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EFFECT OF PIPERINE ON MODULATING SKIN WOUND HEALING AND AS AN ANTIMICROBIAL AGENT IN VIVO: A SYSTEMATIC REVIEW OF PRECLINICAL STUDIES

EFEITO DA PIPERINA NA MODULAÇÃO DA CICATRIZAÇÃO DE FERIDAS NA PELE E COMO AGENTE ANTIMICROBIANO IN VIVO: UMA REVISÃO SISTEMÁTICA DE ESTUDOS PRÉ-CLÍNICOS

EFECTO DE LA PIPERINA EN LA MODULACIÓN DE LA CICATRIZACIÓN DE HERIDAS CUTÁNEAS Y COMO AGENTE ANTIMICROBIANO IN VIVO: UNA REVISIÓN SISTEMÁTICA DE ESTUDIOS PRECLÍNICOS

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ABSTRACT

To analyze the healing and antimicrobial action of piperine on skin wounds induced in rodents. This is a systematic review conducted in Medline (via PubMed), Embase, Science Direct, and Web of Science. The following descriptors were used: piperine, wound healing, wounds, lesions, surgical wound, skin wound, antimicrobial, antibacterial agent, antifungal agent, antibacterial and antifungal, combined with the Boolean operators AND and OR. There were no restrictions on language or date of publication. The search resulted in 5,618 records, of which three studies were eligible for qualitative synthesis. In wounds infected with Staphylococcus aureus, the use of microemulsion hydrogel with piperine showed a 75.33% reduction on the 10th day of treatment, accompanied by a reduction in colony-forming units, preservation of tissue architecture, and a decrease in inflammatory infiltrate. In the Aspergillus fumigatus keratitis model, the application of piperine eye

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drops proved safe and reduced the clinical scores of corneal infection, fungal load, and pyroptosis markers. In excision wounds, Aloe vera gel combined with piperine achieved 80.46% retraction on the 14th day of the experiment, an effect comparable to that of sulfadiazine. The evidence indicates the potential of piperine in the treatment of skin wounds and as an antimicrobial agent. However, limitations in the consistency and quantity of studies require further investigation to confirm its efficacy and clinical safety.

KEYWORDS: Piperine. Healing. Wounds. Antifungal Agents. Anti-Bacterial Agents.

RESUMO
Analisar a ação cicatrizante e antimicrobiana da piperina em feridas cutâneas induzidas em roedores. Trata-se de uma revisão sistemática realizada nas bases Medline (via PubMed), Embase, ScienceDirect e Web of Science, sem restrição de idioma ou data de publicação. Foram utilizados os descritores piperina, cicatrização de feridas, feridas, lesões, ferida cirúrgica, ferida cutânea, antimicrobiano, agente antibacteriano, agente antifúngico, antibacteriano e antifúngico, combinados com os operadores booleanos AND e OR. A busca resultou em 5.618 registros, dos quais três estudos foram elegíveis para a síntese qualitativa. Em feridas infectadas por Staphylococcus aureus, o uso de hidrogel em microemulsão contendo piperina demonstrou retração de 75,33% no 10º dia de tratamento, acompanhada de redução das Unidades Formadoras de Colônia, preservação da arquitetura tecidual e diminuição do infiltrado inflamatório. No modelo de ceratite por Aspergillus fumigatus, a aplicação de colírio contendo piperina mostrou-se segura e reduziu os escores clínicos da infecção corneana, a carga fúngica e os marcadores de piroptose. Em feridas por excisão, o gel de Aloe vera combinado com piperina alcançou 80,46% de retração no 14º dia do experimento, efeito comparável ao da sulfadiazina. As evidências indicam o potencial da piperina no tratamento de feridas cutâneas e como agente antimicrobiano. No entanto, limitações quanto à consistência e ao número de estudos exigem investigações adicionais para confirmar sua eficácia e segurança clínica.

PALAVRAS-CHAVE: Piperina. Cicatrização. Feridas. Agentes Antifúngicos. Agentes Antibacterianos.

RESUMEN
Analizar la acción cicatrizante y antimicrobiana de la piperina en heridas cutáneas inducidas en roedores. Se trata de una revisión sistemática, realizada en Medline (a través de PubMed), Embase, Science Direct y Web of Science. Se utilizaron los descriptores: piperina, cicatrización de heridas, heridas, lesiones, herida quirúrgica, herida cutánea, antimicrobiano, agente antibacteriano, agente antifúngico, antibacteriano y antifúngico, combinados con los operadores booleanos AND y OR. Sin restricciones en cuanto al idioma o la fecha de publicación. La búsqueda dio como resultado 5618 registros, de los cuales tres estudios fueron elegibles para la síntesis cualitativa. En heridas infectadas con Staphylococcus aureus, el uso de hidrogel en microemulsión con piperina demostró una retracción del 75,33 % en el décimo día de tratamiento, acompañada de una reducción de las unidades formadoras de colonias, la preservación de la arquitectura tisular y la disminución del infiltrado inflamatorio. En el modelo de queratitis por Aspergillus fumigatus, la aplicación de colirio de piperina demostró ser segura y redujo las puntuaciones clínicas de la infección corneal, la carga fúngica y los marcadores de piroptosis. En heridas por escisión, el gel de Aloe vera combinado con piperina alcanzó una retracción del 80,46 % en el decimocuarto día del experimento, un efecto comparable al de la sulfadiazina. Las pruebas indican el potencial de la piperina en el tratamiento de heridas cutáneas y como agente antimicrobiano. Sin embargo, las limitaciones en la consistencia y la cantidad de los estudios requieren investigaciones adicionales para confirmar su eficacia y seguridad clínica.

PALABRAS CLAVE: Piperina. Cicatrización. Heridas. Agentes antifúngicos. Agentes antibacterianos.

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INTRODUCTION

Wound healing is a complex and dynamic biological process, essential for restoring tissue integrity after injury. This mechanism is based on the coordinated interaction between different cell types, inflammatory mediators, growth factors, and Extracellular Matrix (ECM) components, which act synergistically to promote skin repair.[1,2]

The healing process is classically divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Hemostasis ensures the containment of bleeding through clot formation; inflammation promotes the cleaning of cellular debris and microorganisms; the proliferative phase is characterized by angiogenesis, matrix deposition, and keratinocyte migration; and finally, remodeling results in the final scar, marked by collagen reorganization and progressive increase in tissue resistance.[3]

Despite advances in medicine and biotechnology, many conventional treatments for infected wounds have limited efficacy, as well as high costs, side effects, or antimicrobial resistance. In this scenario, there is growing interest in therapeutic alternatives based on natural compounds, which offer multiple pharmacological properties and greater biocompatibility.[4]

Piperine, an alkaloid found predominantly in the species Piper nigrum (black pepper), has attracted the attention of the scientific community due to its various biological activities. Among these, its anti-inflammatory, antioxidant, antimicrobial, and healing potential stand out.[5–9]

Preclinical studies indicate that piperine modulates the healing process, accelerating tissue regeneration and inhibiting the growth of pathogenic microorganisms that compromise wound integrity.[10–12]

However, although preclinical experimental studies indicate promising results for piperine,[5–7,10] the lack of a systematic review compiling the antimicrobial and healing effects in preclinical models represents a gap in knowledge. This absence of synthesis limits the validation of the compound's real applicability and compromises progression to clinical trials.

This review is justified by the urgency to summarize the scientific evidence on the potential of piperine as a healing and antimicrobial agent in skin wounds. By synthesizing these data, this work contributes to the development of new therapeutic approaches based on natural compounds, in addition to supporting future clinical research and safer and more effective therapeutic decisions in wound management.

Despite growing interest in natural compounds for tissue repair, this research revealed a gap in the literature: to date, there has been no systematic review focused specifically on the therapeutic effects of piperine on skin wound healing and its associated antimicrobial action. Therefore, the objective of this study was to evaluate, through a systematic review, the healing and antimicrobial action of piperine in skin wound repair in rodents.

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MATERIALS AND METHODS

Protocol and Registration

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[13] The protocol is registered in the PROSPERO (International Prospective Register of Systematic Reviews) database under registration number CRD420251106097. The research was guided by the following question: Does piperine have healing and antimicrobial action in experimentally induced skin wounds in animals?

Study design

This review followed the PICOS strategy, based on Kitchenham,[14] in which P (Population/Patient): rodents with experimentally induced skin wounds; I (Intervention): treatment with piperine; C (Comparison): standard treatment for healing or vehicle; O (Outcome): wound healing or antimicrobial activity; and S (Study design): experimental studies in animal models of healing, using negative control or standard treatment for wound healing; and studies on antimicrobial activity.

Search Strategy

On May 19, 2025, a systematic literature search was conducted in the Medline (via PubMed), Embase, Science Direct, and Web of Science databases, with no language or publication period restrictions. The search strategy was developed using Health Sciences Descriptors (DeCS) and corresponding keywords, adapted to the specific syntax of each database. The following terms were used: *piperine, wound healing, wounds, injuries, surgical wound, cutaneous wound, antimicrobial, antibacterial agent, antifungal agent, antibacterial, and antifungal*; connected by the Boolean operators AND and OR. Additionally, a manual search (backward citation searching) was performed on the reference lists of the included studies to identify potentially eligible publications that were not captured in the initial search. A new search was conducted on December 9, 2025, to ensure that the materials used were up to date, but no studies were retrieved.

Selection and Eligibility Criteria

In vivo experimental studies investigating the healing potential of piperine (isolated or in extracts) in rodent skin wounds were included, with no restrictions on language or date. For the analysis of antimicrobial activity, studies with in vivo tests (antibacterial or antifungal) were selected.

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Exclusion criteria were strictly applied to ensure reproducibility, discarding: Studies that did not analyze the direct pharmacological action of piperine on the repair process or pathogens and publications with incomplete methodological descriptions, specifically those that omitted the dose administered, the method of lesion induction, or the treatment time.

Study Selection and Data Extraction

The selection of studies was performed blindly and independently by three reviewers (HCSM, TS, and VRM) using the Rayyan platform (QCRI) (duplicates were evaluated prior to screening). The process occurred in two consecutive stages: initial screening of titles and abstracts, followed by full-text reading to confirm eligibility. Any disagreements between the main reviewers (HCSM and TS) were resolved by a third independent reviewer (VRM), who acted blind to ensure impartiality.

Data extraction was conducted independently by two reviewers (HCSM and TS) using a standardized form that included: sample characteristics (species, strain, sex), intervention details (piperine concentration and vehicle used), wound induction models, healing outcomes, and microbiological parameters. At the end of the process, three articles met the inclusion criteria and were selected for qualitative analysis. The detailed flow of identification, screening, and inclusion, structured according to PRISMA recommendations, is illustrated in Figure 1.[13]

Limitations of the Evidence

The significant reduction in the initial number (5,618 records) to the final sample of three studies highlights the scarcity of robust evidence on the subject. This sample limitation reflects the rigor of the inclusion criteria and points to the following determining factors:

1. Deviation from the Specific Scope: The vast majority of records were excluded in the first phase because they dealt with healing without focusing specifically on piperine, resulting in a high rate of noise in the search results.
2. Methodological Fragility: During the full reading, it was observed that some studies did not have a control group, which would compromise the validity of the qualitative synthesis.
3. Scientific Incipiency: The small number of studies that met the eligibility criteria demonstrates that the topic is still in an exploratory stage, lacking publications with experimental or observational designs with a high level of evidence.

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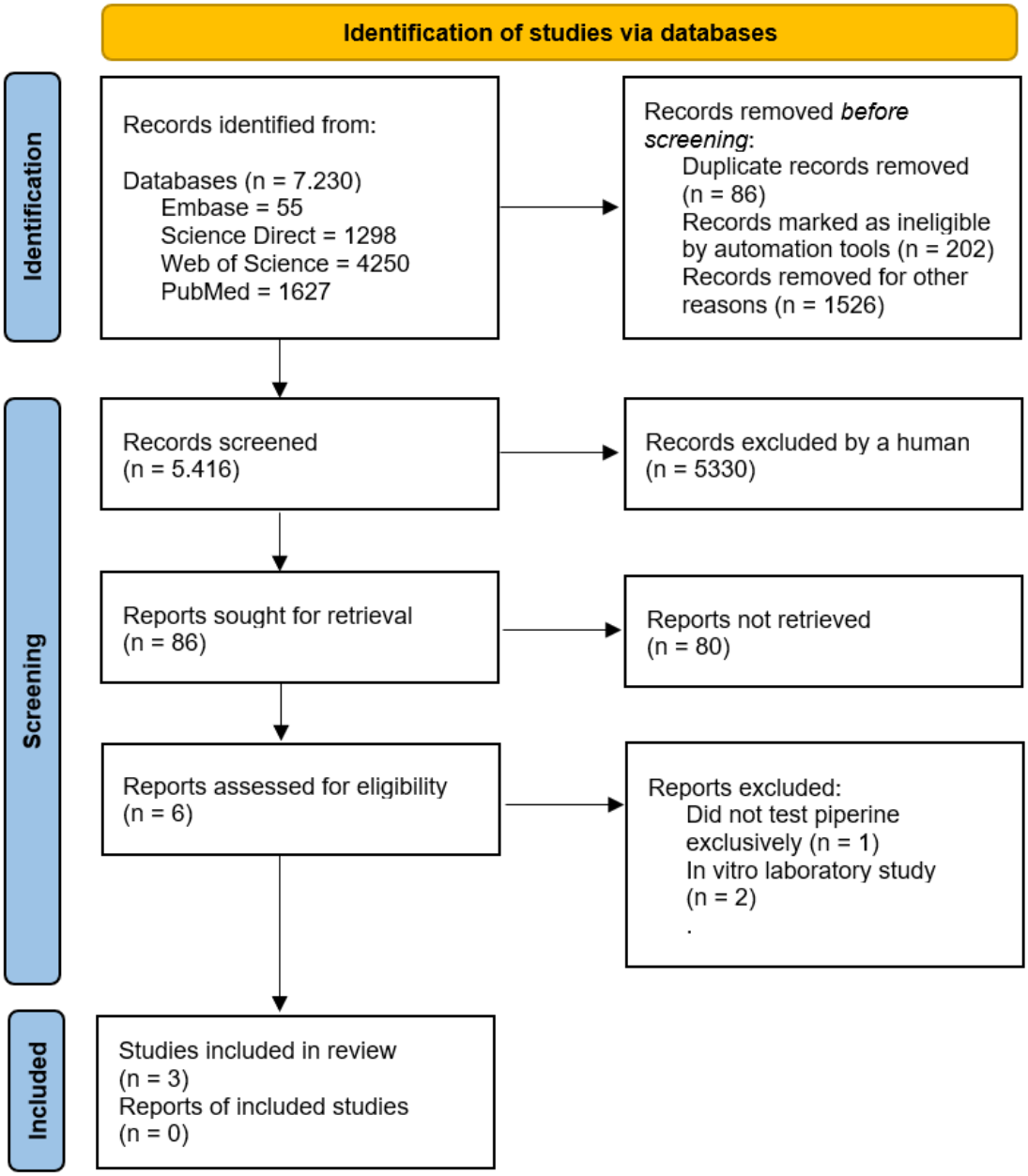

Fig. 1. Flow diagram of study selection and screening.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were assessed independently by three reviewers using the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) tool for animal studies. Disagreements were resolved by consensus.

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RESULTS

Piperine was evaluated in experimental models of skin wounds and fungal keratitis in three studies included in this review. Hydrogel and microemulsion formulations demonstrated efficacy in reducing bacterial load and improving healing in wounds infected with *Staphylococcus aureus*.[15] Topical application of piperine (30 µg/mL) in an experimental model of fungal keratitis caused by Aspergillus fumigatus was safe, resulting in improved clinical scores for corneal infection (opacity, lesion area, and surface irregularity) and fungal load (Colony Forming Units (CFU)). In addition, the treatment decreased pyroptosis markers, associated with inhibition of the mTOR/HIF-1α pathway [16]. The hydrogel associated with piperine accelerated the healing of excisional wounds, enhancing lesion contraction and collagen deposition.[10]

Table 1 compiles the selected studies—covering design, models, and outcomes—allowing a comparative analysis of the efficacy of piperine as a healing and antimicrobial agent in animal models.

Table 1. Summary of selected articles on the action of piperine as a healing and antimicrobial agent in rodents

Author/year	Methodology	Results
Lin *et al.* [15]	**Formulation:** 1:1 microemulsion hydrogel (Pip-ME-gels). **Wound type:** S. aureus-infected excisional skin wound in rats (n=6). Topical treatment once daily for 14 days. **Comparator:** Mupirocin (Bactroban) **Evaluation:** healing (area), CFU, histology.	Wound closure: 75.33% on day 10 (negative control = 57.83%). ↓ CFU of the wound (reduction in bacterial load from day 3, with a small amount remaining on day 7). In the Mup-Pip-ME-gels group: reconstituted epidermis; fibroblast density; organized collagen deposition.
Li *et al.* [16]	**Formulation**: Piperine ophthalmic solution 30 µg/mL (0.003% w/v). **Experimental protocol**: Adm. 4×/day in a model of keratitis in mice induced by *A. fumigatus*. **Evaluation**: Clinical score on days 1, 3, and 5. **Fungal load (CFU)** measured on day 3; **HE** on day 3 (n = 3/group).	No clinical signs of corneal and conjunctival toxicity. ↓ corneal fungal load. ↓ inflammatory infiltrate and preservation of corneal architecture. Suppression of NLRP3 inflammasome and pyroptosis markers (caspase-1, GSDMD, IL-1β, IL-18). Inhibition of the mTOR/HIF-1α pathway.

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Author/year	Methodology	Results
		Synergism with natamycin.
Alsareii *et al*. [10].	**Formulation:** piperine 0.5% w/w (m/m) in hydrogel (Carbopol 934 0.3%; glycerin 5%; *Aloe vera* 10%). **Experimental groups:** Negative control; placebo hydrogel; hydrogel with piperine (0.5% w/w) and positive control (1% silver sulfadiazine cream). **Model:** Excisional skin wounds in Wistar rats (n=6) **Evaluation:** • Wound retraction measurements: 1st, 5th, 9th, and 14th days • Histology • Cell proliferation markers.	↑ wound regression (80.46% piperine vs. 65.10% placebo). Histology: Abundant collagen, thick epidermis, and papillary dermis formed in the piperine group; less pronounced findings in placebo and control. Ki-67 (cell proliferation marker): focal ↑ positive expression in the epidermal basal layer.

Legenda: ↓ - decrease; ↑ - increase; Pip - piperine; ME – microemulsion; Mup – mupirocin; HE - Hematoxylin-eosin; CFU - Colony Forming Units; NLRP3 - inflammasome; GSDMD - Gasdermin D; IL-18 - interleukin 18; IL1β - interleukin 1beta; HIF-1α - hypoxia-inducible factors 1-alpha; mTOR – Mechanistic Target of Rapamycin; Ki-67 – protein.

Table 2 presents the results of the risk of bias assessment of the studies included. An unsatisfactory description of items related to random sequence generation, allocation concealment, random accommodation, and blinding of caregivers and investigators (items 1, 3, 4, and 5, respectively) was observed. In the study by Lin et al.[15], the authors reported random assessment of outcomes, blinding of the outcome assessor, and treatment of incomplete data (items 6, 7, and 8). Alsareii et al.[10] pointed out baseline characteristics, the presence of incomplete outcome data, and selective reporting of outcomes (items 2, 8, and 9).

Therefore, the lack of data on allocation concealment and blinding makes it impossible to verify methodological quality, increasing the risk of performance and detection bias. However, it should be noted that Lin et al.[15] and Alsareii et al.[10] presented an adequate report on the initial comparability of the groups and the integrity of the data.

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Table 2 Risk of bias of the included studies obtained using the SYRCLE tool

	Domain	Type of bias	Lin *et al.* [15]	Li *et al.* [16]	Alsareii *et al.* [10]
1	Sequence generation	Selection	?	?	?
2	Baseline characteristics	Selection	?	?	L
3	Allocation concealment	Selection	?	?	?
4	Random housing	Performance	?	?	?
5	Blinding caregivers and investigators	Performance	?	?	?
6	Random outcome assessment	Detection	L	?	?
7	Blinding outcome assessor	Detection	L	?	?
8	Incomplete outcome data	Attrition	L	?	L
9	Selective outcome reporting	Report	?	?	L
10	Other sources of bias	Other	L	?	L

Key: L – low risk; ? – uncertain risk
Source: SYRCLE's risk of bias tool for animal studies.

DISCUSSION

Based on the three studies analyzed, it can be observed that isolated piperine has healing, antimicrobial, and immunomodulatory potential. However, its effectiveness depends on a suitable vehicle that increases local bioavailability, as shown in Figure 2.[10,15,16]

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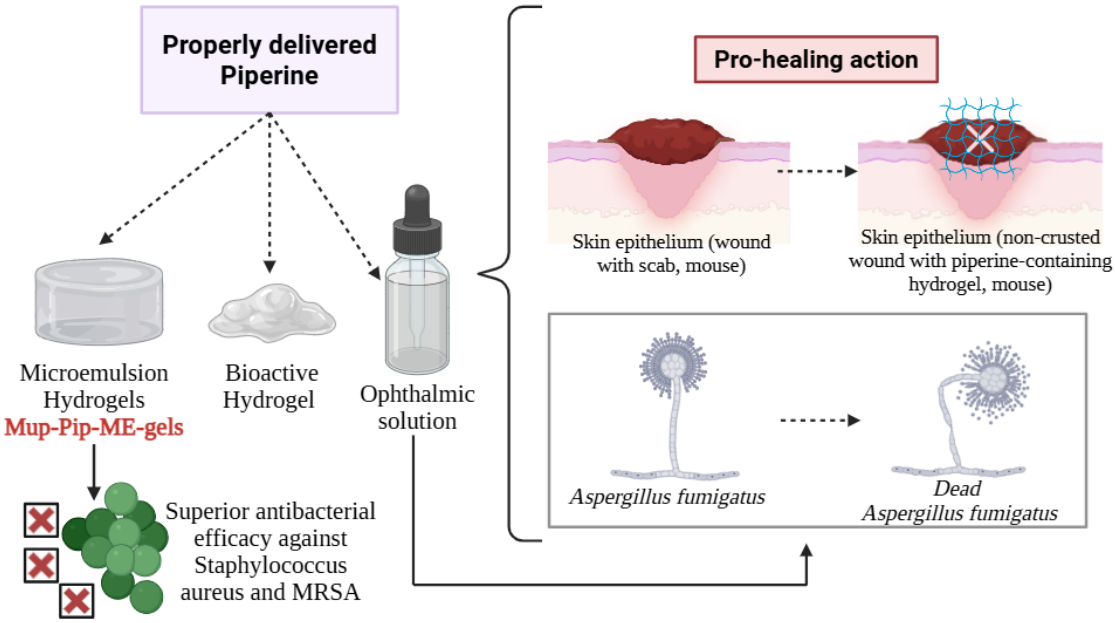

Fig. 2. Graphical summary of the methods used in the three studies analyzed. The efficacy of piperine includes inhibition of fungal growth and protection against pyroptosis in fungal keratitis caused by *Aspergillus fumigatus*. In the treatment of infected wounds, the strategic combination of piperine and mupirocin in microemulsion hydrogels (Mup-Pip-ME-gels) has demonstrated superior antibacterial efficacy against *Staphylococcus aureus* and Methicillin-Resistant *Staphylococcus aureus* (MRSA). In addition to its antimicrobial action, piperine accelerates the wound healing process by promoting granulation, reducing inflammation, and favoring collagen formation and re-epithelialization, highlighting its high potential for tissue regeneration.
Source: Adapted from the results of studies by Lin et al.[15], Li *et al.*[16], and Alsareii *et al.*[10]. Created with BioRender.com.

However, the interpretation of these results must consider the methodological characteristics of the included studies. The assessment of risk of bias showed variations in how some methodological aspects were described, especially regarding randomization procedures, allocation concealment, and blinding. Although some studies adequately presented the baseline characteristics of participants and the treatment of incomplete data, in other cases, methodological information was limited, which led to the classification of some domains as uncertain. Thus, these aspects were considered in the interpretation of the evidence presented in this review.

In this regard, the study conducted by Alsareii *et al.*[10] demonstrated that, on the 14th day of treatment, a bioactive hydrogel composed of Carbopol 934, *Aloe vera*, and piperine achieved 80.46% retraction of excisional wounds, showing efficacy comparable to 1% silver sulfadiazine and superior to the placebo gel. Histological analysis revealed increased collagen deposition, thicker epithelialization, and positive staining for Ki-67 in the basal epidermal layers, indicating increased cell proliferation. The authors attributed these effects to the controlled release of piperine at the wound site, combined with the anti-inflammatory and emollient properties of the hydrogel matrix.

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These findings are consistent with growing evidence supporting hydrogels as advanced biomimetic platforms for wound treatment. Such systems maintain a moist and bioactive microenvironment while allowing for the sustained release of therapeutic agents, thereby promoting essential repair processes such as cell proliferation, angiogenesis, ECM deposition, and re-epithelialization.[17-20] In particular, *Aloe vera*-based hydrogels and carbopol matrices can improve dermal retention and facilitate the incorporation of bioactive compounds with antimicrobial and anti-inflammatory properties.[21] In addition, hybrid delivery systems, such as microemulsion formulations in hydrogels, combine the high solubilization and permeation capacity of microemulsions with the fluidity and adhesion of gels, resulting in improved local bioavailability and sustained therapeutic effects.[22]

In line with this technological logic, Lin et al.[15] demonstrated that microemulsified hydrogels loaded with piperine were effective against *Staphylococcus aureus* in infected wound models. Although the antibacterial activity was lower than that observed with mupirocin (the control antibiotic), the formulation significantly reduced the bacterial load, presenting favorable physicochemical characteristics, including stability, pH suitable for topical application, and spherical nanostructural morphology. These properties increase transdermal diffusion and tissue retention, allowing piperine to reach therapeutic concentrations in the epidermis and dermis. Additional evidence from Das et al.[12] further demonstrated that microemulsified piperine exhibits antibiofilm activity against *Staphylococcus aureus*, maintaining antimicrobial efficacy on the skin for up to seven days and reducing biofilm formation in in vitro and ex vivo models.

In addition to its antibacterial activity, piperine has also been shown to interfere with biofilm formation by pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, acting through mechanisms that include the induction of Reactive Oxygen Species (ROS), interference with the hydrophobicity of the bacterial surface, and disruption of the integrity of the extracellular matrix.[12,24] These findings may highlight the multifunctional antimicrobial potential of the compound and reinforce its role as a promising bioactive molecule for the treatment of infected wounds.

It is important to note that, although most studies included in this review have focused on skin wound models, recent investigations have expanded the evaluation of piperine to other contexts of epithelial injuries that share similar inflammatory and tissue repair mechanisms. A notable example is fungal keratitis, a condition characterized by epithelial damage, microbial invasion, and intense inflammatory response in corneal tissue. The inclusion of this model provides complementary evidence on the antimicrobial and immunomodulatory potential of piperine in epithelial healing processes.

In a model of fungal keratitis caused by *Aspergillus fumigatus*, piperine demonstrated antifungal and immunomodulatory activity without cytotoxicity at concentrations up to 30µg/mL in ophthalmic solution. Treatment reduced fungal growth, biofilm formation, and conidia adhesion,

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while in vivo experiments showed decreased fungal load, reduced inflammatory infiltration, and lower expression of pyroptosis markers such as NLRP3, caspase-1, GSDMD, and IL-1β. These effects were associated with inhibition of the mTOR/HIF-1α signaling pathway, suggesting a metabolic-immunological modulation mechanism relevant to severe fungal infections.[16]

A complementary study conducted by Jansook *et al*.[25] developed a nanostructured piperine formulation based on cyclodextrin and in situ gelation for ocular administration. The system demonstrated good ocular tolerability, absence of cytotoxicity in cell assays, and no irritation in HET-CAM tests, indicating that controlled release technologies can improve the safety and retention of piperine in sensitive tissues such as the cornea.

Naturally occurring alkaloids have high biological activity and, when administered ophthalmically, are typically used in low concentrations due to the sensitivity of the corneal epithelium and the potential for local toxicity. Thus, the safety of compounds in this group is established by cytotoxicity and ocular tolerability tests, rather than universal concentration limits, with concentrations in the μg/mL range considered compatible with experimental ophthalmic use when not associated with epithelial damage or significant inflammation.[26,27]

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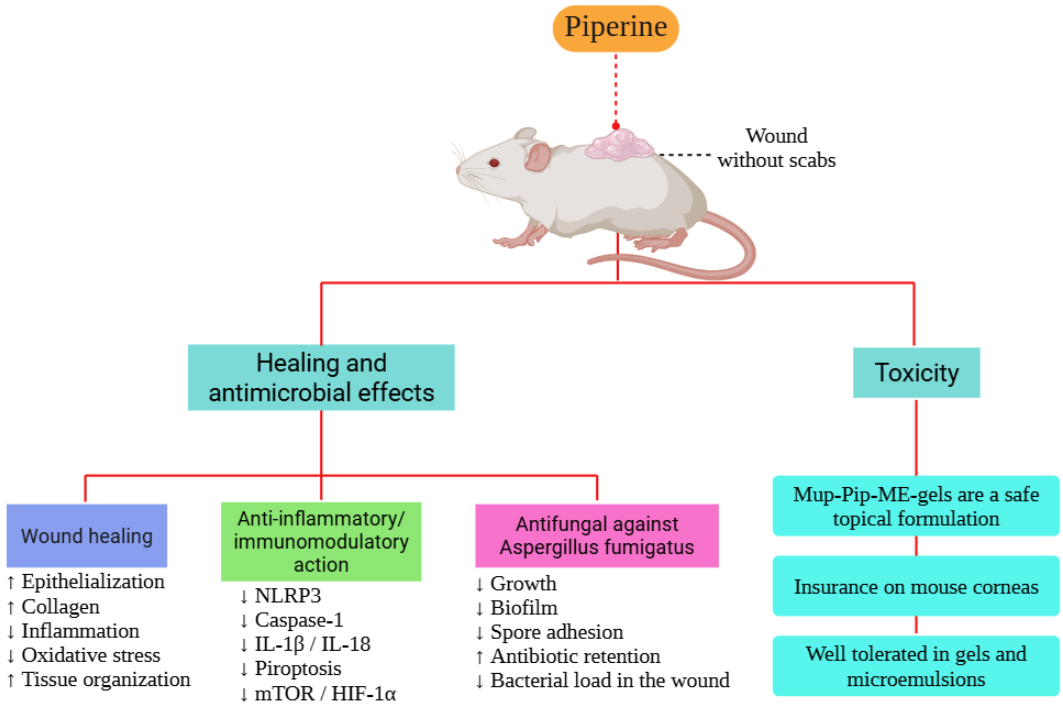

Fig. 3. Representation of the possible biological actions of piperine in wound healing in experimental models. The healing process involves increased re-epithelialization and collagen deposition, associated with reduced inflammation, oxidative stress, and tissue disorganization. Piperine stands out for its anti-inflammatory and immunomodulatory action, acting in the modulation of the NLRP3/caspase-1 inflammasome, in the reduction of pro-inflammatory cytokines (IL-1β, IL-18), inhibiting pyroptosis, and regulating mTOR/HIF-1α pathways, which promotes a superior tissue response to infection. Additionally, the compound demonstrates antifungal potential against *Aspergillus fumigatus*. There is no cellular toxicity, good tolerability in mouse corneas, and compatibility with topical formulations. IL-1β: Interleukin-1 beta; NLRP3: NLR Family Pyrin Domain Containing 3; Caspase-1: Cysteine-aspartate protease 1; IL-18: Interleukin-18; mTOR/HIF-1α: Mammalian Target of Rapamycin / Hypoxia-Inducible Factor-1 alpha.
Source: Lin *et al*.[15], Li *et al*.[16] and Alsareii *et al*.[10]. Created with BioRender.com.

Collectively, these findings demonstrate that piperine acts through multiple complementary mechanisms, combining antimicrobial, antioxidant, anti-inflammatory, and tissue repair activities (Fig. 3). In skin tissue, these effects are associated with accelerated wound closure, increased collagen deposition, and enhanced epithelial proliferation[10,15], while in corneal tissue, they manifest mainly through reduced inflammatory signaling and protection against fungal infections.[16]

The therapeutic efficacy of piperine appears to depend on the delivery technology employed, with hydrogels and microemulsions emerging as effective strategies to overcome its low aqueous solubility and optimize local bioavailability.[28,29] Consequently, piperine stands out as a pleiotropic phytocompound capable of integrating antimicrobial, anti-inflammatory, and regenerative responses.

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Although the results are promising, this review has important limitations. In addition to the heterogeneity of experimental designs, formulations, and outcome measures, the risk of bias assessment revealed insufficient reporting of critical methodological aspects, particularly randomization procedures, allocation concealment, and blinding. These limitations reduce the internal validity of the included studies and constrain the robustness of the conclusions. Consequently, direct comparison between studies remains limited, and the magnitude of the observed therapeutic effects should be interpreted with caution.

However, the identification of consistent patterns of multifactorial activity and the validation of delivery technologies, such as hydrogels and microemulsions, provide a solid pharmacotechnical basis for future translational studies aimed at standardizing formulations, optimizing dosing strategies, and exploring molecular biomarkers associated with wound repair.

CONCLUSION

This systematic review suggests that piperine acts as a promising bioactive agent, with evidence of antimicrobial, anti-inflammatory, and healing properties in experimental models. The preclinical evidence analyzed (cutaneous, infectious, and ocular) indicates a potential for modulating the repair process, with a possible reduction in infections and acceleration of tissue regeneration. However, the small number of studies selected means that these findings are preliminary. These results highlight the versatility of piperine, but also demonstrate the need for more extensive, standardized investigations and, in the future, translational clinical studies to validate its safety and efficacy in humans, strengthening its applicability in new therapies based on phytochemicals and controlled release systems.

Consent for publication

All authors have read and approved the final manuscript and consent to its publication.

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Declaration of competing interest

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H.C.S.M: Conceptualization, Investigation, Validation, Writing – original draft and Writing – review & editing; T.S: Conceptualization, Investigation, Validation, Writing – original draft and Writing – review & editing; V.R.M: Investigation, Methodology, Validation, Writing – original draft and Writing – review & editing; S.M.M: Supervision; R.A.B.F., J.R.S.J and A.L.M.M.F.: Visualization; M.C.C.M: Conceptualization, Project administration, Supervision and Writing – review & editing.

Appendix

CFU - Colony Forming Units

ECM – Extracellular Matrix

GSDMD - Gasdermin D

GSDMD-N - N-terminal fragment of the Gasdermin D protein

HE - Hematoxylin-eosin

HET-CAM - Hen's Egg Test - Chorioallantoic Membrane

HIF-1α - Hypoxia-Inducible Factors 1-alpha

IL-18 – Interleukin 18

IL1β – Interleukin 1beta

Ki-67 – Protein

MRSA – Methicillin-Resistant *Staphylococcus aureus*

mTOR – Mechanistic Target of Rapamycin

Mup-Pip-ME-gels – Mupirocin and Piperine Microemulsion Hydrogel

NLRP3 – inflammasome

PICOS - Population/Patient, Intervention, Comparison, Outcome, Study design

PIP – Piperine

Pip-ME-gel – Piperine Microemulsion Hydrogel

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - International Prospective Register of Systematic Reviews

ROS – Reactive Oxygen Species

SYRCLE – Systematic Review Centre for Laboratory Animal Experimentation

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