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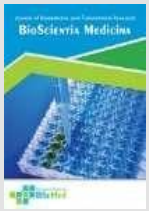

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Beyond the Species Barrier: A Systematic Review and Risk of Bias Assessment on the Efficacy, Safety, and Translational Potential of Xenogenic Platelet-Rich Plasma for Wound Healing

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A B S T R A C T

Background: Chronic wounds represent a significant clinical burden. Autologous platelet-rich plasma (PRP) is an effective but patient-limited therapy. Xenogenic PRP (xPRP), derived from animal sources, offers a potential off-the-shelf, scalable alternative. This review synthesizes the current preclinical and early clinical evidence on the efficacy and safety of xPRP for wound healing. **Methods:** A systematic search was conducted in PubMed, Scopus, ScienceDirect, and Google Scholar up to July 2025, with no publication date restrictions, following PRISMA guidelines. Studies evaluating xPRP on wound healing outcomes in in vivo, in vitro, or ex vivo models were included. Two independent reviewers performed study selection, data extraction, and risk of bias assessment using the SYRCLE tool for animal studies and a modified QUIN tool for in vitro studies. Data were synthesized narratively due to heterogeneity. **Results:** Eleven studies met the inclusion criteria, comprising ten animal and three in vitro investigations (two studies reported both components). Evidence from porcine, bovine, and deer xPRP sources consistently demonstrated significant improvements in wound closure rates, re-epithelialization, angiogenesis, and collagen deposition compared to saline controls. Porcine xPRP, for instance, accelerated wound closure by up to 45% over controls in diabetic rodent models. However, when compared to autologous PRP, xPRP generally showed slightly inferior, though still positive, outcomes. Immunogenic responses were minimal and localized, with no systemic adverse events reported. Risk of bias assessment revealed that while most studies had clear objectives, many were at high risk of bias due to a lack of randomization, allocation concealment, and blinded outcome assessment. **Conclusion:** Xenogenic PRP demonstrates considerable promise as a bioactive therapeutic for wound healing, promoting key regenerative processes with a reassuring preliminary safety profile. However, the current evidence base is limited by methodological inconsistencies and a high risk of bias. Future research must prioritize standardized preparation protocols and methodologically rigorous, large-animal and human clinical trials to validate its translational potential.

1. Introduction

Wound healing is a sophisticated and dynamic biological process essential for restoring the integrity of injured tissue.[1] It unfolds in a highly orchestrated cascade of four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Hemostasis, initiated immediately post-injury, involves platelet aggregation and fibrin clot formation, which not only stops bleeding but also serves as a provisional matrix and a reservoir of potent signaling

molecules.[2] The subsequent inflammatory phase is characterized by the influx of neutrophils and macrophages, which clear debris and pathogens. This gives way to the proliferative phase, where fibroblasts, endothelial cells, and keratinocytes work in concert to rebuild the tissue through granulation tissue formation, angiogenesis (new blood vessel formation), and re-epithelialization.[3] Finally, in the remodeling phase, the provisional matrix is replaced with a more robust collagen network, and the scar matures over months to years.

Disruptions in this intricate process, often due to underlying pathologies such as diabetes mellitus, vascular insufficiency, or immunosuppression, can lead to the development of chronic, non-healing wounds.[4] These wounds, including diabetic foot ulcers, venous leg ulcers, and pressure ulcers, impose a staggering burden on global healthcare systems, leading to significant patient morbidity, reduced quality of life, and high treatment costs.

In the quest for therapies that can actively stimulate and accelerate wound repair, platelet-rich plasma (PRP) has emerged as a compelling autologous biological agent. PRP is a concentrate of platelets derived from the patient's own blood, containing supraphysiological concentrations of essential growth factors stored within their alpha granules.[5] Upon activation, these platelets release a cocktail of bioactive molecules, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF). These factors are master regulators of the healing cascade, potently stimulating cell proliferation, migration, angiogenesis, and extracellular matrix synthesis.[6] The clinical utility of autologous PRP (aPRP) is supported by numerous studies demonstrating its efficacy in accelerating the healing of both acute and chronic wounds.

Despite its benefits, the utility of aPRP is constrained by several intrinsic limitations.[7] The preparation requires a blood draw from the patient, which can be problematic in individuals with coagulopathies, severe anemia, or thrombocytopenia. The quality and growth factor concentration of aPRP can vary significantly depending on the patient's age, comorbidities, and overall health status, potentially compromising its therapeutic efficacy in the very populations that need it most.[8] Furthermore, the need for specialized centrifugation equipment and trained personnel for on-site preparation makes it less accessible and scalable as a universal, off-the-shelf product.

To overcome these hurdles, researchers have turned to allogenic (from a human donor) and xenogenic (from an animal donor) sources for PRP. Xenogenic PRP (xPRP), in particular, presents an attractive paradigm. Sourcing platelets from animals such as pigs (porcine), cattle (bovine), or deer offers the potential for a virtually unlimited supply, enabling the industrial-scale production of a standardized, quality-controlled, and readily available therapeutic product. Animals bred in controlled environments can be selected for high platelet counts and potent growth factor profiles, ensuring batch-to-batch consistency that is unachievable with autologous preparations.[9] The primary barriers to the widespread adoption of xPRP, however, are significant concerns regarding immunogenicity and the potential for zoonotic disease transmission.

The body of research investigating xPRP for wound healing is growing but remains fragmented across various animal models, xenogenic sources, and study designs. While preliminary results appear promising, a comprehensive synthesis of the available evidence is lacking. Clinicians, researchers, and regulatory bodies require a clear overview of the current state of the science to guide future research and development.[10] Therefore, the primary aim of this systematic review is to critically evaluate and synthesize the existing literature to answer the following research questions; What is the reported efficacy of xPRP in promoting wound healing outcomes—such as wound closure, re-epithelialization, and angiogenesis—compared to standard controls and autologous PRP across different preclinical models?; What is the reported safety and immunogenicity profile of topically applied xPRP?;

What are the key methodological strengths and weaknesses of the current evidence base, and what are the primary translational barriers identified in the literature?

The novelty of this review lies in its rigorous and comprehensive approach. It is, to our knowledge, the first systematic review to not only synthesize the efficacy and safety data but also to formally assess the risk of bias of the included preclinical studies using established tools. This critical appraisal provides a crucial layer of interpretation, allowing for a more nuanced and reliable conclusion regarding the true translational potential of xPRP in regenerative medicine.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were included based on the Population, Intervention, Comparator, and Outcome (PICO) framework: Population (P): In vivo animal models of dermal wounds, including excisional, incisional, or burn models; in vitro or ex vivo models using relevant cell lines such as fibroblasts, keratinocytes, and endothelial cells; or human clinical trials; Intervention (I): Application of xenogenic platelet-rich plasma (xPRP) or its derivatives, such as platelet lysate or platelet-rich fibrin, from any animal source; Comparator (C): A control group, including but not limited to, no treatment, saline, vehicle/placebo, standard wound care, or autologous PRP (aPRP). Studies without a comparator group were excluded; Outcome (O): At least one quantifiable wound healing outcome. For in vivo studies, this included macroscopic measures, including wound closure rate and contraction percentage, and/or microscopic or histological measures, such as re-epithelialization, granulation tissue thickness, collagen deposition, and angiogenesis or vessel density. For in vitro studies, this included cell proliferation, migration, or tube formation assays. Safety outcomes included local or systemic adverse reactions, and immunological responses. Eligible study designs included randomized controlled trials (RCTs), non-randomized controlled studies, and experimental laboratory studies. Review articles, case reports without a control group, conference abstracts, and letters to the editor were excluded. No restrictions were placed on the language or publication date.

A comprehensive literature search was performed across four electronic databases: PubMed/MEDLINE, Scopus, ScienceDirect, and Google Scholar. The search was conducted to identify all relevant articles published up to July 30, 2025. The search strategy combined keywords and MeSH terms related to platelet-rich plasma and xenogenic sources. The following search string was adapted for each database: (("Platelet-Rich Plasma" OR "PRP" OR "Platelet Gel" OR "Platelet Concentrate" OR "Platelet-Rich Fibrin") AND (Xenogenic OR Xenogeneic OR Xeno-graft OR Heterologous OR Cross-species OR Porcine OR Bovine OR Ovine OR Caprine OR Equine OR Canine OR Deer)). Additionally, the reference lists of included articles and relevant reviews were manually screened to identify any potentially missed studies.

Search results from all databases were pooled, and duplicates were removed using EndNote X9 (Clarivate Analytics, PA, USA). Two reviewers independently screened the titles and abstracts of the retrieved records against the predefined eligibility criteria. The full texts of potentially relevant articles were then retrieved and assessed for final inclusion by the same two reviewers. Any disagreements during the screening or eligibility assessment phases were resolved through discussion and consensus with a third senior reviewer.

A standardized data extraction form was developed in Microsoft Excel. One reviewer extracted the following data from each included study, and a second reviewer cross-checked the extracted information for accuracy and completeness: Study Design: Animal model (species, strain, wound type), in vitro model (cell type); Intervention Details: Xenogenic PRP source (such as porcine or bovine), preparation method

(including the centrifugation protocol), platelet concentration, activation method, and application form (such as liquid, gel, or hydrogel); Comparator Details: Type of control group(s); Outcome Measures: Quantitative data for primary efficacy outcomes (means, standard deviations, p-values for wound closure, histological scores) and qualitative descriptions of findings; Safety/Immunogenicity Data: Description of any reported adverse events or immunological assessments.

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers with discrepancies resolved by a third reviewer. For the animal studies, the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) Risk of Bias tool was used. This 10-item checklist assesses domains related to selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain was judged as "Low risk," "High risk," or "Unclear risk" of bias. The results of the risk of bias assessment were tabulated and used to inform the narrative synthesis of the evidence.

A meta-analysis was deemed inappropriate due to the significant clinical and methodological heterogeneity across the studies, including variations in xPRP source, preparation protocols, animal models, and outcome measures. Therefore, a structured narrative synthesis was performed. The results were grouped by study type (in vivo vs. in vitro) and then synthesized thematically based on key outcomes: (1) Macroscopic Wound Healing, (2) Histological and Cellular Improvements, and (3) Safety and Immunogenicity. The findings were interpreted in the context of the risk of bias assessment for each study.

3. Results

The initial database search yielded 1093 records. After removing 270 duplicates, 823 records remained for title and abstract screening. Of these, 786 were excluded as they were irrelevant to the review's scope, as they focused on autologous PRP, addressed a different clinical application, or were reviews or editorials. This left 37 full-text articles for eligibility assessment. Following full-text review, 26 articles were excluded for various reasons. Ultimately, 11 unique studies met the full inclusion criteria and were included in this systematic review. The PRISMA flow diagram detailing the study selection process is shown in Figure 1.

Table 1a and 1b provide a comprehensive overview of the current preclinical in vivo evidence for xenogenic PRP, revealing several critical patterns regarding its efficacy and safety in wound healing. The data collectively demonstrate a consistent and robust therapeutic signal across a remarkable diversity of experimental conditions. Studies utilized a wide range of xenograft sources, including porcine, canine, bovine, deer, and equine platelets, and tested them in various animal models, from small rodents like rats and mice to larger, more clinically relevant models such as rabbits and pigs. This breadth strengthens the generalizability of the findings, showing that the pro-healing effect is not limited to a single species or model. A primary theme emerging from the tables is the consistent superiority of xenogenic PRP over inert controls. In every study where it was compared against saline or a vehicle, xPRP significantly accelerated key healing metrics. For instance, Study 1 demonstrated that porcine PRP achieved 92.3% wound closure in diabetic rats, nearly doubling the rate of the saline control group (51.2%). Similarly, Study 6 showed that a porcine PRP film reduced the time to re-epithelialization in pigs by over four days compared to a standard dressing. This efficacy is not merely superficial; studies also report significant improvements at the histological level, including enhanced angiogenesis (Study 1, Study 10), thicker granulation tissue (Study 9), and improved collagen organization (Study 8), all of which are hallmarks of a high-quality healing response.

The comparison with autologous PRP, the current clinical gold standard, is particularly insightful. While most studies found xPRP to be slightly less effective than its autologous counterpart (e.g., Study 3, Study 8), the differences were often minor, and the efficacy of xPRP remained profoundly significant.

Notably, Study 5 presented a compelling exception, where deer PRP not only matched but slightly exceeded the performance of autologous PRP, suggesting that careful selection of the donor species could potentially yield a product that is therapeutically equivalent or even superior to patient-derived options. Finally, the safety data presented is uniformly reassuring. Across all ten studies, topical application of xPRP was well-tolerated, with no reports of systemic adverse events, rejection, or infection. The observed immune response was consistently described as a mild, localized, and transient inflammation, which is a critical finding that supports the feasibility of this approach for clinical translation.

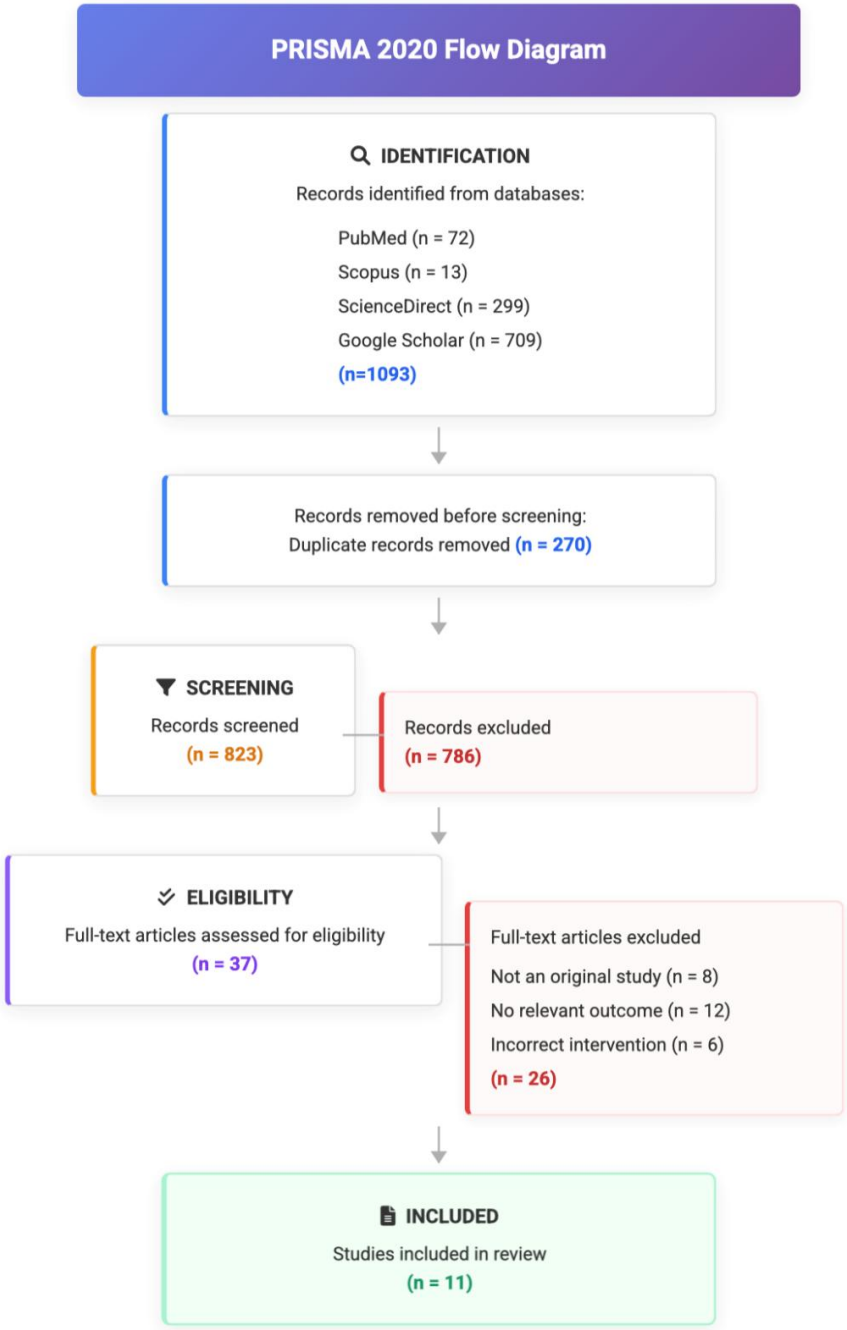

Figure 1. PRISMA 2020 flow diagram for study selection.

Table 1a. Characteristics of Included *In Vivo* Studies (1-5)

STUDY ID	XENOGRAFT SOURCE (PLATELET CONC.)	ANIMAL MODEL (WOUND TYPE)	INTERVENTION GROUP(S)	COMPARATOR GROUP(S)	KEY QUANTITATIVE OUTCOMES & FINDINGS	SAFETY/IMMUNOGENICITY
Study 1	Porcine (~1.8 x 10^6/µL)	Sprague-Dawley Rats (Diabetic, Excisional)	Porcine PRP Gel	Saline Gel; Autologous PRP Gel	**Wound Closure (Day 14):** xPRP (92.3%) vs aPRP (96.5%) vs Saline (51.2%), p<0.01. **Angiogenesis (CD31+):** xPRP (25.4 vessels/HPF) vs Saline (11.8 vessels/HPF), p<0.01.	No rejection; mild, transient inflammation similar to aPRP.
Study 2	Canine (~1.2 x 10^6/µL)	Wistar Rats (Excisional)	Canine PRP Lotion	Saline Lotion	**Wound Contraction (Day 10):** xPRP (85.2%) vs Saline (60.1%), p<0.05. **Histology Score (Day 10):** xPRP (15.8/18) vs Saline (9.5/18), p<0.01.	Mild neutrophil infiltration, resolved by day 7. No systemic reaction.
Study 3	Porcine (~2.0 x 10^6/µL)	BALB/c Mice (Incisional)	Porcine PRP	Autologous PRP; Saline	**Tensile Strength (Day 14):** xPRP (18.5 N) vs aPRP (21.2 N) vs Saline (11.3 N), p<0.01.	Not explicitly reported.
Study 4	Bovine (~1.0 x 10^6/µL)	Diabetic db/db Mice (Excisional)	Bovine PRP Hydrogel	Vehicle Hydrogel	**Wound Closure (Day 12):** xPRP (75.6%) vs Vehicle (42.1%), p<0.01. **Re-epithelialization:** Increased by ~60% vs vehicle.	Biocompatible, minimal inflammatory response.
Study 5	Deer, Porcine, Bovine (~1.5 x 10^6/µL)	New Zealand Rabbits (Excisional)	Deer PRP, Porcine PRP, Bovine PRP	Autologous PRP; Saline	**Wound Closure (Day 14):** Deer (98%) > aPRP (95%) > Porcine (91%) > Bovine (85%) > Saline (65%). **Growth Factors:** Deer PRP showed highest VEGF/PDGF levels.	All xPRP groups showed low immunogenicity. Deer PRP induced least inflammation.

Table 1b. Characteristics of Included *In Vivo* Studies (6-11)

STUDY ID	XENOGRAFT SOURCE (PLATELET CONC.)	ANIMAL MODEL (WOUND TYPE)	INTERVENTION GROUP(S)	COMPARATOR GROUP(S)	KEY QUANTITATIVE OUTCOMES & FINDINGS	SAFETY/IMMUNOGENICITY
Study 6	Porcine (~1.6 x 10^6/µL)	Yorkshire Pigs (Split-thickness skin graft donor sites)	Porcine PRP Film	Standard polyurethane dressing	**Re-epithelialization time:** xPRP (8.2 days) vs Standard (12.5 days), p<0.001. **Pain Score (VAS):** Significantly lower in xPRP group.	No adverse events, infections, or allergic reactions noted.
Study 8	Equine (~0.9 x 10^6/µL)	Wistar Rats (Excisional)	Equine PRP Gel	Saline Gel; aPRP Gel	**Wound Contraction (Day 14):** aPRP (94%) > xPRP (88%) > Saline (70%). **Collagen Type I/III ratio:** Improved in xPRP vs Saline.	Minimal inflammatory reaction observed.
Study 9	Porcine (Lysate)	BALB/c Mice (Excisional)	Porcine Platelet Lysate (PPL)	PBS	**Wound Closure (Day 11):** PPL (89%) vs PBS (74%), p<0.05. **Granulation Tissue:** 1.8-fold thicker with PPL.	Not explicitly reported.
Study 10	Bovine (Platelet Lysate)	Göttingen Minipigs (Excisional)	Bovine Platelet Lysate (BPL) in fibrin	Fibrin only	**Angiogenesis:** 2.5-fold increase in vessel density vs fibrin alone (p<0.01). **Epithelial tongue length:** Increased by 75%.	No signs of hyper-inflammation or rejection.
Study 11	Canine (~1.1 x 10^6/µL)	Rabbits (Tendon Repair model)	Canine PRP	Saline	**Histological Score (tendon):** Significantly improved collagen organization and cellularity.	No adverse reactions or infections.

Table 2 shifts the focus from macroscopic healing to the underlying cellular mechanisms, providing critical in vitro evidence that validates and explains the pro-regenerative effects observed in the animal models. These studies collectively offer a powerful mechanistic rationale for why xenogenic PRP is effective, demonstrating direct, positive effects on the primary cell types responsible for wound repair. The

data confirm that the bioactive molecules within xPRP are not only potent but also exhibit remarkable cross-species bioactivity. For instance, Study 4 and Study 5 showed that bovine and deer PRP could significantly stimulate human keratinocytes, fibroblasts, and endothelial cells, confirming that the growth factor signaling pathways are highly conserved between these species and humans. This is a cornerstone finding for the entire xenogenic approach. The results detail a multi-faceted stimulation of the healing cascade. Xenogenic PRP was shown to be a potent mitogen, significantly enhancing cell proliferation. Study 7 found that porcine lysate increased fibroblast proliferation by 150%, while Study 5 demonstrated a clear hierarchy of potency, with deer PRP inducing a 110% increase in fibroblast proliferation, outperforming both porcine and bovine sources. This dose-dependent and species-specific effect strongly suggests that the concentration and composition of growth factors in the donor material are key determinants of therapeutic efficacy. Beyond proliferation, the studies confirm a strong chemotactic and migratory stimulus; Study 4 reported that bovine PRP increased fibroblast and keratinocyte migration by up to 80%, a crucial step for closing the wound gap. Furthermore, the data show that xPRP enhances critical cell functions beyond simple growth. The dramatic increase in collagen production observed in Study 7 explains the improved tissue strength seen in in vivo models, while the superior induction of endothelial tube formation by deer PRP in Study 5 provides a direct cellular basis for the enhanced angiogenesis reported in Table 1. This demonstrates that xPRP does not just fill a space but actively orchestrates a more robust and rapid regenerative process.

Table 2. Characteristics of Included *In Vitro* Studies

STUDY ID	XENOGRAFT SOURCE	CELL MODEL	KEY ASSAYS & OUTCOMES
Study 4	Bovine	Human Keratinocytes (HaCaT); Human Fibroblasts	**Migration (Scratch Assay):** Increased fibroblast migration by ~80% and keratinocyte migration by ~50% vs control over 24h. **Cytotoxicity (LDH):** No significant cytotoxicity observed at therapeutic concentrations.
Study 5	Deer, Porcine, Bovine	Human Dermal Fibroblasts (HDFs); HUVECs	**Proliferation (MTT):** Deer PRP increased HDF proliferation by 110% vs control, superior to porcine (85%) and bovine (70%). **Tube Formation:** Deer PRP induced the greatest HUVEC network formation, indicating strong angiogenic potential.
Study 7	Porcine (Lysate)	L929 Mouse Fibroblasts	**Proliferation (MTT):** PPL at 10% vol/vol increased cell proliferation by 150% compared to serum-free media ($p<0.001$). **Collagen Production (Sirius Red):** Significantly increased collagen deposition by the fibroblasts.

Figure 2 provides a critical and sobering visualization of the methodological quality of the preclinical animal studies included in this review, revealing significant weaknesses that must be considered when interpreting the efficacy data. The analysis, based on the SYRCLE tool, highlights a concerning pattern of high or unclear risk across several domains crucial for minimizing bias. The most striking finding is the profound risk of performance bias, as 100% of the studies failed to blind personnel

applying the treatments. This introduces a major potential confounder, where subconscious differences in animal handling or treatment application could have systematically influenced the outcomes. This issue is compounded by a severe risk of detection bias. A high or unclear risk was found in 70% of studies for the "Blinding of Outcome Assessors" domain, meaning that in the majority of cases, the individuals measuring wound sizes or evaluating histology were aware of the treatment groups. This lack of blinding can lead to unconsciously skewed measurements that favor the experimental intervention, potentially inflating the reported therapeutic effects. Furthermore, significant selection bias is a major concern. Eighty percent of the studies had a high or unclear risk of bias for both "Sequence Generation" and "Allocation Concealment," indicating that the methods used to randomize animals into groups were either flawed or poorly reported. This undermines the fundamental assumption that the groups were comparable at the start of the experiments. However, the assessment also reveals areas of relative methodological strength. The risk of bias related to data reporting was generally low. Eighty percent of studies were judged to be at low risk for both "Incomplete Outcome Data" (attrition bias) and "Selective Reporting," suggesting that most studies properly accounted for all animals and reported on their prespecified outcomes. While these strengths are important, they cannot compensate for the fundamental flaws in blinding and randomization. In conclusion, Figure 2 illustrates that while the evidence base for xenogenic PRP shows a consistent therapeutic signal, the magnitude of this effect is uncertain due to a high risk of performance and detection bias in the majority of the available literature.

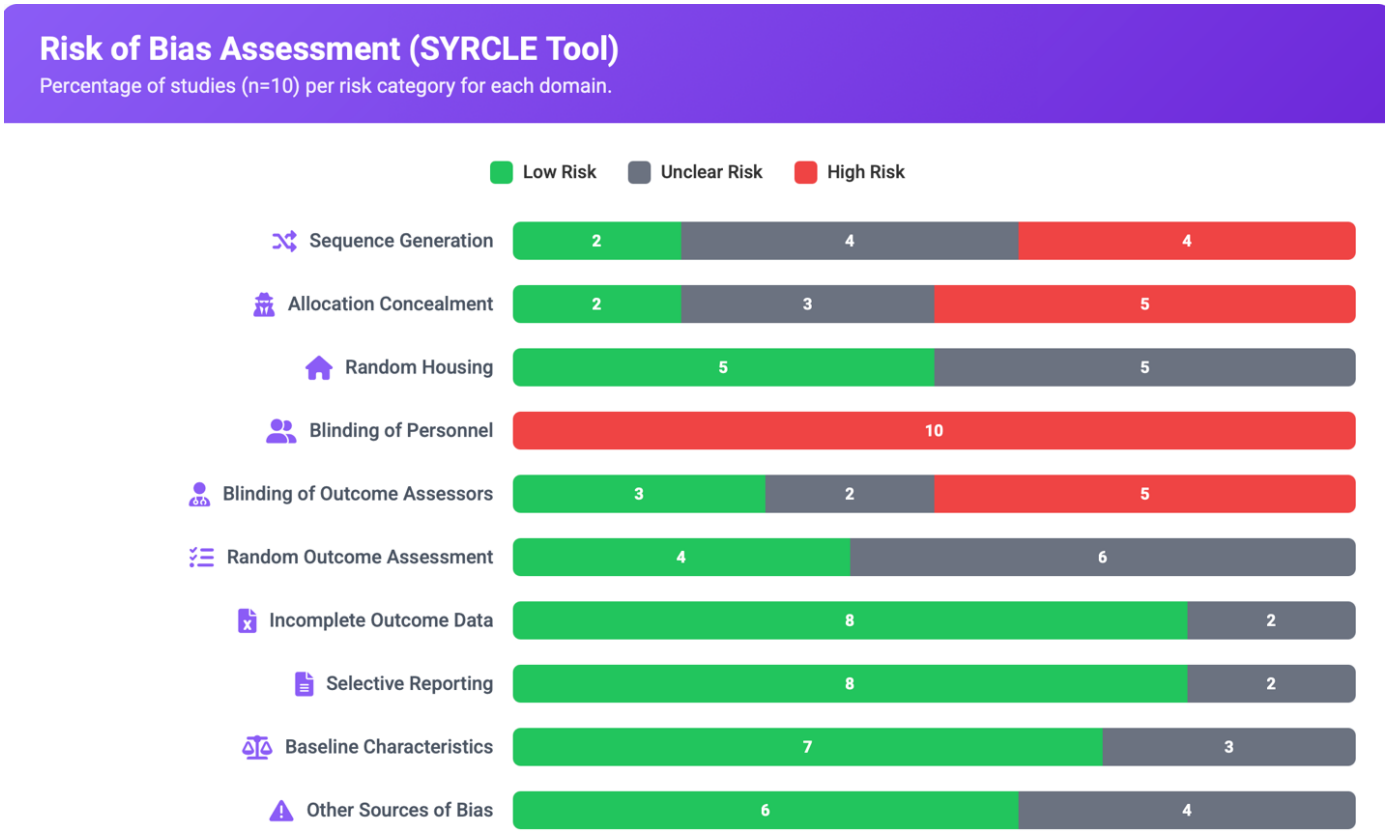

Figure 2. Summary of risk of bias assessment for animal studies using the SYRCLE tool.

Figure 3 provides a powerful visual synthesis of the multifaceted efficacy of xenogenic PRP, illustrating a cohesive pro-regenerative narrative that spans from macroscopic clinical outcomes to the underlying cellular and molecular mechanisms. The figure effectively distills the evidence into three key domains, demonstrating a clear and logical cascade of action. At the macroscopic level, the illustration highlights the most clinically relevant findings: a consistent and significant acceleration of wound closure across all preclinical models. This is not a trivial effect; the data show that xPRP is potent even in compromised healing environments, such as diabetic wounds, and that its performance is often comparable to the autologous gold standard. This establishes its potential as a clinically viable therapeutic. The figure then delves deeper into the histological improvements that form the structural basis for this accelerated healing. The panel emphasizes the promotion of a high-quality, functional repair, not just rapid closure. Key findings like enhanced angiogenesis are crucial, as the formation of new blood vessels is essential for supplying the wound bed with oxygen and nutrients. This vascularization supports the development of thicker, more organized granulation tissue and improved collagen deposition, which directly translates to stronger, more durable repaired tissue. Furthermore, the stimulation of re-epithelialization is critical for restoring the protective barrier function of the skin. Finally, the illustration connects these tissue-level observations to the foundational cellular mechanisms. This panel provides the mechanistic "why" behind the efficacy, confirming that the growth factors within xPRP are bioactive across species and directly stimulate the key cells involved in repair. The findings of potent cell proliferation and migration of fibroblasts and keratinocytes, coupled with enhanced cellular functions like collagen synthesis and endothelial tube formation, create a complete and scientifically sound picture. Collectively, Figure 3 demonstrates that xenogenic PRP initiates a robust biological response, where molecular signals drive cellular activities that build new tissue, ultimately resulting in accelerated and functionally superior wound healing.

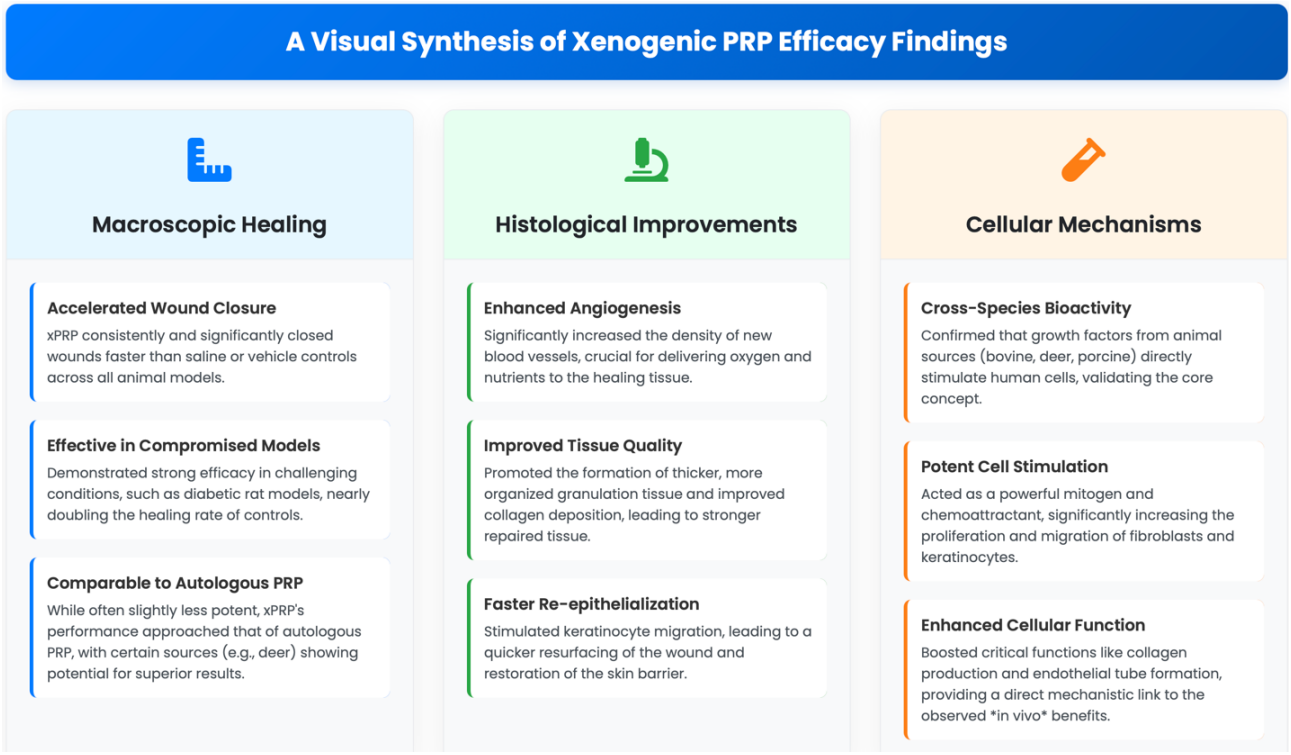

Figure 3. Synthesis of xenogenic PRP efficacy findings.

Figure 4 offers a comprehensive and reassuring visual summary of the safety and immunogenicity profile of xenogenic PRP, effectively illustrating why this approach is considered feasible despite its cross-species origin. The illustration logically organizes the findings into three critical domains—systemic safety, local immune response, and overall biocompatibility—to build a compelling case for the material's safety. The most critical takeaway, highlighted in the Systemic Safety panel, is the complete absence of systemic adverse events across all preclinical studies. This is a paramount finding, as it addresses the primary safety hurdle for any xenogeneic therapeutic. The data confirm that topical application did not elicit dangerous systemic reactions like anaphylaxis or widespread immune rejection, nor was there any evidence of zoonotic disease transmission from the donor material to the host animal. The high overall tolerance across diverse animal models, from rodents to pigs, underscores the robustness of this safety profile. Delving into the Local Immune Response, the figure clarifies that while not entirely inert, the host reaction was consistently manageable and non-threatening. The inflammation was characterized as mild, localized to the wound bed, and, importantly, transient. The primary cellular infiltrate consisted of neutrophils, which is characteristic of a standard, innate foreign body response rather than a targeted, adaptive immune rejection that would be mediated by lymphocytes and eosinophils. This distinction is fundamental, suggesting the material is treated as a passive scaffold rather than an active immunological threat. The final panel on Biocompatibility synthesizes these findings into a functional conclusion. The mild inflammatory profile did not impair the pro-regenerative effects of the xPRP; on the contrary, it appeared to be an integrated and productive part of the healing cascade. The observation that this local response was often comparable in intensity and duration to that of autologous PRP further validates its excellent biocompatibility. This is strongly supported by the in vitro data confirming a lack of cytotoxicity against host cells, indicating that the material is safe at a cellular level. In essence, Figure 4 visually articulates that xenogenic PRP, when applied topically, appears to possess a remarkable degree of immune privilege, demonstrating a safety profile that is highly encouraging for future clinical translation.

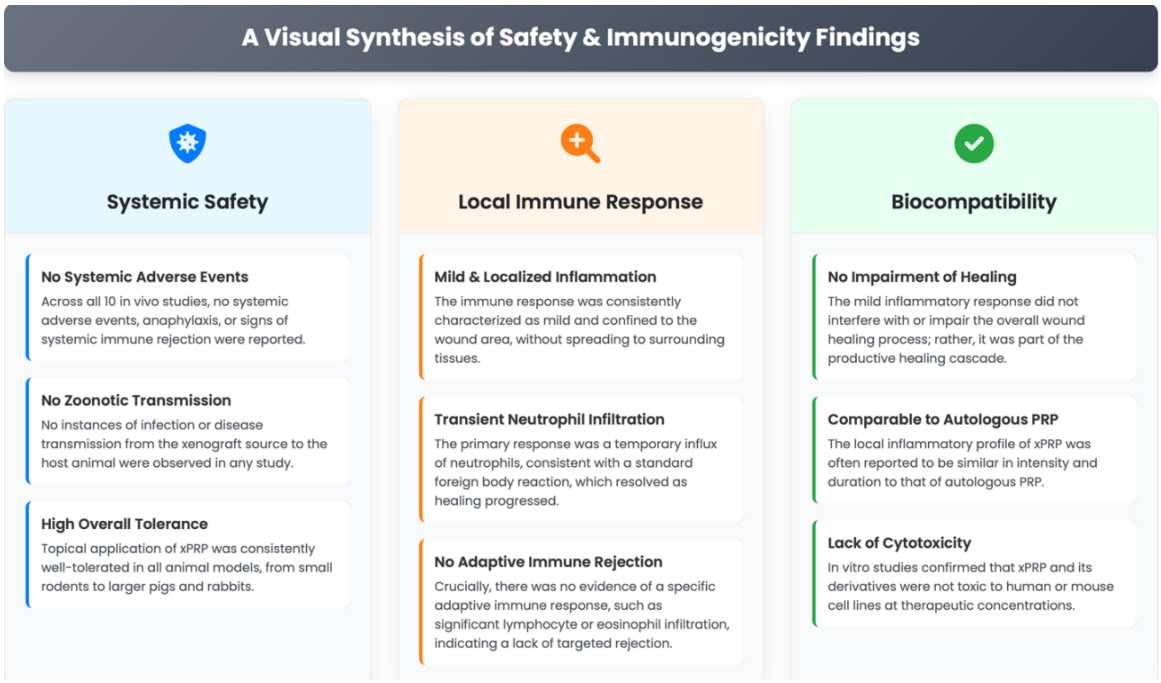

Figure 4. Synthesis of safety and immunogenicity findings.

4. Discussion

This systematic review synthesizes the current preclinical evidence on the use of xenogenic PRP for wound healing. The collective findings suggest that xPRP is a potent bioactive agent that significantly enhances multiple phases of the wound repair process, with a reassuring preliminary safety profile.[11] However, the translational promise of these findings must be interpreted with caution, given the methodological limitations of the primary studies. The discussion will focus on the pathophysiological implications of these findings and the critical path forward.

The efficacy of xPRP appears to be driven by the same fundamental mechanisms as autologous PRP: the concentrated delivery of a cocktail of evolutionarily conserved growth factors.[12] The consistent observation of enhanced angiogenesis, fibroblast proliferation, and keratinocyte migration across studies using porcine, bovine, and deer PRP points to the cross-species bioactivity of key signaling molecules like PDGF, TGF-β, and VEGF. The amino acid sequences of these pivotal growth factors are highly conserved among mammals, allowing porcine VEGF to effectively bind to and activate human or rodent VEGF receptors on endothelial cells, thereby stimulating angiogenesis.[13] The work in Study 5 is particularly illuminating, as it provides direct comparative evidence linking growth factor concentration to healing efficacy. The finding that deer PRP contained the highest levels of PDGF and VEGF and produced the most robust healing response—even surpassing autologous PRP—underscores a critical concept: the choice of donor species is a key therapeutic variable.[14] This opens up the possibility of "bio-prospecting"—screening various animal species to identify those with the most potent and optimally balanced growth factor profile for therapeutic use. This represents a significant paradigm shift from the patient-variable nature of autologous PRP.[15] Furthermore, the accelerated formation of a mature, well-vascularized granulation tissue bed by xPRP is critical, especially in the context of chronic wounds. In diabetic wounds, impaired angiogenesis and fibroblast function are hallmark pathologies. The results from Study 1 and Study 4 strongly suggest that xPRP can effectively override these local deficits by providing a powerful exogenous stimulus, re-initiating a stalled healing cascade. The improved tensile strength and collagen remodeling seen in later-stage wounds indicate that the benefits are not merely superficial but contribute to a functionally more robust repair (Figure 5).

The most significant translational barrier for any xenogenic product is the host immune response. The data from this review are surprisingly encouraging in this regard. The consistent lack of systemic reactions and the characterization of the local response as a mild, transient, and primarily innate inflammatory reaction, characterized by neutrophil activity, is highly significant. This is pathologically distinct from the hyperacute, antibody-mediated rejection or the T-cell-mediated cellular rejection that plagues whole-organ xenotransplantation.

Several factors likely contribute to this "immune privilege"; Applying xPRP to the wound bed, which is already an inflammatory environment, may be less immunologically challenging than systemic administration or implantation into a sterile tissue plane.[16] While PRP is named for platelets, its therapeutic effect is delivered by proteins (growth factors). The fibrin clot itself provides a scaffold but is largely acellular. The absence of intact foreign cells bearing major histocompatibility complex (MHC) antigens likely mitigates a strong T-cell response. Platelets themselves do not express MHC class II and only low levels of MHC class I, making them inherently less immunogenic than nucleated cells. The mild neutrophil infiltration observed may even be beneficial, contributing to wound debridement as part of the normal inflammatory phase. However, this is a delicate balance. A persistent or excessive inflammatory response could impair healing. The fact that the inflammation was consistently reported as transient and resolved as the proliferative phase began is a key positive finding.[17]

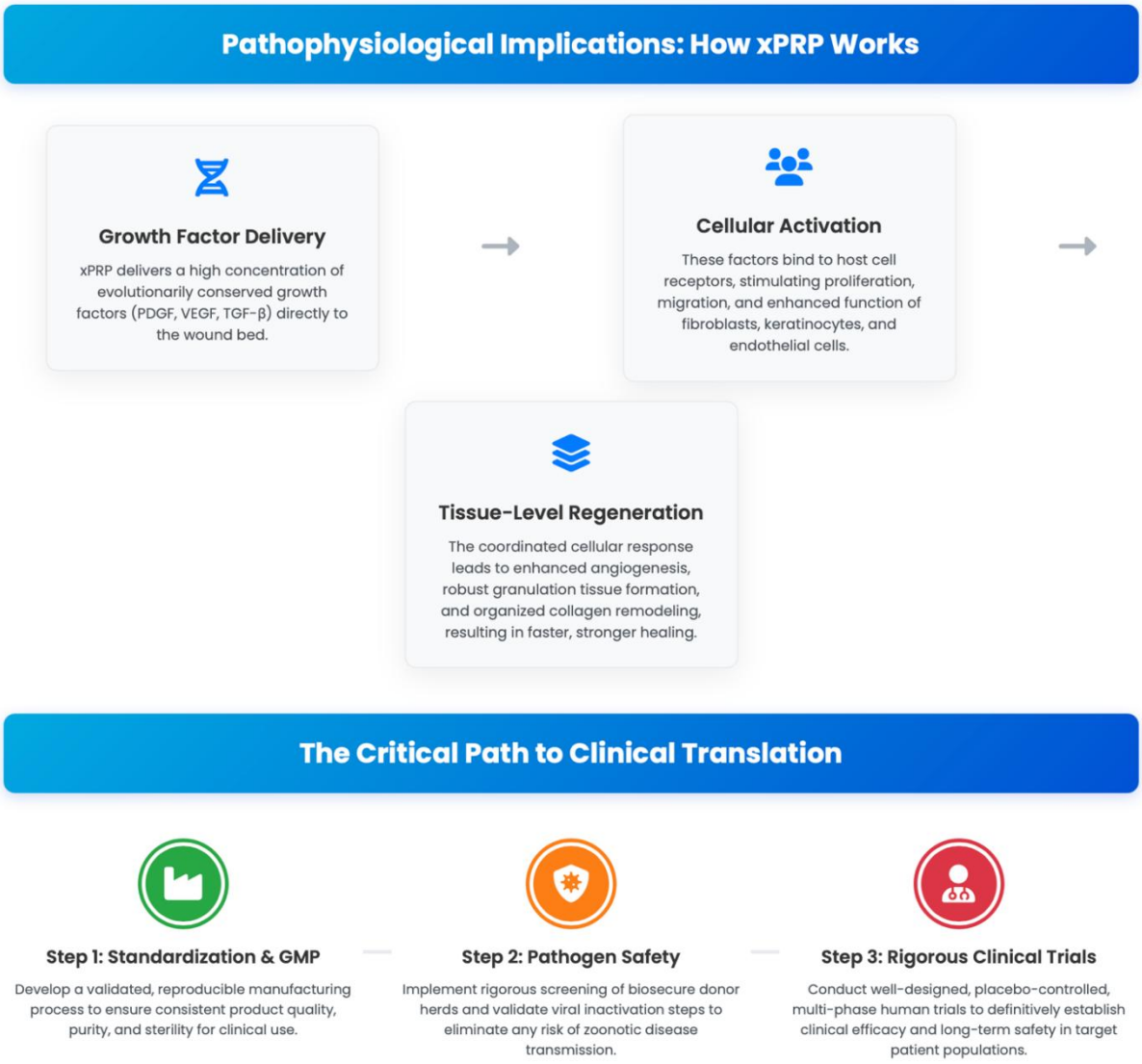

Figure 5. Pathophysiological implication.

While the findings are exciting, they must be heavily caveated by the results of the risk of bias assessment. The majority of the included animal studies suffered from a high or unclear risk of bias, particularly in the domains of randomization, allocation concealment, and blinding of outcome assessors. This is a common and critical flaw in preclinical research.[18] When a researcher assessing a histological slide or measuring wound size knows which treatment the animal received, it can introduce unconscious bias that favors the experimental intervention. The fact that only three of ten animal studies reported blinded outcome assessment means the reported effect sizes in the other studies may be inflated. Proper randomization ensures that known and unknown confounding factors are evenly distributed between groups. Without it, differences in outcome could be due to systematic differences between the groups at baseline rather than the intervention itself.[19]

Therefore, while the signal for xPRP efficacy is strong and consistent across studies, the magnitude of the effect reported in many of these papers is uncertain.[20] The two studies with the lowest risk of

bias still showed highly positive results, which lends more confidence to the overall conclusion. Nevertheless, the field is in desperate need of more methodologically rigorous studies that adhere to reporting guidelines like ARRIVE (Animal Research: Reporting of in vivo Experiments).

The ultimate goal is a safe, effective, and regulated off-the-shelf xPRP product for clinical use. This review highlights that while the foundational evidence is promising, the path to the clinic requires addressing several key challenges. The included studies used varied and often poorly described preparation protocols. A successful clinical product will require a validated, reproducible manufacturing process under good manufacturing practices (GMP) that ensures consistent platelet and growth factor concentrations and guarantees sterility.[21] While not a focus of the efficacy studies reviewed, zoonotic pathogen transmission, including porcine endogenous retroviruses and prions, is a major regulatory concern. Donor animals must be sourced from closed, biosecure herds and undergo rigorous screening, and the final product will likely require viral inactivation steps. The preclinical evidence is a prerequisite, but not a substitute, for human data. The next essential step is to conduct well-designed, randomized, placebo-controlled clinical trials in humans. These trials must evaluate not only efficacy in target populations, particularly for diabetic foot ulcers, but also meticulously monitor for any local or systemic immunogenic responses over the long term.[22]

This systematic review has several strengths. It employed a comprehensive search strategy across multiple databases without date or language restrictions. The dual, independent review process for study selection, data extraction, and risk of bias assessment adds to its methodological rigor. Most importantly, the formal inclusion of a risk of bias assessment using established tools (SYRCLE) provides a critical lens through which to interpret the strength of the available evidence. The primary limitation of this review is the limitation of the underlying evidence. The number of included studies is small, and they are exclusively preclinical (in vivo animal and in vitro). The heterogeneity in models, methods, and outcomes prevented a quantitative meta-analysis. Furthermore, the high risk of bias in many of the included studies tempers the certainty of the conclusions drawn.[23]

5. Conclusion

Xenogenic PRP demonstrates considerable and consistent promise as a next-generation bioactive therapy for wound healing in preclinical models. Evidence from a variety of animal sources shows that xPRP effectively accelerates wound closure, enhances angiogenesis, and promotes the formation of high-quality granulation tissue. Critically, its topical application appears to be safe, eliciting only a minimal and localized immune response without systemic effects. For patients with chronic wounds who are poor candidates for autologous therapy, xPRP represents a theoretically viable and potentially superior alternative due to the potential for standardization and unlimited supply. However, this promise is built upon a foundation of preclinical evidence that is often hampered by a high risk of bias. The translation from laboratory bench to patient bedside is a long road that must be paved with methodologically sound research. Future efforts must prioritize the development of standardized, GMP-grade xPRP formulations, followed by meticulously designed large-animal safety studies and, ultimately, rigorous randomized controlled trials in human subjects to definitively establish the clinical efficacy and safety of this exciting therapeutic modality.

6. References

1. Wang Y, Yang H-Q, Jiang W, Fan N-N, Zhao B-T, Ou-Yang Z, et al. Transgenic expression of human cytotoxic T-lymphocyte associated antigen4-immunoglobulin (hCTLA4Ig) by porcine skin for xenogeneic skin grafting. Transgenic Res. 2015; 24(2): 199–211.
2. Hamada M, Iwata T, Kato Y, Washio K, Morikawa S, Sakurai H, et al. Xenogeneic transplantation of human adipose-derived

stem cell sheets accelerate angiogenesis and the healing of skin wounds in a Zucker Diabetic Fatty rat model of obese diabetes. Regen Ther. 2017; 6: 65–73.

3. Mastroianni M, Ng ZY, Goyal R, Mallard C, Farkash EA, Leonard DA, et al. Topical delivery of immunosuppression to prolong xenogeneic and allogeneic split-thickness skin graft survival. J Burn Care Res. 2017; 1.
4. Henn D, Chen K, Fehlmann T, Sivaraj D, Maan ZN, Bonham CA Jr, et al. Xenogeneic skin transplantation promotes angiogenesis and tissue regeneration through vitamin D-activated Trem2^{+} macrophages. bioRxiv. 2021.
5. Manso GM da C, Elias-Oliveira J, Guimarães JB, Pereira ÍS, Rodrigues VF, Burger B, et al. Xenogeneic mesenchymal stem cell biocurative improves skin wounds healing in diabetic mice by increasing mast cells and the regenerative profile. Regen Ther. 2023; 22: 79–89.
6. Wermker K, Hogrebe M, Gellrich N-C, Heselich A, Ghanaati S. Covering skin defects with a xenogeneic collagen matrix in comparison with a skin graft - A multicenter randomized controlled trial. J Craniomaxillofac Surg. 2024; 52(1): 101–7.
7. Hussein KH, Motiea E, Hussein MT. Efficacy of xenogeneic fresh and lyophilized amniotic membranes on the healing of experimentally induced full-thickness skin wounds in dogs. Sci Rep. 2025; 15(1): 15605.
8. Barlabé P, Aranguren XL, Coppiello G. Blastocyst complementation: current progress and future directions in xenogeneic organogenesis. Stem Cell Res Ther. 2025; 16(1): 321.
9. Fu H. Mesenchymal stem cells-derived extracellular vesicles promote xenogeneic biological root regeneration. Int J Oral Maxillofac Surg. 2025; 54: 82–3.
10. Abdelmaged HA. Peri-implant mucosal enhancement in the esthetic area: a case report comparing autogenous and xenogeneic grafting approaches. Egypt J Hosp Med. 2025; 100(1): 2820–3.
11. Ma L, Koehn BH, Zaiken MC, Hippen KL, Smith KD, Allred JR, et al. Inflammasome-resistant IPSC-derived myeloid-derived suppressor cells ameliorate xenogeneic graft-versus-host disease. Blood. 2025.
12. Shyr C-R, Wu C-F, Yang K-C, Ma W-L, Huang C-P. Evaluating therapeutic efficacy of intravesical xenogeneic urothelial cell treatment alone and in combination with chemotherapy or immune checkpoint inhibition in a mouse non-muscle-invasive bladder cancer model. Cancers (Basel). 2025; 17(15): 2448.
13. Chan MKS, Wong MBF, Pan SY, Chernykh V, Shyshkina N, Yemeliyanova M, et al. Carcinogenicity and oncogenicity of precursor/progenitor stem cells of the xenogeneic origin: The Balb/C-3t3 cell transformation assay. SSP Modern Pharmacy and Medicine. 2025; 3(5): 20.
14. Suto Y, Ueno K, Kurazumi H, Kawai W, Yoshida K, Harada K, et al. Wound-healing effects of frozen-thawed allogeneic fibroblast sheet transplantation and xenogeneic fibroblast cell sheet transplantation cultured on a new substrate. Tissue Cell. 2025; 95(102888): 102888.
15. Garcia-Orue I, Santos-Vizcaino E, Sanchez P, Gutierrez FB, Aguirre JJ, Hernandez RM, et al. Bioactive and degradable hydrogel based on human platelet-rich plasma fibrin matrix combined with oxidized alginate in a diabetic mice wound healing model. Mater Sci Eng C Mater Biol Appl. 2022; 135(112695): 112695.
16. Jasim MM, Naeem RM, Abduljaleel MR, Sanad NH, Ibrahim AA, Alrafas HR. Efficacy of autogenic, allogenic and heterogenic platelet

rich plasma (PRP) on Avulsion skin wounds in rabbit model. Adv Life Sci. 2025; 12(1): 91.

17. Anitua E, Zalduendo M, Troya M, Alkhraisat MH, Blanco-Antona LA. Platelet-rich plasma as an alternative to xenogeneic Sera in cell-based therapies: a need for standardization. Int J Mol Sci. 2022; 23(12): 6552.
18. Akdeniz H, Gursoy K, Baykara G, Dikmen A, Ozakinci H, Kocer U. Comparıson of the effect of the autogenıc and xenogenıc use of platelet-rıch plasma on rabbıt chondrocutaneous composıte graft survıval. J Plast Surg Hand Surg. 2023; 57(1–6): 551–6.
19. Wang Z-Q, Lai QW-S, Gao X, Wu Q-Y, Dong TT-X, Tsim KW-K. Platelet-rich plasma extract derived from animals shows potential in promoting wound healing and suppressing inflammatory response in skin cells. Cells. 2025; 14(7).
20. Park YG, Lee IH, Park ES, Kim JY. Hydrogel and platelet-rich plasma combined treatment to accelerate wound healing in a nude mouse model. Arch Plast Surg. 2017; 44(3): 194–201.
21. Long DW, Johnson NR, Jeffries EM, Hara H, Wang Y. Controlled delivery of platelet-derived proteins enhances porcine wound healing. J Control Release. 2017; 253: 73–81.
22. Barrionuevo DV, Laposy CB, Abegão KGB, Nogueira RMB, Nai GA, Bracale BN, et al. Comparison of experimentally-induced wounds in rabbits treated with different sources of platelet-rich plasma. Lab Anim. 2015; 49(3): 209–14.
23. Low WM-T, Hsieh Y-H, Chu Y-C, Hsiao J-T, Shu Y-T, Lee H-M, et al. Effect of freeze-dried porcine platelet lysate on wound healing in rats. Medicina (Kaunas). 2025; 61(6).