134	2018	10.1016/j.phymed.2017.09.024	Review	English	Scopus/Web of Science/PubMed/Dimensions
135	2013	10.4161/org.24945	Review	English	Scopus
136	2019	10.1016/j.ijbiomac.2018.11.226	Article	English	Scopus
137	2020	10.3390/pharmaceutics12060484	Article	English	Scopus/Web of Science/PubMed/Dimensions
138	2019	10.1016/j.jconrel.2019.10.050	Article	English	Scopus/Web of Science
139	2016	10.1021/acsami.6b00739	Article	English	Scopus/Web of Science/PubMed/Dimensions
140	2017	10.1016/j.actbio.2017.08.001	Article	English	Scopus/Web of Science/PubMed/Dimensions
141	2016	10.1016/j.ijpharm.2016.08.053	Article	English	Scopus/Web of Science/PubMed/Dimensions
142	2014	10.1371/journal.pone.0101300	Article	English	Scopus
143	2016	10.1097/01.asw.0000490362.64517.d7	Article	English	Scopus/Web of Science
144	2016	10.1016/j.actbio.2016.09.035	Article	English	Scopus/Web of Science/PubMed/Dimensions
145	2013	10.1016/b978-0-12-420045-6.00001-8	Book chapter	English	Scopus

146	2017	10.1016/j.carbpol.2016.09.051	Article	English	Scopus/Web of Science/PubMed/Dimensions
147	2012	10.3791/3527	Article	English	Scopus/Web of Science/PubMed/Dimensions
148	2013	10.1007/s10934-012-9655-1	Article	English	Scopus/Web of Science/Dimensions
149	2018	10.1016/j.ijbiomac.2018.04.010	Article	English	Scopus/Web of Science
150	2017	10.3389/fphys.2017.00904	Article	English	Scopus
151	2012	10.1007/s00289-012-0761-7	Article	English	Scopus/Web of Science/Dimensions
152	2018	10.1186/s12929-018-0491-8	Review	English	Scopus
153	2019	10.1088/2053-1591/ab5533	Article	English	Scopus/Web of Science/Dimensions
154	2020	10.1016/j.ijbiomac.2020.03.161	Article	English	Scopus/Web of Science/PubMed/Dimensions
155	2020	10.1016/j.ijbiomac.2020.06.181	Article	English	Scopus/Web of Science/PubMed/Dimensions
156	2012	10.3969/j.issn.1673-5374.2012.29.002	Article	English	Scopus/Web of Science/PubMed/Dimensions
157	2019	10.1021/acsami.9b09123	Article	English	Scopus/Web of Science/PubMed/Dimensions
158	2018	10.1680/jbibn.17.00036	Article	English	Scopus/Web of Science/Dimensions
159	2017	10.1016/j.ijpharm.2017.06.024	Article	English	Scopus
160	2017	10.1039/c7bm00095b	Article	English	Scopus
161	2019	10.1016/j.carbpol.2019.115302	Article	English	Scopus/PubMed/Dimensions
162	2017	10.1016/j.msec.2017.08.052	Article	English	Scopus/Web of Science/PubMed/Dimensions
163	2011	10.1002/lsm.21076	Article	English	Scopus/Web of Science/PubMed/Dimensions
164	2017	10.1016/j.tibtech.2017.05.005	Review	English	Scopus
165	2017	10.1021/acsbiomaterials.7b00681	Article	English	Scopus/Web of Science/PubMed/Dimensions

166	2020	10.3233/bme-201076	Article	English	Scopus/Web of Science/PubMed/Dimensions
167	2016	10.1007/s10561-016-9585-2	Article	English	Scopus/PubMed/Dimensions
168	2019	10.1016/j.msec.2019.01.073	Article	English	Scopus/Web of Science/PubMed/Dimensions
169	2017	10.1016/j.msec.2017.02.076	Article	English	Scopus/Web of Science/PubMed/Dimensions
170	2014	10.1111/wrr.12171	Article	English	Scopus/Web of Science/PubMed
171	2019	10.1021/acsami.8b18931	Article	English	Scopus/Web of Science/PubMed/Dimensions
172	2018	10.1016/j.apmt.2018.07.006	Article	English	Scopus/Web of Science/Dimensions
173	2018	10.1016/j.ijbiomac.2018.02.073	Article	English	Scopus/Web of Science/PubMed/Dimensions
174	2017	10.1039/c7py00038c	Article	English	Scopus/Web of Science/Dimensions
175	2020	10.3390/pharmaceutics12010056	Article	English	Scopus/Web of Science/PubMed/Dimensions
176	2019	10.1088/1748-605x/ab026c	Article	English	Scopus/Web of Science/PubMed/Dimensions
177	2019	10.1016/j.ijbiomac.2019.05.156	Article	English	Scopus
178	2013	10.1016/j.carbpol.2013.06.022	Article	English	Scopus/Web of Science/PubMed/Dimensions
179	2019	10.2147/dddt.s219224	Article	English	Scopus/Web of Science/PubMed/Dimensions
180	2016	10.1016/j.ijbiomac.2016.09.083	Article	English	Scopus/Web of Science/PubMed/Dimensions
181	2011	10.1007/s13233-011-0812-1	Article	English	Scopus/Web of Science/Dimensions
182	2017	10.1002/jbm.b.33394	Article	English	Scopus/Web of Science/PubMed/Dimensions
183	2019	10.2147/ijn.s214359	Article	English	Scopus/Web of Science/PubMed/Dimensions

184	2018	10.1016/j.ijbiomac.2018.08.057	Article	English	Scopus/Web of Science/PubMed/Dimensions
185	2017	10.1002/jbm.a.36097	Article	English	Scopus/Web of Science/PubMed/Dimensions
186	2020	10.1016/j.xphs.2020.06.005	Article	English	Scopus
187	2018	10.13005/bpj/1400	Article	English	Scopus
188	2020	10.1016/j.carbpol.2020.116106	Article	English	Scopus/Web of Science/PubMed/Dimensions
189	2020	10.1016/j.colsurfb.2019.110749	Article	English	Scopus/Web of Science/PubMed/Dimensions
190	2019	10.1016/j.actbio.2019.10.012	Article	English	Scopus/Web of Science/PubMed/Dimensions
191	2017	10.1016/j.msec.2017.05.116	Article	English	Scopus/Web of Science/PubMed/Dimensions
192	2011	10.1371/journal.pone.0021744	Article	English	Scopus
193	2019	10.1016/j.ijbiomac.2019.08.158	Article	English	Scopus/PubMed/Dimensions
194	2013	10.1080/09205063.2012.718613	Article	English	Scopus
195	2019	10.3390/ma12142223	Article	English	Scopus/Web of Science/PubMed/Dimensions
196	2010	10.1016/j.ijpharm.2010.03.024	Article	English	Scopus/Web of Science/PubMed/Dimensions
197	2009	10.1021/bm900670n	Article	English	Scopus
198	2008	10.1021/bm701049g	Article	English	Scopus
199	2010	10.1016/j.biomaterials.2009.09.022	Article	English	Scopus
200	1998	10.1080/02844319850158462	Article	English	Scopus/Web of Science/PubMed/Dimensions
201	1994	10.1016/0142-9612(94)90209-7	Article	English	Scopus
202	2017	10.18520/cs/v112/i12/2392-2404	Review	English	Web of Science

203	2023	10.1016/j.compositesb.2023.110549	Article	English	Web of Science
204	2018	10.3390/pharmaceutics10020042	Review	English	Web of Science
205	2023	10.1016/j.jddst.2023.104549	Review	English	Web of Science
206	2018	10.2217/nnm-2018-0099	Article	English	Web of Science
207	2018	10.1016/j.carbpol.2018.02.003	Review	English	Web of Science
208	2021	10.1016/j.ijbiomac.2021.10.128	Article	English	Web of Science
209	2021	10.3390/molecules26164784	Review	English	Web of Science
210	2020	10.1016/j.msec.2020.110643	Article	English	Web of Science
211	2012	10.1021/am201669z	Article	English	Web of Science
212	2018	10.3892/etm.2017.5552	Article	English	Web of Science
213	2023	10.3390/ijms24054962	Review	English	Web of Science
214	2023	10.1007/s00289-023-04879-2	Article: Early Access	English	Web of Science
215	2020	10.1039/d0ra03704d	Article	English	Web of Science/PubMed/Dimensions
216	2021	10.3390/polym13132104	Review	English	Web of Science
217	2022	10.1016/j.ajps.2022.01.001	Review	English	Web of Science
218	2014	10.1002/jbm.b.33032	Article	English	Web of Science
219	2021	10.1016/j.ijbiomac.2020.11.168	Article	English	Web of Science
220	2021	10.1016/j.ijbiomac.2020.10.206	Article	English	Web of Science
221	2009	10.1002/jbm.b.31307	Article	English	Web of Science
222	2020	10.3390/ijms21062070	Article	English	Web of Science
223	2019	10.1007/s13346-019-00660-z	Article	English	Web of Science
224	2015	10.1002/jbm.a.35512	Article	English	Web of Science
225	2022	10.1177/08839115211073155	Article	English	Web of Science
226	2017	10.1016/j.ijbiomac.2017.06.124	Article	English	Web of Science
227	2020	10.1016/j.matpr.2020.05.686	Proceedings Paper	English	Web of Science
228	2021	10.1007/s00289-020-03429-4	Article	English	Web of Science
229	2020	10.3390/ma13102407	Review	English	Web of Science
230	2019	10.1021/acs.nanolett.9b00367	Article	English	Web of Science

231	2019	10.1177/1534734619849982	Article	English	Web of Science
232	2020	10.1002/adhm.202000035	Article	English	Web of Science
233	2013	10.1016/j.ijpharm.2012.11.045	Article	English	Web of Science
234	2015	10.1691/ph.2015.4126	Article	English	Web of Science
235	2018	10.1016/j.bioactmat.2017.11.003	Review	English	Web of Science
236	2019	10.1007/s10965-019-1874-6	Article	English	Web of Science
237	2021	10.1016/j.ijpharm.2020.120068	Article	English	Web of Science
238	2021	10.1016/j.jddst.2021.102789	Article	English	Web of Science
239	2018	10.1016/j.apmt.2018.03.001	Article	English	Web of Science
240	2023	10.3390/gels9070591	Review	English	Web of Science
241	2020	10.1016/j.ijbiomac.2019.10.166	Article	English	Web of Science
242	2022	10.1007/s10570-021-04412-6	Review	English	Web of Science
243	2021	10.1106/mex.2021.1877	Article	English	Web of Science
244	2018	10.1016/j.msec.2018.04.077	Article	English	Web of Science
245	2021	10.1016/j.cej.2021.129578	Article	English	Web of Science
246	2018	10.1038/s41598-018-32208-5	Article	English	Web of Science
247	2019	10.1016/j.jddst.2018.12.003	Article	English	Web of Science
248	2021	10.1016/j.ijpharm.2021.120270	Review	English	Web of Science
249	2021	10.3390/ma14092270	Article	English	Web of Science
250	2023	10.1007/s00289-023-04763-z	Article: Early Access	English	Web of Science
251	2023	10.1021/acs.biomac.2c01520	Article	English	Web of Science
252	2023	10.3390/polym15153323	Article	English	Web of Science
253	2023	10.1007/s00289-022-04358-0	Article	English	Web of Science
254	2020	10.1038/s41598-020-65268-7	Article	English	Web of Science
255	2016	10.3389/fphys.2016.00341	Review	English	Web of Science
256	2018	10.1039/c8bm00492g	Article	English	Web of Science
257	2023	10.1080/09205063.2023.2170138	Article	English	Web of Science
258	2019	10.1016/j.msec.2019.03.005	Article	English	Web of Science
259	2021	10.3390/polym13183191	Article	English	Web of Science

260	2011	10.1016/j.biomaterials.2010.08.087	Article	English	Web of Science
261	2018	10.1016/j.carbpol.2017.12.033	Article	English	Web of Science
262	2020	10.2147/ijn.s225197	Article	English	Web of Science
263	2020	10.1002/pen.25410	Review	English	Web of Science
264	2018	10.30466/vrf.2018.29979	Article	English	Web of Science
265	2021	10.1016/j.ijbiomac.2021.02.025	Article	English	Web of Science
266	2020	10.22038/ijbms.2020.34324.8156	Article	English	Web of Science
267	2023	10.1007/s00289-023-04915-1	Article: Early Access	English	Web of Science
268	2023	10.1080/09205063.2022.2116209	Article	English	Web of Science
269	2022	10.1016/j.ceramint.2022.05.037	Article	English	Web of Science
270	2022	10.1007/s42247-022-00418-3	Article	English	Web of Science
271	2010	10.1002/wnan.100	Review	English	Web of Science
272	2023	10.1016/j.ijbiomac.2023.123631	Article	English	Web of Science
273	2021	10.1016/j.ajps.2020.10.001	Review	English	Web of Science
274	2022	10.1002/btm2.10244	Article	English	Web of Science
275	2021	10.1016/j.carbpol.2020.117296	Article	English	Web of Science
276	2023	10.1016/j.jddst.2023.104456	Article	English	Web of Science
277	2023	10.1016/j.ijbiomac.2023.123278	Article	English	Web of Science
278	2014	10.1021/nn503719n	Article	English	Web of Science
279	2018	10.3390/polym10111221	Review	English	Web of Science
280	2020	10.2147/ccid.s282143	Review	English	Web of Science
281	2013	10.1021/am403436y	Article	English	Web of Science
282	2018	10.1016/j.jphotobiol.2018.02.018	Article	English	Web of Science/PubMed
283	2023	10.1016/j.apsusc.2022.155799	Article	English	Web of Science
284	2017	10.1016/j.msec.2017.03.272	Article	English	Web of Science
285	2016	10.1088/1748-6041/11/5/055009	Article	English	Web of Science
286	2019	10.1016/j.ijbiomac.2018.10.120	Review	English	Web of Science
287	2022	10.1177/1528083720976348	Article	English	Web of Science

288	2009	10.1002/lsm.20774	Article	English	Web of Science/PubMed/Dimensions
289	2023	10.3390/jfb14070357	Article	English	Web of Science
290	2014	10.1021/am502948g	Article	English	Web of Science
291	2018	10.2147/ijn.s177256	Article	English	Web of Science
292	2016	10.1021/acsbiomaterials.6b00550	Article	English	Web of Science
293	2021	10.1038/s41598-021-82963-1	Article	English	Web of Science
294	2023	10.1080/10667857.2023.2223018	Article	English	Web of Science
295	2021	10.1039/d1tb01934a	Article	English	Web of Science
296	2020	10.3390/pharmaceutics12070634	Article	English	Web of Science
297	2023	10.1002/biof.1945	Review: Early Access	English	Web of Science
298	2020	10.1007/s12221-020-9402-1	Article	English	Web of Science
299	2021	10.1016/j.lfs.2020.118640	Article	English	Web of Science
300	2012	10.3727/096368911x612503	Article	English	Web of Science
301	2015	10.2174/1381612821666150901104601	Article	English	Web of Science
302	2021	10.3390/biomimetics6010006	Review	English	Web of Science
303	2022	10.3390/pharmaceutics14010191	Review	English	Web of Science
304	2017	10.1016/j.msec.2017.03.005	Article	English	Web of Science
305	2021	10.1016/j.cej.2021.129951	Article	English	Web of Science
306	2018	10.1007/s40883-018-0066-y	Article	English	Web of Science
307	2010	10.1002/jbm.a.32511	Article	English	Web of Science
308	2020	10.1590/0104-1428.06820	Article	English	Web of Science
309	2023	10.1002/slct.202203692	Article	English	Web of Science
310	2023	10.1049/mna2.12171	Article	English	Web of Science
311	2018	10.1088/2057-1976/aaabf0	Article	English	Web of Science
312	2009	10.1016/j.biomaterials.2008.12.075	Article	English	Web of Science
313	2016	10.1021/acs.jpcc.6b00957	Article	English	Web of Science

314	2017	10.1016/j.ijbiomac.2017.06.044	Article	English	Web of Science
315	2020	10.3390/ma13112631	Article	English	Web of Science
316	2018	10.1016/j.carbpol.2018.03.044	Article	English	Web of Science
317	2021	10.1016/j.jddst.2021.102415	Article	English	Web of Science
318	2022	10.1016/j.ijbiomac.2022.10.049	Article	English	Web of Science
319	2020	10.3390/mi11040441	Article	English	Web of Science
320	2022	10.1016/j.colsurfb.2022.112589	Article	English	Web of Science
321	2022	10.1002/app.52139	Article	English	Web of Science
322	2023	10.1016/j.ijbiomac.2023.125330	Article	English	Web of Science
323	2023	10.17576/jsm-2023-5205-16	Article	English	Web of Science
324	2015	10.1371/journal.pone.0135153	Article	English	Web of Science
325	2022	10.1080/10717544.2022.2112995	Article	English	Web of Science/PubMed
326	2013	10.1016/j.jconrel.2013.03.026	Article	English	Web of Science
327	2011	10.1039/c1sm05293d	Review	English	Web of Science
328	2007	10.2217/17435889.2.4.483	Review	English	Web of Science
329	2022	10.3390/polym14051010	Article	English	Web of Science
330	2013	10.1080/15685543.2013.764510	Article	English	Web of Science
331	2019	10.1016/j.msec.2019.02.092	Article	English	Web of Science
332	2016	10.1016/j.carbpol.2016.07.053	Article	English	Web of Science
333	2022	10.1016/j.mtcomm.2022.104599	Article	English	Web of Science
334	2014	10.1088/1758-5082/6/3/035012	Article	English	Web of Science
335	2012	10.2109/jcersj2.120.555	Article	English	Web of Science
336	2023	10.1016/j.jddst.2023.104710	Article	English	Web of Science
337	2022	10.3389/fbioe.2022.913912	Review	English	Web of Science
338	2019	10.1089/ten.tea.2019.0021	Article	English	Web of Science/PubMed/Dimensions
339	2017	10.1016/j.msec.2017.03.226	Review	English	Web of Science
340	2021	10.3390/ijms22179216	Article	English	Web of Science
341	2009	10.1016/j.actbio.2009.05.031	Article	English	Web of Science
342	2013	10.1002/term.492	Article	English	Web of Science

343	2012	10.1088/1748-6041/7/2/024101	Article	English	Web of Science
344	2018	10.1016/j.ijbiomac.2018.07.154	Review	English	Web of Science
345	2021	10.1021/acsami.1c09804	Article	English	Web of Science
346	2018	10.1016/j.ymeth.2017.08.015	Article	English	Web of Science
347	2002	10.1002/jbm.1260	Article	English	PubMed
348	2002	10.1016/s0142-9612(02)00162-x	Article	English	PubMed
349	2003	10.1016/s0142-9612(03)00220-5	Article	English	PubMed
350	2005	10.1016/j.biomaterials.2005.03.006	Article	English	PubMed
351	2006	10.1021/bm050754b	Article	English	PubMed
352	2006	10.1007/s10047-005-0313-0	Article	English	PubMed
353	2008	10.1002/jbm.a.31223	Article	English	PubMed
354	2008	10.1016/j.biomaterials.2008.07.034	Article	English	PubMed
355	2009	10.1163/092050609x12457417534295	Article	English	PubMed
356	2010	10.1097/prs.0b013e3181cc9665	Article	English	PubMed
357	2010	10.1186/1479-5876-8-59	Article	English	PubMed
358	2010	10.1007/s11427-010-0036-1	Article	English	PubMed
359	2010	10.1016/j.biomaterials.2010.06.013	Article	English	PubMed
360	2012	10.1002/jbm.a.33282	Article	English	PubMed
361	2013	10.1016/j.ijpharm.2012.06.004	Article	English	PubMed
362	2012	10.1016/j.ijpharm.2012.08.001	Article	English	PubMed
363	2013	10.1016/j.actbio.2013.03.025	Article	English	PubMed
364	2013	10.1016/j.actbio.2013.04.017	Article	English	PubMed
365	2013	10.1016/j.ijpharm.2013.05.012	Article	English	PubMed
366	2017	10.1002/term.1912	Article	English	PubMed
367	2014	10.1155/2014/493732	Article	English	PubMed
368	2014	10.3390/jfb5030183	Article	English	PubMed

369	2015	10.1177/0885328214553959	Article	English	PubMed
370	2014	10.1002/jps.24205	Article	English	PubMed
371	2015	10.1111/wrr.12239	Article	English	PubMed
372	2015	10.1080/09205063.2015.1061349	Article	English	PubMed
373	2016	10.1002/jbm.b.33487	Article	English	PubMed
374	2016	10.3109/03639045.2015.1075030	Article	English	PubMed
375	2015	10.1016/j.surg.2015.06.040	Article	English	PubMed
376	2016	10.1111/wrr.12372	Article	English	PubMed
377	2016	10.1016/j.ejps.2015.12.026	Article	English	PubMed
378	2016	10.1021/acsami.6b04369	Article	English	PubMed
379	2016	10.1016/j.msec.2016.05.027	Article	English	PubMed
380	2016	10.1021/acsami.6b07463	Article	English	PubMed
381	2016	10.1016/j.actbio.2016.09.009	Article	English	PubMed
382	2017	10.1016/j.msec.2016.08.086	Article	English	PubMed
383	2017	10.1016/j.ijbiomac.2016.10.080	Article	English	PubMed
384	2017	10.1016/j.actbio.2017.03.011	Article	English	PubMed
385	2017	10.5966/sctm.2016-0275	Article	English	PubMed
386	2017	10.1021/acs.biomac.7b00111	Article	English	PubMed
387	2018	10.1080/08982104.2017.1335319	Article	English	PubMed
388	2017	10.1002/jbm.a.36135	Article	English	PubMed
389	2017	10.1039/c7bm00174f	Article	English	PubMed
390	2017	10.1021/acsbiomaterials.7b00189	Article	English	PubMed
391	2018	10.1016/j.ijbiomac.2017.12.022	Article	English	PubMed
392	2018	10.1080/21691401.2018.1430698	Article	English	PubMed
393	2018	10.1166/jnn.2018.14378	Article	English	PubMed
394	2018	10.1016/j.actbio.2018.02.031	Article	English	PubMed
395	2018	10.3390/ma11040569	Article	English	PubMed
396	2018	10.3791/56810	Article	English	PubMed
397	2018	10.1016/j.actbio.2018.04.043	Article	English	PubMed

398	2018	10.1016/j.ijbiomac.2018.05.066	Article	English	PubMed
399	2018	10.12968/jowc.2018.27.6.394	Article	English	PubMed/Dimensions
400	2018	10.1016/j.ijbiomac.2018.07.018	Article	English	PubMed
401	2018	10.2147/ijn.s165005	Article	English	PubMed
402	2018	10.1016/j.biomaterials.2018.08.044	Article	English	PubMed
403	2018	10.1016/j.msec.2018.08.005	Article	English	PubMed
404	2018	10.3390/polym10090987	Article	English	PubMed
405	2019	10.21873/invivo.11531	Article	English	PubMed
406	2019	10.1080/02652048.2019.1612476	Article	English	PubMed
407	2019	10.1016/j.colsurfb.2019.04.043	Article	English	PubMed
408	2019	10.1016/j.ijbiomac.2019.04.195	Article	English	PubMed
409	2019	10.1039/c9ra02628b	Article	English	PubMed
410	2019	10.1016/j.ijpharm.2019.118487	Article	English	PubMed
411	2019	10.3390/pharmaceutics11070314	Article	English	PubMed
412	2019	10.1016/j.msec.2019.109815	Article	English	PubMed
413	2019	10.1016/j.intimp.2019.105764	Article	English	PubMed
414	2019	10.1016/j.ijpharm.2019.118648	Article	English	PubMed
415	2019	10.1016/j.carbpol.2019.115191	Article	English	PubMed
416	2020	10.1002/jbm.b.34487	Article	English	PubMed
417	2019	10.1016/j.msec.2019.110040	Article	English	PubMed
418	2020	10.1016/j.carbpol.2019.115296	Article	English	PubMed
419	2019	10.3390/polym11101679	Article	English	PubMed
420	2019	10.2478/acph-2019-0049	Article	English	PubMed
421	2019	10.1039/c9ra06913e	Article	English	PubMed
422	2019	10.1166/jbn.2019.2865	Article	English	PubMed
423	2020	10.1016/j.ijbiomac.2020.01.127	Article	English	PubMed
424	2020	10.1002/mabi.201900385	Article	English	PubMed
425	2020	10.1186/s12951-020-00602-9	Article	English	PubMed

426	2020	10.1039/dotb00361a	Article	English	PubMed
427	2020	10.1016/j.xphs.2020.03.028	Article	English	PubMed
428	2020	10.1691/ph.2020.9179	-		PubMed
429	2020	10.12968/jowc.2020.29.5.270	Article	English	PubMed
430	2020	10.1016/j.carbpol.2020.116315	Article	English	PubMed
431	2020	10.1016/j.ijbiomac.2020.06.253	Article	English	PubMed
432	2020	10.1088/1748-605x/aba878	Article		PubMed
433	2020	10.1097/01.asw.0000666912.86854.2b	Article	English	PubMed
434	2020	10.1016/j.ijbiomac.2020.08.093	Article	English	PubMed
435	2020	10.1016/j.carbpol.2020.116754	Article	English	PubMed
436	2021	10.1002/lary.29118	Article	English	PubMed
437	2020	10.3390/pharmaceutics12100983	Article	English	PubMed
438	2021	10.1016/j.ijbiomac.2020.10.204	Article	English	PubMed
439	2020	10.2147/ijn.s278631	Article	English	PubMed
440	2021	10.1016/j.ijbiomac.2020.11.153	Article	English	PubMed
441	2020	10.1016/j.jsps.2020.09.007	Article	English	PubMed
442	2021	10.1016/j.msec.2020.111385	Article	English	PubMed
443	2021	10.1016/j.msec.2020.111447	Article	English	PubMed
444	2021	10.1080/03639045.2020.1863420	Article	English	PubMed
445	2021	10.1002/adhm.202001591	Article	English	PubMed
446	2021	10.2147/ijn.s266692	Article	English	PubMed
447	2021	10.1016/j.ijbiomac.2021.01.157	Article	English	PubMed
448	2021	10.1016/j.ijpharm.2021.120313	Article	English	PubMed
449	2021	10.1016/j.carbpol.2020.117598	Article	English	PubMed
450	2021	10.1039/d0bm01960g	Article	English	PubMed
451	2021	10.1002/mabi.202000432	Article	English	PubMed
452	2021	10.1080/13543776.2021.1903433	Article	English	PubMed
453	2020	10.1155/2020/8868618	Article	English	PubMed

454	2021	10.1016/j.carbpol.2021.117939	Article	English	PubMed
455	2021	10.1016/j.carbpol.2021.118065	Article	English	PubMed
456	2021	10.1016/j.colsurfb.2021.111922	Article	English	PubMed
457	2021	10.3390/ijms22126451	Article	English	PubMed
458	2022	10.2174/1567201818666210720150929	Article	English	PubMed
459	2021	10.1016/j.carbpol.2021.118272	Article	English	PubMed
460	2021	10.1097/jcma.0000000000000589	Article	English	PubMed
461	2021	10.3390/molecules26154659	-		PubMed
462	2021	10.1016/j.carbpol.2021.118482	Article	English	PubMed
463	2021	10.1016/j.msec.2021.112263	Article	English	PubMed
464	2021	10.1016/j.ijbiomac.2021.09.034	Article	English	PubMed
465	2021	10.1016/j.ijbiomac.2021.10.033	Article	English	PubMed
466	2022	10.1080/09205063.2021.1992590	Article	English	PubMed
467	2021	10.1016/j.ijbiomac.2021.10.166	Article	English	PubMed
468	2021	10.3390/ijms222111474	Article	English	PubMed/Dimensions
469	2022	10.1016/j.ijbiomac.2021.12.073	Article	English	PubMed
470	2022	10.1021/acsami.1c21039	Article	English	PubMed
471	2022	10.3390/ijms23031249	Article	English	PubMed
472	2022	10.1021/acsinfecdis.1c00496	Article	English	PubMed
473	2021	10.1016/j.bioactmat.2021.10.043	Article	English	PubMed
474	2022	10.1002/marc.202200031	Article	English	PubMed
475	2022	10.1016/j.ijbiomac.2022.04.026	Article	English	PubMed
476	2023	10.2174/1567201819666220414092342	Article	English	PubMed
477	2022	10.3389/fbioe.2022.878588	Article		PubMed
478	2022	10.1016/j.ijbiomac.2022.06.130	Article	English	PubMed
479	2022	10.1016/j.carbpol.2022.119722	Article	English	PubMed

480	2022	10.1021/acsami.2c04323	Article	English	PubMed
481	2022	10.1016/j.ijbiomac.2022.07.186	Article	English	PubMed
482	2022	10.1016/j.ijbiomac.2022.08.151	Article	English	PubMed
483	2022	10.3389/fbioe.2022.943695	Article		PubMed
484	2022	10.1016/j.ijbiomac.2022.09.128	Article	English	PubMed
485	2022	10.1016/j.ijbiomac.2022.09.177	Article	English	PubMed
486	2022	10.1016/j.bioactmat.2022.09.005	Article	English	PubMed
487	2022	10.1016/j.colsurfb.2022.112902	Article	English	PubMed
488	2022	10.1016/j.carbpol.2022.120126	Article	English	PubMed
489	2022	10.3389/fmicb.2022.1023083	Article		PubMed
490	2022	10.3389/fbioe.2022.989180	Article		PubMed
491	2023	10.1016/j.ijbiomac.2022.10.130	Article	English	PubMed
492	2022	10.1016/j.bioadv.2022.213166	Article	English	PubMed
493	2022	10.1016/j.ijbiomac.2022.10.249	Article	English	PubMed
494	2022	10.1016/j.bioadv.2022.213175	Article	English	PubMed
495	2023	10.1016/j.ijbiomac.2022.12.003	Article	English	PubMed
496	2022	10.3390/pharmaceutics14122736	Article	English	PubMed
497	2023	10.4103/1673-5374.357914	Article	English	PubMed
498	2023	10.1002/jbm.b.35215	Article	English	PubMed
499	2023	10.1016/j.carbpol.2022.120349	Article	English	PubMed
500	2022	10.3390/gels9010027	Article	English	PubMed
501	2023	10.3390/mi14010137	Article	English	PubMed
502	2023	10.1021/acsabm.2c00903	Article	English	PubMed
503	2023	10.1016/j.biomaterials.2023.122029	Article	English	PubMed
504	2023	10.1002/advs.202206585	Article	English	PubMed
505	2023	10.1016/j.ijbiomac.2023.124106	Article	English	PubMed
506	2023	10.1186/s12951-023-01847-w	Article	English	PubMed
507	2023	10.3390/polym15061376	Article	English	PubMed

508	2023	10.1016/j.ijbiomac.2023.124447	Article	English	PubMed
509	2023	10.1039/d3bm00169e	Article	English	PubMed
510	2023	10.21873/invivo.13180	Article	English	PubMed
511	2023	10.1016/j.bioadv.2023.213432	Article	English	PubMed
512	2023	10.1016/j.ijbiomac.2023.125226	Article	English	PubMed
513	2023	10.3390/polym15112559	Article	English	PubMed
514	2023	10.1016/j.carbpol.2023.121050	Article	English	PubMed
515	2023	10.3390/polym15122724	Article	English	PubMed
516	2023	10.1007/s12010-023-04665-w	Article	English	PubMed
517	2023	10.1016/j.heliyon.2023.e17704	Article	English	PubMed
518	2023	10.1016/j.biopha.2023.115156	Article	English	PubMed
519	2023	10.1002/marc.202300325	Article	English	PubMed
520	2023	10.1016/j.bioactmat.2023.07.005	Article	English	PubMed
521	2023	10.1016/j.actbio.2023.08.038	Article	English	PubMed
522	2021	10.1080/07853890.2021.1896112	Article	English	Dimensions
523	2014	10.1166/jcc.2014.1080	Article	English	Dimensions
524	2023	10.21203/rs.3.rs-2687852/v1	Posted Content		Dimensions
525	2017	10.1201/9781315370569-3	Book Chapter		Dimensions
526	2021	10.21203/rs.3.rs-889558/v1	Posted Content		Dimensions
527	2020	10.1093/jbcr/iraa024.261	Article	English	Dimensions
528	2012	10.22270/jddt.v2i3.166	Article		Dimensions
529	2023	10.5530/jyp.2023.15.62	Article		Dimensions
530	2022	10.2139/ssrn.4107039	Article	English	Dimensions
531	2003	10.1055/s-2004-815647	Article	English	Dimensions
532	2021		Article	English	Scopus
533	2017		Conference paper	English	Scopus
534	2017		Conference paper	English	Scopus
535	2017		Conference paper	English	Scopus
536	2011		Book chapter	English	Scopus

537	2010		Article	English	Scopus
538	2010		Article	Chinese	Web of Science
539	2021		Article	English	Web of Science
540	2015		Article	English	Web of Science
541	2019		Article	English	Web of Science
542	2018		Review	English	Web of Science
543	2012		Review	English	Web of Science

Table S5. Number of articles selected by year of publication.

Continent	Country	Year	Articles (n)	Reference
America	Brazil	2020	1	[1]
	United States	2022	1	[2]
Europe	Belgium	2021	1	[3]
	Romania	2023 (2)	2	[4,5]
	Turkey	2022	1	[6]
Africa	Egypt	2019 (1)/ 2020 (1)	2	[7,8]
	South Africa	2023	1	[9]
Asia	Bangladesh	2020	1	[10]
	China	2016 (2)/ 2017 (1)/ 2018 (1)/ 2019 (1)/ 2020 (2)/ 2021 (1)/ 2022 (1)/ 2023 (4)	13	[11–23]
	India	2015 (1)/ 2017 (1)/ 2021 (1)/ 2022 (1)	4	[24–27]
	Iran	2016 (1)/ 2020 (1)/ 2022 (1)/ 2023 (1)	4	[28–31]
	Iraq	2022	1	[32]
	Malaysia	2020	1	[33]
	Pakistan	2021	1	[34]
	Qatar	2018 (1)/ 2023 (1)	2	[35,36]
	South Korea	2021 (1)/ 2023 (1)	2	[37,38]
	Taiwan	2021 (1)/ 2022 (1)	2	[39,40]

Table S6 Results of the risk of bias test for animal experiments (SYRCLE) of the studies that carried out this analysis.

				Answer for each Study																														
Item	**Type of bias**	**Domain**	**Review authors judgment**	**L001**	**L002**	**L004**	**L005**	**L007**	**L008**	**L009**	**L010**	**L011**	**L013**	**L014**	**L015**	**L016**	**L017**	**L018**	**L019**	**L020**	**L021**	**L022**	**L023**	**L024**	**L026**	**L029**	**L030**	**L031**	**L033**	**L034**	**L036**	**L037**	**L039**	**L040**
1	Selection bias	Sequence generation	Was the allocation sequence adequately generated and applied? (*)	N	U	Y	Y	Y	N	N	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	N	U	Y	N	N	U	U	U	Y	U	Y
2	Selection bias	Baseline characteristics	Were the groups similar at baseline, or were they adjusted for confounders in the analysis?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Selection bias	Allocation concealment	Was the allocation adequately concealed? (*)	U	U	U	U	U	U	Y	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
4	Performance bias	Random Housing	Were the animals randomly housed during the experiment?	U	U	U	N	N	U	N	N	N	U	U	U	U	U	U	Y	U	U	U	N	U	U	N	U	U	U	U	U	U	U	U
5	Performance bias	Blinding	Were the caregivers and/or investigators blinded from knowing which intervention each animal received during the experiment?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
6	Detection bias	Random outcome assessment	Were animals selected at random for outcome assessment?	U	N	U	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	U	N	N	N	N	N
7	Detection bias	Blinding	Was the outcome assessor blinded?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	U	N

8	Attrition bias	Incomplete outcome data	Were incomplete outcome data adequately addressed? (*)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Reporting bias	Selective outcome reporting	Are reports of the study free of selective outcome reporting? (*)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Other	Other type of bias	Was the study apparently free of other problems that could result in a high risk of bias? (*)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

L001 - [24]

L002 - [29]

L004 - [34]

L005 - [40]

L007 - [31]

L008 - [32]

L009 - [23]

L010 - [13]

L011 - [14]

L013 - [4]

L014 - [25]

L015 - [11]

L016 - [8]

L017 - [27]

L018 - [12]

L019 - [18]

L020 - [19]

L021 - [17]

L022 - [10]

L023 - [7]

L024 - [35]

L026 - [22]

L029 - [37]

L030 - [36]

L031 - [15]

L033 - [1]

L034 - [30]

L036 - [39]

L037 - [26]

L039 - [16]

L040 - [20]

Table S7 Results of the risk of bias test for non-randomized studies (MINORS) of the studies that performed this analysis.

	Answer for each Study																																							
Item	**L001**	**L002**	**L003**	**L004**	**L005**	**L006**	**L007**	**L008**	**L009**	**L010**	**L011**	**L012**	**L013**	**L014**	**L015**	**L016**	**L017**	**L018**	**L019**	**L020**	**L021**	**L022**	**L023**	**L024**	**L025**	**L026**	**L027**	**L028**	**L029**	**L030**	**L031**	**L032**	**L033**	**L034**	**L035**	**L036**	**L037**	**L038**	**L039**	**L040**
1. Clearly stated aim	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3. Prospective data collection	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
4. End points appropriate to the study aims	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2
5. Unbiased assessments of the study endpoint	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0
6. Follow-up period	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

appropriate to the study aim																																								
7. Less than 5% loss to follow up	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8. Prospective calculation of the sample size	1	1	1	2	1	1	2	1	1	1	1	1	1	1	1	1	1	1	2	2	1	1	1	1	1	0	1	1	1	2	1	1	0	1	1	1	1	0	1	1
9. An adequate control group	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	1	2	2	2	2	2	2	2	2
11. Baseline equivalence of groups	1	1	2	1	2	2	1	2	2	2	1	1	2	1	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2
12. Adequate statistical analyses	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	2	2	2	2	2	1	1	2
Total Score	17	16	18	18	18	17	17	18	16	18	17	17	18	17	18	18	18	18	19	19	18	18	17	16	15	15	17	16	16	19	18	16	18	18	19	19	19	16	17	18

L001 - [24]
L002 - [29]
L003 - [2]
L004 - [34]
L005 - [40]
L006 - [5]
L007 - [31]
L008 - [32]
L009 - [23]

L010 - [13]

L011 - [14]

L012 - [38]

L013 - [4]

L014 - [25]

L015 - [11]

L016 - [8]

L017 - [27]

L018 - [12]

L019 - [18]

L020 - [19]

L021 - [17]

L022 - [10]

L023 - [7]

L024 - [35]

L025 - [6]

L026 - [22]

L027 - [28]

L028 - [3]

L029 - [37]

L030 - [36]

L031 - [15]

L032 - [9]

L033 - [1]

L034 - [30]

L035 - [33]

L036 - [39]

L037 - [26]

L038 - [21]

L039 - [16]

L040 - [20]

Table S8 General characteristics of the selected studies.

Objective	General Strategy	Number (in vitro)	Number (*in vivo*)	Reference
Develop wound dressings containing chitosan as a biodegradable matrix, silver nanoparticles as an antimicrobial agent, calcium alginate nanoparticles as a hemostatic agent, and fresh blood to supply growth factors for chronic diabetic wound healing.	Chitosan-based hydrogel incorporates silver nanoparticles (AgNP) and lignite nanoparticles.	5	4	[24]
Produce chitosan-alginate (CA) membranes containing docosahexaenoic acid (DHA) and mesenchymal stem cells (MSCs) in order to investigate their antibacterial and antibiofilm activities against burn infections caused by Pseudomonas aeruginosa.	Chitosan-alginate-based membrane with docosahexaenoic acid (DHA) and mesenchymal stem cells (MSCs) for burn infections.	4	4	[29]
Evaluate the physical, mechanical, degradation, and cytocompatibility properties of electrospun chitosan-elastin co-electrospun membranes loaded with MgP for skin wound healing applications.	Electrospun chitosan-elastin co-electrospun membranes loaded with MgP.	13	-	[2]
Investigate the microwave-enabled physically cross-linked polymer blend films alone and in combination with modified-chitosan curcumin nanoparticles to facilitate skin tissue regeneration following 2nd degree burn wounds in animals.	Cross-linked polymer blend films alone and in combination with modified-chitosan curcumin nanoparticles.	-	4	[34]
Design, fabricate, and explore a new type of chitosan-based heterogeneous composite hydrogel containing PFC emulsions (PEs), EGF-loaded nanoparticles (ENPs), and the antimicrobials polyhexamethylene biguanide (PHMB) named PEENPPCH for diabetic wound treatment.	The chitosan-based heterogeneous composite hydrogel containing PFC emulsions (PEs), EGF-loaded nanoparticles (ENPs), and the antimicrobials polyhexamethylene biguanide (PHMB) named PEENPPCH.	15	6	[40]
PVA and Chitosan allow the incorporation of bioactive agents due to their high surface-area-to-volume ratio. The interesting point was incorporating usnic acid into the structure as a natural and suitable alternative for burn wound treatment that avoids improper or overuse of antibiotics and other invasive biomolecules.	Electrospun Nanofibrous Mesh Based on PVA, Chitosan, and Usnic Acid for Applications in Wound Healing.	4	-	[5]
A combination of Polycaprolactone (PCL), chitosan (CH), and the internal layer of oak fruit (Jaft) is used to incorporate the mechanical properties of synthetic polymers, biological properties of natural polymers, and the antibacterial activity of Jaft.	A combination of polycaprolactone (PCL), chitosan (CH), and the internal layer of oak fruit (jaft) is needed.	7	3	[31]
Develop a drug-delivery wound dressing by incorporation of mequinol into the matrix of electrospun chitosan/carboxymethyl cellulose (CMC)-based scaffolds.	Incorporation of mequinol into the matrix of electrospun chitosan/carboxymethyl cellulose (CMC)-based scaffolds.	13	3	[32]

Promote wound healing with a new type of wound dressing made with a mixing of oxidized hyaluronic acid (OHA) and succinyl chitosan (SCS) for diabetes. An ideal dressing should protect the wound from infection, provide a moist wound environment to the wound area, and promote cell growth and tissue regeneration.	Mixing of oxidized hyaluronic acid (OHA) and succinyl chitosan (SCS).	5	5	[23]
Promote wound healing in patients with diabetes with the use of wound intrinsic cross-linking of bioactive maleylated chitosan/thiolated hyaluronan (mCH/tHA) multilayer coatings on poly(L-lactic acid) (PLLA) nanofibrous mats (P-mCH/ tHA)that not only provide physical protection but also provide a favorable microenvironment for healing at the for sustained release of insulin (IN) and compared with pure PLLA and PLLA mats coated with native CH/HA multilayers (P-CH/HA).	Bioactive maleylated chitosan/thiolated hyaluronan (mCH/tHA) multilayer coatings on poly(L-lactic acid) (PLLA) nanofibrous mats (P-mCH/ tHA).	5	5	[13]
Test the efficacy of Bletilla striata polysaccharide (BSP), carboxymethyl chitosan (CMC), baicalin (BA), and silver titanate (ST) in wound dressings to fight infection, promote healing, and provide superior biocompatibility.	Bletilla striata polysaccharide (BSP), carboxymethyl chitosan (CMC), baicalin (BA), and silver titanate (ST) in a wound dressing.	3	4	[14]
Develop a nanocomposite scaffold composed of chitosan (CS), poly (vinyl alcohol) (PVA), and phytogenic iron oxide nanoparticles (FeO NPs) for accelerated anemia-associated diabetic wound healing. The aqueous leaves extract of Pinus densiflora (PD) was utilized to synthesize iron oxide nanoparticles (FeO NPs).	Nanocomposite scaffold composed of chitosan (CS), poly (vinyl alcohol) (PVA), and photogenic iron oxide nanoparticles (FeO NPs)	26	-	[38]
Prepare quaternary chitosan-based nanofibers as bioabsorbable wound dressings. To this aim, fully biodegradable chitosan/N, N, N-trimethyl chitosan (TMC) nanofibers were designed and prepared via electrospinning, using poly(ethylene glycol) as a sacrificial additive.	Fully biodegradable chitosan/N, N, N-trimethyl chitosan (TMC) nanofibers.	4	4	[4]
Explore the potential of silk-based hydrogels for diabetic wound healing, aiming to leverage the natural properties of silk, including slow biodegradation, superior mechanical characteristics, and biocompatibility, to develop an effective wound-healing material, formulating a hydrogel that combines silk with chitosan–alginate beads, dextrin, and recombinant human epidermal growth factor.	Hydrogel that combines silk with chitosan–alginate beads, dextrin, and recombinant human epidermal growth factor.	-	6	[25]
Prepare a piezoelectric and photothermal dual functional film and realize the combination of heat and electrical stimulation therapy for wound healing.	Piezoelectric and photothermal dual functional film.	-	6	[11]
Provide a new and innovative wound care product that reduces inflammation, clears infection, and improves healing in an animal model of pressure ulcers in diabetic rats by using ointment, hydrogel, and nanofiber dressings that were synthesized using 5% turmeric, 1% oregano, and 1% chitosan nanoparticles.	Ointment, hydrogel, and nanofiber dressings were synthesized using 5% turmeric, 1% oregano, and 1% chitosan nanoparticles.	4	5	[8]

The study aims to develop L-glutamic acid (LG) loaded chitosan (CS) hydrogels to treat diabetic wounds.	L-glutamic acid (LG) loaded chitosan (CS) hydrogels	7	3	[27]
This paper aims to evaluate the wound-healing activity of the CMC-COP sponges. In vitro tests were performed in rabbits, including cell viability scratch wound healing and scald wound healing experiments.	CMC-COP sponges.	8	4	[12]
This study aimed to improve the protein delivery performance of polyester nanofibers by rationally designing a particle preloading method. Positively charged chitosan nanoparticles (CNPs) were used as carriers to adsorb negatively charged proteins in mild conditions and as primary barriers for protein release.	Protein delivery performance of polyester nanofibers by charged chitosan nanoparticles (CNPs).	5	2	[18]
Fabricate a waterproof and breathable composite liquid dressing (CLD) that forms a barrier to bacteria and shortens the healing time of diabetic rat skin ulcers.	Waterproof and breathable composite liquid dressing (CLD).	12	5	[19]
Loading isolated exosomes derived from gingival mesenchymal stem cells (GMSCs) to the chitosan/silk hydrogel sponge to evaluate the effects of this novel non-invasive method on skin defects in diabetic rats.	Chitosan/silk hydrogel sponge loaded with isolated exosomes derived from gingival mesenchymal stem cells (GMSCs)	4	3	[17]
Investigate the efficacy of amnion and collagen-based hydrogels on cutaneous burn wound healing in rats with covering membranes.	Amnion and collagen-based hydrogels.	17	3	[10]
Develop an active wound healing by integrating *P. granatum* peel crude extract (PGPC), ethyl acetate fraction (PGPEA), and their silver nanoforms (Ag NPs) along with methacrylate chitosan hydrogel.	*P. granatum* peel crude extract (PGPC), ethyl acetate fraction (PGPEA), and their silver nanoforms (Ag NPs) along with methacrylated chitosan hydrogel.	24	4	[7]
The present study aims to see the effects of nanofiber mats composed of a combination of chitosan, polyvinyl alcohol (PVA), and Zinc oxide (ZnO) as a practical option for faster healing of diabetic wounds due to the wound-healing activities of chitosan-PVA nanofibers and antibacterial properties of ZnO.	Nanofiber mats combine chitosan, polyvinyl alcohol (PVA), and Zinc oxide (ZnO).	4	3	[35]
This study aims to investigate the potential applications of wound dressing materials incorporating herbal extracts, specifically *Hypericum perforatum* extract (HPE) in alginate films.	Wound dressing materials incorporate herbal extracts, specifically Hypericum perforatum extract (HPE), in alginate films.	20	-	[6]
The objective of this study is to develop an improved wound dressing material focusing on fabricating porous keratin-chitosan/n-ZnO nanocomposite (KCBZNs) bandages by incorporating nano-ZnO into a keratin-chitosan hydrogel.	Porous keratin-chitosan/n-ZnO nanocomposite (KCBZNs) bandages by incorporating nano-ZnO into a keratin-chitosan hydrogel.	3	3	[22]

This study aims to design a hybrid three-dimensional scaffold (CPCP) based on collagen/chitosan modified by PEG/PCL composite that can imitate the differentiation pattern of both epidermis/dermis cells via mimicking the structure and function of human skin.	Hybrid three-dimensional scaffold (CPCP) based on collagen/chitosan modified by PEG/PCL composite	5	-	[28]
The main goal of this study is to produce a layer-by-layer self-assembled siRNA-loaded gold nanoparticles with two different outer layers—Chitosan (AuNP@CS) and Poly L-arginine (AuNP@PLA)	layer-by-layer self-assembled siRNA-loaded gold nanoparticles with two different outer layers—Chitosan (AuNP@CS) and Poly L-arginine (AuNP@PLA)	23	-	[3]
The objective of this study is to evaluate the effectiveness of a novel combinatorial therapy in the treatment of diabetic foot ulcers. The study focuses on developing and assessing a nanoemulgel, a combination of oregano essential oil nanoemulsion and low-level laser therapy, in conjunction with a hydrogel-based healing patch.	Nanoemulgel, a combination of oregano essential oil nanoemulsion and low-level laser therapy, in conjunction with a hydrogel-based healing patch.	7	4	[37]
This study aims to develop a Chitosan-Polyvinyl alcohol (CS-PVA) based hydrogel containing an oxygen-releasing nanoparticle, calcium peroxide (CPO).	Chitosan-polyvinyl alcohol (CS-PVA) based hydrogel containing an oxygen-releasing nanoparticle, calcium peroxide (CPO).	40	2	[36]
The objective of this study is to fabricate its composites with TiO2 nanoparticles in order to enhance the efficacy of HpPVP hydrogel as a wound dressing material	HpPVP hydrogel enhanced with TiO2 nanoparticles	13	3	[15]
This study aims to develop wound dressings from a combination of sodium alginate and Poloxamer-407. B02, B08, and B13 are loaded with a combination of ZnO NPs and ciprofloxacin or ciprofloxacin that can absorb excess exudates, prevent bacterial infections, provide a soothing effect, and are easy to remove without causing pain.	Wound dressings from a combination of sodium alginate and Poloxamer-407. B02, B08, and B13 are loaded with ZnO NPs and ciprofloxacin or ciprofloxacin.	60	-	[9]
This study aims to design and characterize a chitosan film containing ATRA loaded in SLN and evaluate its efficacy in promoting wound healing in a diabetic mice model. Therefore, this study was the first to evaluate chitosan film containing SLN-ATRA for treating diabetic wounds.	Chitosan film containing all-trans retinoic acid (ATRA) loaded in solid lipid particles (SLN)	3	2	[1]
A sodium carboxymethyl chitosan-recombinant human epidermal growth factor conjugate (NaCMCh-rhEGF) was developed to identify improved therapeutics. Conjugation is believed to protect rhEGF against proteolysis and mediate rhEGF release by α-amylase.	Chitosan-based hydrogel as a carrier for NaCMCh-rhEGF nanoparticles	17	5	[30]

This study aims to use DsiRNA-loaded AuNPs, synthesized using CLRE and HLRE, and incorporate them into thermoresponsive gels prepared from pluronic (PF-127), a polymer that converts into gel at body temperature. Then, PF-127 is used to prepare the thermoresponsive gel because it improves drug permeation through the skin.	Dual therapy consists of Dicer subtracting small interfering RNA (DsiRNA) and AuNPs incorporated into a thermoresponsive gel made of pluronic and polyethylene glycol.	60	-	[33]
The goal of this study is to improve the efficiency of diabetic wound healing through a synthetic chitosan-based composite hydrogel named SNPECHG incorporating silver ions (Ag+) and nanoparticle-encapsulated epidermal growth factor (EGF).	Synthetic chitosan-based composite hydrogel named SNPECHG incorporating silver ions (Ag+) and nanoparticle-encapsulated epidermal growth factor (EGF)	146	6	[39]
The current study aimed to formulate an epidermal growth factor loaded with chitosan nanoparticles impregnated with thermos-responsive injectable hydrogel with protease inhibitor.	Epidermal Growth Factor loaded Chitosan nanoparticle impregnated with thermos-responsive injectable hydrogel with protease inhibitor	46	4	[26]
This study aims to produce porous PLA nanofiber membranes with angiogenic, anti-inflammatory, and antibacterial properties with possible applications in diabetic wound healing was developed.	porous poly (L-lactic acid) nanofiber membranes with sulfated chitosan (SCS) combined with polydopamine-gentamicin (PDA-GS) modified onto porous PLA nanofiber membrane surfaces	32	-	[21]
The goal of this study is to encapsulate mupirocin (MP) and cerium oxide nanoparticles (CeNPs) into a polyvinyl alcohol/chitosan (PVA/CS) polymer and then fabricate a PVA/chitosan nanofiber membrane wound dressing using electrostatic spinning,	PVA/chitosan nanofiber dressing with encapsulated mupirocin (MP) and cerium oxide nanoparticles (CeNPs)	59	4	[16]
This study aims to develop a potential wound dressing by incorporating fumaria officinalis extract-loaded chitosan nanoparticles (FOE-CHNPs) into calcium alginate hydrogel. Then, evaluate its microarchitecture, cytotoxicity, cell migration activity, cytoprotective potential, porosity, in vitro anti-inflammatory activity, and drug release profile.	Wound dressing developed by incorporating fumaria officinalis extract-loaded chitosan nanoparticles (FOE-CHNPs) into calcium alginate hydrogel	12	5	[20]

The abbreviations that appear throughout the table are those used in each study.

Table S9 The highest ultimate tensile strength values are presented in the studies conducting this analysis.

Material used	Highest final tensile strength presented in the study (tensile test) (kPa)	Reference
Chitosan-Elastin (CE)	50	[2]
Sodium Alginate, Pectin, Glycerol, Tween-80 and Distilled Water Blend (5 min treated)	9940 ± 80	[34]
chitosan/carboxymethyl cellulose (CMC)/0.3% mequinol	1.810	[32]
P-chitosan(CH)/hyaluronan(HA)	1530 ± 275	[13]
Chitosan (CS) / N, N, N-trimethyl chitosan (TMC) / poly(ethylene oxide) (PEO) NCT19	12650	[4]
Polydopamine-coated (8mg/mL) chitosan film (CM@DA)	18.8 ± 0.7	[11]
keratin-chitosan/n-ZnO nanocomposite bandages (KCBNs)	330	[22]
collagen / Polyethylene glycol (PEG) / Chitosan/poly (ε-caprolactone) (PCL)	14000	[28]

The abbreviations that appear throughout the table are those used in each study.

Table S10 Maximum membrane length values are presented in this analysis's studies.

Material used	Maximum membrane extension (tensile test) (%)	Reference
Chitosan	10	[2]
Sodium Alginate, Pectin, Glycerol, Tween-80 and Distilled Water Blend (5 min treated)	66.66 ± 3.29	[34]
chitosan/carboxymethyl cellulose (CMC)/0.3% mequinol	95	[32]
Poly (L-lactic acid) (PLLA)	56.80 ± 12.11	[13]
Chitosan (CS) / N, N, N-trimethyl chitosan (TMC) / poly(ethylene oxide) (PEO) NCT7	17.2	[4]
Polydopamine-coated (8mg/mL) chitosan film (CM@DA)	11	[11]
keratin-chitosan/n-ZnO nanocomposite bandages (KCBNs)	63	[22]
collagen / Polyethylene glycol (PEG) / Chitosan/poly (ε-caprolactone) (PCL)	245	[28]

The abbreviations that appear throughout the table are those used in each study.

Table S11 Contact angle values at t1 in the studies performed in this analysis.

Material used	Contact angle at t1 (°)	Reference
Chitosan (C)	105.90 ± 12.15°	[2]
Chitosan-Elastin (CE)	49.51 ± 10.08°	
Chitosan-MgP (CMg)	114.84 ± 13.07°	
Chitosan-Elastin-MgP (CEMg)	52.72 ± 20.17°	
PCL	124.7 ± 1.17 °	[31]
PCL/CH	113.2 ± 3.9°;	
PCL/Jaft	96.89 ± 1.3°	
PCL/CH/Jaft	109.2 ± 1.8°	
Chitosan/CMC/0.3% mequinol scaffold	64.13 ± 5.29°	[32]
Chitosan/CMC scaffold	73.86 ± 6.75°	
P-CH/HÁ	27.6 ± 6.2°	[13]
P-mCH/tHA nanofibrous mats	27.6 ± 2.3°	
Poly(lactic acid) (PLA)/ Bovine serum albumin (BSA) loaded chitosan nanoparticles (CNP) nanofiber mats	130 ± 3°	[18]
Collagen/Polyethylene glycol (PEG)/Chitosan-poly(ε-caprolactone) (PCL)/Scaffold (CPCP)	60.15°	[28]
PEG/Chi/PCL (PCP)	68.40°	
Collagen/chitosan (CC)	65.43°	
Polyethylene glycol (PEG)/ Chitosan-poly(ε-caprolactone) (PCL) (PEPC)	105.87°	
Hydrogel-Glycerol (HG/G);	Not Informed	[37]
Nanoemulgel (NEG);		
Celulose nanoemulgel (C-NEG).		
PLA nanofiber membrane	110°	[21]
PLA nanofiber membrane + SCS coating	39°	
PVA-CS	46.75°	[16]
PVA-CS-MP	40.47°	
PVA-CS-CeNPs	60.94°	
PVA-CS-CeNPs-MP	50.73°	

The abbreviations that appear throughout the table are those used in each study.

Table S12. Cell viability parameters in the studies that carried out this analysis.

Used material	Cell utilized	Cells/well	Duration (days)	Cell Viability Effects	Reference
chitosan/alginate (CA) chitosan/alginate-docosahexaenoic acid (CA-DHA)	Mesenchymal stem cells (MSC)	1.5×10^5	3	No significant differences were observed in the proliferation index of the cells exposed to the different membranes.	[29]
Chitosan (C) Chitosan-Elastin (CE) Chitosan-MgP (CMg) Chitosan-Elastin-MgP (CEMg) Magnesium-phosphate particles (MgP)	NIH3T3 Fibroblasts	3×10^4 1×10^4	5 3	The C and CMg membranes showed a low number of viable cells on the first day, with a minimal increase in viable cells over the five days of culture. The CE and CEMg membranes had a higher number of viable cells on the first day and increased the number of viable cells stained over the 5 days of culture. From a concentration of 0.1 ng/mL to 0.1 mg/mL, cytocompatibility increased. At a concentration of 1 mg/mL, there was a sign of cytotoxicity on the first day, which was circumvented on the third day. There was a cytotoxicity signal for the 10 mg/mL concentration on the first and third days.	[2]
Chitosan-based heterogeneous composite hydrogel encapsulating perfluorocarbon emulsions, epidermal growth factor (EGF)-loaded chitosan nanoparticles, and polyhexamethylene biguanide (PHMB) named $P_EE_{NP}PCH$	KERTr cells	Not informed	1	All groups showed viability >90%, indicating that the cytotoxicity of PEENPPCH containing ≤4000 ppm PHMB was negligible.	[40]
5% Polyvinyl alcohol (PVA) 2%Chitosan (CS) Usnic Acid (UA)	Amniotic fluid stem cells (AFSC)	3×10^3	3	The 5%PVA_2%CS group had values similar to those of the control at the start, and over time, a brief increase was recorded, followed by a considerable decrease. The 5%PVA_2%CS_UA group, on the other hand, had values similar to those of the control group at the start and showed extraordinary results after 48 and 72 hours, increasing cell viability by almost 30 percent compared to the control group.	[5]
5% Polyvinyl alcoho (PVA) 2%Chitosan (CS).					

Polycaprolactone (PCL) Polycaprolactone (PCL)/Chitosan (CH) Polycaprolactone (PCL)/Jaft Polycaprolactone (PCL)/Chitosan (CH)/Jaft	Fibroblast cells	1 x 10^5	3	Cell viability increased in all groups of scaffolds compared to the control. PCL/CH scaffolds have higher cell viability compared to PCL scaffolds. PCL/Jaft can increase biocompatibility compared to the control group and PCL. PCL/CH/Jaft supports showed increased attachment, proliferation, and preservation of their natural shape on the PCL/CH/Jaft support.	[31]
Chitosan/CMC Chitosan/CMC/0.3%Mequinol Chitosan/CMC/0.6%Mequinol Chitosan/CMC/0.9%Mequinol	L929 cells	Not informed	7	On the first day, no statistically significant difference existed between the groups studied. On the third and seventh day, relative cell viability in the scaffolds loaded with 0.3% mequinol was significantly higher than in the other formulations. The relative cell viability for the chitosan/CMC/0.3%Mequinol scaffolds on days 3 and 7 was measured at 127.59 ± 13.95% and 125.64 ± 9.77%, respectively.	[32]
Same concentration of hydrogels: Gel-1, Gel-2, Gel-3, Gel-4, Gel-5, ILM-Gel-4, EGF-Gel-4 and ILM-EGF-Gel-4; ILM-Gel-4 at different concentrations: 50, 100, 200, 400, and 800 μg/mL.	3T3 cells	5 x 10^4	2	The cell viability of all the samples is close to or above 100 percent, indicating the excellent cell compatibility and low toxicity of the composite hydrogels prepared. No significant differences were found between the Gel-4 and ILM-Gel-4 samples after cell culture for 48 hours.	[23]
Baicalin (BA), silver titanate (ST), *Bletilla striata* polysaccharide (BSP), and Carboxymethyl chitosan (CMC) (BA/ST/BSP/CMC)	Lung fibroblast cells (L929 cells)	5 x 10^3	1	There was no significant cytotoxicity of BA/ST/BSP/CMC at varying concentrations (1, 10, 100, and 1000 μg/mL) against L929 cells after 24 h incubation.	[14]
Pinus densiflora (PD)-FeO NPs incorporated with Chitosan (CS)/ poly vinyl alcohol (PVA)	Human embryonic kidney cell line (HEK-293 cells)	Not informed	1	PD-FeO NPs incorporated with CS/PVA did not cause cytotoxicity or increased cell viability.	[38]
NC NCT3 NCT7 NCT19	Normal dermal human fibroblasts (NHDF)	3.5 x 10^4	7	Cell viability increased as the N, N, N-trimethyl chitosan (TMC) content decreased from 60 to 90 percent. According to the ISO standard for medical devices (10993-5:2009), samples with cell viability >70% can be safely used as medical devices in contact with cells, so NCT 7 and NCT19 are suitable for these bioapplications.	[4]
No treatment; Alginate + Ointment (10 and 20 mg/mL) Hydrogel (10 and 20 mg/mL) Nanofiber (10 and 20 mg/mL)	L929 cells	5 x 10^3	1	The Ointment and hydrogel significantly increased cell viability compared to the untreated control (negative control). Silver alginate was significantly toxic, causing 90 percent cell death. The nanofibres also showed a 50% reduction in cell survival rate in a concentration-dependent manner.	[8]

Control Loaded Chitosan (CS) Loaded Chitosan (CS) + L-glutamic acid (LG) 0.25% Loaded Chitosan (CS) + L-glutamic acid (LG) 0.50% Loaded Chitosan (CS) + L-glutamic acid (LG) 1%	Fibroblast cell lines (NIH 3T3)	5×10^4	3	Compared to the control (tissue culture plate), the CS and CS + LG hydrogels showed no significant difference in cell viability. Analysis of the images stained with DAPI showed that the CS + LG hydrogels had an almost similar number of cells compared to the CS hydrogel. The CS and CS + LG hydrogels showed no cytotoxicity compared to the control.	[27]
carboxymethyl chitosan (CMC) carboxymethyl chitosan (CMC) - collagen peptides (COP12) carboxymethyl chitosan (CMC) - collagen peptides (COP26) carboxymethyl chitosan (CMC) - collagen peptides (COP58)	L929 cells	6×10^3	Not informed	Cell viability of approximately >80% was observed for the CMC-COP samples (concentrations between 25-150 μg/mL). At 200 μg/mL values, viability fell to between 55-70%, showing a certain degree of loss in cytocompatibility.	[12]
polylactic acid (PLA) / Bovine serum albumin fraction V (BSA) loaded with chitosan nanoparticles nanofibers.	L929 mouse fibroblast cells	5×10^3	1	The nanofibres showed no apparent cytotoxicity, with all the concentrations tested having viability values of >80%.	[18]
Negative control Amnion Gel; Collagen Gel Amnion Collagen Gel Amnion Collagen Gel-Membrane.	Brine shrimp cells	Not informed	2	The Brine shrimp lethality bioassay shows mortality percentages of <10% for all tests.	[10]
MCs hydrogel PGPC extract PGPC extract/hydrogel Ag-NPs PGPC Ag-NPs PGPC/hydrogel PGPEA fraction PGPEA fraction/hydrogel Ag-NPs PGPEA Ag-NPs PGPEA/hydrogel Doxorubicin	Human normal cell line (HFB4)	5×10^3	1	The cytotoxicity was low in PGPC and PGPEA. On the other hand, the PGPEA and PGPC of Ag NPs were relatively high. However, all active compounds showed acceptable cytotoxicity after encapsulation into the hydrogels.	[7]

Alginate film (Al) Hypericum perforatum extract incorporated alginate films (HPE/Al)	L929 cells Fibroblast cell line	1 x 10^4	Not informed		The results show that Al and Al/HPE films have no cytotoxic effects on L929 cells. In addition, all film compositions showed a proliferative effect on the fibroblast cell line. There was a decrease in cell viability as the concentration of the extract increased, but no cytotoxic effect was observed at all the concentrations studied. The lowest cell viability was 85% ± 7.2 at the 20 μg/mL extract concentration.	[6]
AuNPs@CS, AuNPs@PLA, RNAiMAX, jetPRIME®, and Naked siRNA, all at different concentrations (5, 10, 20, 30, and 40 nM of siRNA) AuNPs@CS, AuNPs@PLA, RNAiMAX, jetPRIME®, and Naked siRNA (30 nM of siRNA) DES at different concentrations (5, 10, 15, 20, 25, and 30 μM) DES at different concentrations (0, 10, and 20 μM)	NIH-3T3 murine fibroblast cells	8 x 10^3	0.167	0.833	Toxicity increases with increasing NP concentration, with AuNP@PLA slightly less toxic than AuNP@CS. For the same concentrations of siRNA, Lipofectamine® RNAiMAX, jetPRIME®, and naked siRNA did not induce any significant toxic effects. From there, considering 30 percent loss of metabolic activity as an acceptable level of cytotoxicity, 30 nM was selected as the highest concentration allowed. Treatment of NIH-3T3 cells with DES also caused concentration-dependent toxicity, from which 20 μM DES was selected as the maximum concentration. The effect of combining NP treatment with DES on cell viability was also evaluated. The addition of DES reduced viability in a concentration-dependent manner compared to NPs or transfection reagents alone but was generally well tolerated in the concentration range applied (10 and 20 μM) for all nanoformulations.	[3]
NEG	NIH/3T3 cells	1.25 x 10^4	1		The cells were viable under NEG at a 128 μg/mL drug concentration. The manufactured gel and LLLT showed no toxicity to normal skin fibroblasts. Cells exposed to NEG exhibited a viability rate of 75.54 ± 1.23 percent after 24 hours. A non-significant decline in cell viability was observed compared to untreated cells (82.78 ± 0.91%), which may be a result of the presence of impurities in the Tween 20 or acetic acid in the NEG, which was involved in the preparation of CS and NE.	[37]
Free rhEGF Conjugated NaCMCh-rhEGF	Mouse fibroblasts (L929)	2.5 x 10^3	3		This test compares the activity of rhEGF and its conjugated form against proteases. It was confirmed that the conjugation of rhEGF with NaCMCh significantly increased its stability against proteolytic degradation. The differences between these two groups were statistically significant at all time points ($p < 0.05$). The biological activity of rhEGF in its conjugated form was assessed by evaluating cell proliferation, and there was a significant difference in cell proliferation between the rhEGF group and the control group ($p < 0.05$).	[30]

AuNPs-CLRE (0.06; 0.125; 0.25; 0.5; 1 mg/mL) AuNPs-HLRE (0.06; 0.125; 0.25; 0.5; 1 mg/mL)	Human dermal fibroblasts (HDFs)	1×10^4	3	Higher concentrations of AuNPs reduced the cell viability of HDFs more than lower concentrations ($p < 0.01$). This effect was more prominent for AuNPs-CLRE than for -HLRE. The cytotoxicity of AuNPs was reported to be concentration-dependent, regardless of the extract used as a reducing agent in synthesizing AuNPs. For example, the cytotoxicity of AuNPs synthesized from pyomelanin purified from Yarrowia lipolytica (a type of yeast) also increased as the concentration of AuNPs was increased from 5 to 160 µg/mL (Tahar et al., 2019). Furthermore, the toxic effect of AuNPs-CLRE and -HLRE may be transient, as the viability of HDFs increased after prolonged incubation at 48 and 72 h, except for high concentrations of AuNPs-HLRE, as cell viability decreased slightly from 68% ± 18 to 59% ± 12 and 74% ± 21 to 65% ± 9 for 0.5 and 1 mg/mL AuNPs, respectively.	[33]
SNPECHG	NIH/3T3 cells KERTr cells	5×10^5	2	The results showed that the cytotoxicities of SNPECHG to NIH/3T3 and KERTr cells were increased in a dose-dependent manner, in which cell viability could be maintained at >90 percent when the concentration of Ag+ in the HTM was <6 mg L-1 (HTM prepared using SNPECHG with ≤24-mM Ag+), but decreased dramatically to <60 percent (P <0. 05) when the concentration of Ag+ in the HTM was raised to >7.5 mg L-1 (HTM prepared using SNPECHG with ≥48-mM Ag+). 05) when the concentration of Ag+ in the HTM was raised to >7.5 mg L-1 (HTM prepared using SNPECHG with ≥48-mM Ag+). These results showed that the ≤24 mM of Ag+ in SNPECHG was not toxic to the cells.	[39]
C-EGF-D IHG EGF-CSNPs	NIH 3T3 fibroblasts cells	-	1	Cytotoxicity tests revealed that the formulation under study had no adverse effects on the cell lines tested. Compared to the control group, C-EGF-D IHG produced significant cell proliferation, which EGF-CSNPs followed. The results indicate that C-EGF-D IHG was biocompatible, as evidenced by the constant growth of fibroblasts. The biopolymer (CS) presence was responsible for the increase in cell proliferation observed in both participants. A significant change was observed in the C-EGF-D IHG group, which can be attributed to the mitogenic activity of EGF associated with the phosphorylation of MAP kinases (MAPKs) P42/44. We confirmed that EGF has mitogenic effects on NIH 3T3 fibroblasts, conjunctival fibroblasts, and airway epithelial cells. The biopolymer is also cell-friendly and biocompatible, and CS allows for favorable cell growth.	[26]
PLA PLA/SCS PLA/SCS/PDA PLA/SCS/PDA-GS	Mouse macrophages cell line (Raw 264.7)	5×10^4	3	All PLA-based porous nanofibres were suitable for cell growth, and SCS may benefit cell proliferation. The following cell viability values were presented: PLA: 99%; PLA/SCS: 123%; PLA/SCS/PDA: 103%; PLA/SCS/PDA-GS: 102.8%.	[21]

PVA-CS PVA-CS-CeNPs PVA-CS-MP PVA-CS-CeNPs-MP	L929 cells	1 x 10^4	1	The activity of L929 cells was not affected until the PM concentration reached 2.5 mg/mL (2.5 %) and the concentration of CeNPs reached 1.5 mg/mL (1.5 %). In particular, the addition of both treatments at the same time did not cause cytotoxicity in the cells when appropriate concentrations were used	[16]
FOE10%-CHNPs/calcium alginate FOE20%-CHNPs/calcium alginate CHNPs/calcium alginate	L929 cells	1 x 10^4	7	On day 7, the FOE20%-CHNPs/calcium alginate group had significantly higher cell viability than the other groups. All the groups with values close to or above 100 percent	[20]

The abbreviations that appear throughout the table are those used in each study.

Table S13 Cumulative release values (%) of substances in the studies that carried out this analysis.

Material used	Released substance	Release médium	Duration (hours)	Cumulative Release (%)	Reference
Chitosan/Ca-AlgNps/AgNPs	Ag ion	Phosphate Buffer Saline (PBS)	72	74.8	[24]
C; PBS; CMg; CEMg	Mg ion	Phosphate Buffer Saline (PBS)	168	Not informed	[2]
P_EE_{NP}PCH	PHMB EGF	PBS DI water	48	PHMB (PBS): 38 PHMB (DI H2O): 7,5 EGF (PBS): 29,9 EGF (DI H2O): 0	[40]
chitosan/CMC/0.3% mequinol scaffolds	Mequinol	Phosphate Buffer Saline (PBS)	120	95	[32]
PEG-b-P(PBA-co-St)	Insulin 100mg/dL Insulin 200mg/dL Insulin 400mg/dL	Phosphate Buffer Saline (PBS)	48	27 39 67	[23]
Original and multilayer-modified PLLA mats	Insulin	Phosphate Buffer Saline (PBS)	216	P_IN: 96.4 CH/HA 76 CH/tHA 62.5	[13]
CS/PVA-PD-FeO NPs Sponge	Iron	Phosphate Buffer Saline (PBS)	24	14.2	[38]
CS + LG hydrogels	L-glutamic acid	Phosphate Buffer Saline (PBS)	96	29	[27]
BSA@CNP nanofiber	Proteins	Phosphate Buffer Saline (PBS)	336	87	[18]
PLA/BSA@CNP nanofiber			672	45	
Waterproof breathable film	Chitosan	Saline Solution	336	18.3	[19]
AuNPs@CS AuNPs@PLA	siRNA	HEPES buffer	168	40 31	[3]
Nanoemulsion Nanoemulgel (NEG)	Oregano essential oil (OEO)	Phosphate Buffer Saline (PBS)	8	82.44 ± 1.77 42.99 ± 1.72	[37]
CS-PVA CS-PVA-CPO-5 CS-PVA-CPO-1	Oxygen	Phosphate Buffer Saline (PBS)	120	0 8.8 10	[36]

ATRA from solution Chitosan film + 50 % free ATRA + 50 % encapsulated SLN-ATRA Chitosan film + SLN-ATRA 100 % encapsulated	All-trans retinoic acid (ATRA)	Phosphate buffered saline (PBS): Ethanol (90:10)	24	56.26 ± 3 3.94 ± 0.9 1.77 ± 0.6	[1]
CMCh based hydrogel Low MW chitosan-based hydrogel Medium MW chitosan-based hydrogel	Growth factor rhEGF	Phosphate buffer (pH = 7.4)	48	79.1 ± 6.3 31.4 ± 4.9 9.2 ± 2.8	[30]
AuNPs-CLRE F6 AuNPs-CLRE F7 AuNPs-CLRE F8 AuNPs-HLRE F9 AuNPs-HLRE F10 AuNPs-HLRE F11	AuNPs DsiRNA	Phosphate Buffer Saline (PBS)	8	Not informed	[33]
SNPECHG	Ag+ CNP-entrapped EGF	Phosphate-buffered saline (PBS) Phosphate buffered saline (PBS) + NaCl DI H2O	48	Not informed	[39]
EGF-CSNPS C-EGF-D IHG	NPS AVG HG AVG DOX	Phosphate buffer	120	97 78 100	[26]
PLA/SCS/PDA-GS nanofiber membranes	GS	Dulbecco's phosphate-buffered saline (DPBS)	168	Not informed	[21]
PVA-CS-based membranes	MP CeNPs	Phosphate-buffered saline (PBS)	168	58 17	[16]
FOE10%-CHNPs/calcium alginate hydrogel FOE20%-CHNPs/calcium alginate hydrogel	FEO-CHNPs	Phosphate-buffered saline (PBS)	48	61.58 ± 3.04 70.24 ± 4.43	[20]

The abbreviations that appear throughout the table are those used in each study.

Table S14. Results of the degradation tests in the studies that carried out this analysis.

Evaluated substance	The substance of the medium used	Duration (days)	Degradation test results	Reference
Chitosan (C) Chitosan-Elastin (CE) Chitosan-MgP (CMg) Chitosan-Elastin-MgP (CEMg)	simulated body fluid	28	All the membranes showed significant reductions in mass during the four-week test period. During the initial two weeks, elastin membranes tended to show more mass loss than non-elastin membranes, especially after the first two weeks. CE and CEMg membranes showed approximately 70 percent mass loss by the fourth week compared to only 50 percent loss for C and CMg membranes.	[2]
Blank chitosan hydrogel (CH) $P_EE_{NP}PCH$	PBS	7	The weight loss of Blank CH was 4.83 ± 1.9 percent, while that of PEENPPCH was 9.63 ± 2.6 percent after seven days.	[40]
PCL PCL/CH PCL/Jaft PCL/CH/Jaft	PBS	21	The results showed that the remaining weight of the PCL, PCL/CH, PCL/Jaft, and PCL/CH/Jaft scaffolds after 1 day was 99.3 ± 1.1; 96 ± 1; 98.3 ± 1.1 and 95 ± 2%, respectively. After 21 days, the remaining weight of the scaffolding reached 78.3 ± 3.5, 68.3 ± 3, 77 ± 4.6 and 67.7 ± 1.5%, respectively. Adding CH improved the scaffolds' degradation characteristics at each time point. On the other hand, jaft did not cause degradation in each period.	[31]
Gel-1 Gel-2 Gel-3 Gel-4 Gel-5 INS-Gel-4	PBS	10	All the samples show similar degradation behavior, and no significant differences exist.	[23]

P P-CH/HA P-mC/tHA	Subcutaneous implantation in fourteen-week-old male mice (C57BL/6)	14	Only a few fibroblasts grew on the PLLA mats, and the mats still maintained their structural integrity, with almost no signs of degradation. A more significant number of fibroblasts grew on P-CH/HÁ and grew all over the P-mCH/tHA. Most importantly, vascularisation was found in the tissue section with multilayer-coated mats (P-CH/HA and P-mCH/tHA), while no microvessel formation was detected in the samples with pure PLLA mats.	[13]
NC NCT19 NCT7 NCT3 NCT7	medium simulating biological fluid medium simulating the exudate over the wound healing period	7 16	Enzymatic degradation showed an increase in the biodegradation rate along the TMC content, reaching statistically significant higher values than pure Chitosan (23%-44% vs. 10%). In a medium miming the exudate's pH during the wound healing period, there was a weight loss of around 20 percent in the first 4 days, which increased slightly to 22 percent by the 14th day and rose sharply to 100 percent on the 17th day.	[4]
CS CS + LG	PBS solution containing lysozyme	20	11 and 13 percent degradation was obtained for all the hydrogels after 20 days of incubation.	[27]
Sample A (0.42 m·mol DVS and 0.0185 m·mol KPS) Sample B (0.84 m·mol DVS and 0.036 m·mol KPS) Sample C (0.84 m·mol DVS and 0.036 m·mol KPS)	Not informed	14	The samples with the highest concentration of KPS and DVS, which have the highest crosslinking density, showed the highest weight loss percentage. In detail, it was found that as the DVS content increases, there is a slight difference in degradation during the first four and seven days. After nine days, there is a drastic change in the behavior of the more crosslinked hydrogel, in which degradation increases, which can be attributed to a decrease in the high connectivity of the biopolymer chain through the cross-linker.	[7]

CPCP PCP CC PEPC	PBS solution containing lysozyme	14	The scaffolds based on natural and synthetic polymers (PEPC and CC) had a higher % degradation than the hybrid scaffolds (CPCP and PCP). A comparison of the % degradation of PEPC and CC showed that the most significant mass loss was recorded for the natural CC scaffold (remaining weight less than 38%). The presence of collagen in the structure of the CPCP scaffold led to a decrease in degradation (~4%) compared to PCP, increasing the surface available for cell proliferation and differentiation.	[28]
HG CHG NEG	PBS	28	The degradation of NEG was higher than that of HG and CHG due to the release of NE globules over time in PBS. The release of the drug created larger voids in the gel structure, leading to more excellent bond breaking, which caused a higher degradation rate of 52.19 ± 0.24%.	[37]
HpPVP HpPVP/TiO2	PBS	7	The manufactured dressings showed degradation of 24 and 27 percent (1st day), 39 and 48 percent (4th day), and 75 and 84 percent (7th day) after immersion in PBS medium, respectively.	[15]
B01 B02 B03 B09	PBS pH 5.5 PBS pH 7.4	21	B01 indicates rapid degradation of the dressing compared to other dressings. The dressings degraded at pH 5.5. The biodegradation rate of the wound dressing was more significant at pH 5.5 than at 7.4.	[9]
GF-CSNPs Lyophilized C-EGF-D IHG	PBS	2	It was confirmed that the addition of DOX and EGF-CS NPs to the hydrogel significantly increased its stability against the proteolytic degradation of EGF compared to free EGF and EGF-CS NPs.	[26]
PVA-CS PVA-CS-CeNPs PVA-CS-MP PVA-CS-MP-CeNPs	PBS	14	There were no significant differences in the remaining mass rates of the four groups of samples.	[16]

The abbreviations that appear throughout the table are those used in each study.

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