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Review

The role of platelet-rich plasma in biomedicine: A comprehensive overview

Zhixin Zhang,[1,2,3,4,5,6,8] Peng Liu,[1,2,3,4,5,6,8] Xinmiao Xue,[1,2,3,4,5,6,8] Zhiyu Zhang,[7] Li Wang,[1,2,3,4,5,6] Yvke Jiang,[1,2,3,4,5,6] Chi Zhang,[1,2,3,4,5,6] Hanwen Zhou,[1,2,3,4,5] Shuhan Lv,[1,2,3,4,5] Weidong Shen,[1,2,3,4,5,6] Shiming Yang,[1,2,3,4,5,6,*] and Fangyuan Wang[1,2,3,4,5,*]

[1]Senior Department of Otolaryngology Head and Neck Surgery, the Sixth Medical Center of Chinese PLA General Hospital, Chinese PLA Medical School, Beijing 100853, China
[2]State Key Laboratory of Hearing and Balance Science, Beijing 100853, China
[3]National Clinical Research Center for Otolaryngologic Diseases, Beijing 100853, China
[4]Key Laboratory of Hearing Science, Ministry of Education, Beijing 100853, China
[5]Beijing Key Laboratory of Hearing Impairment Prevention and Treatment, Beijing 100853, China
[6]Graduate School of Medicine, Chinese PLA General Hospital, Chinese PLA Medical School, Beijing 100853, China
[7]School of Physics and Optoelectronic Engineering Xidian University, Xi'an 710071, China
[8]These authors contributed equally
*Correspondence: shm_yang@163.com (S.Y.), fangyuanwang05@163.com (F.W.)
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SUMMARY

Biomedicine has seen significant advancements in the 21st century, with platelet-rich plasma (PRP) playing a crucial role in clinical practice. This blood derivative, enriched with platelet components, has shown great potential for promoting tissue repair and regeneration. Its wide range of applications and the presence of anti-inflammatory and growth-promoting factors make it a valuable tool in the field of biomedicine. The exploration of PRP in clinical settings has been gaining momentum. Despite its cost-effectiveness, safety, and therapeutic efficacy, the widespread clinical adoption of PRP has been hindered by the absence of consistent preparation standards and standardized treatment protocols. This article provides a comprehensive analysis of the clinical uses, physiological roles, molecular mechanisms, and preparation techniques of PRP in biomedicine. The aim is to offer a thorough understanding of the potential applications and benefits of PRP in medical practice.

INTRODUCTION

Platelet-rich plasma (PRP) has a rich history, dating back to its initial description by Kingsley in 1954 as a blood product with elevated platelet levels.[1,2] The refinement of density gradient centrifugation in the 1960s and 1970s played a pivotal role in the separation of blood components, further advancing the development of PRP. Its first clinical use in cardiac surgery in 1987 demonstrated promising therapeutic effects, leading to its subsequent application in various medical disciplines.[3] While PRP has been utilized for over four decades and has garnered increasing attention, controversies persist regarding its efficacy, choice of therapeutic regimen, and long-term prognostic outcomes.[4] This review aims to delve into the current status of PRP application across clinical departments, its physiological effects, potential mechanisms of action, and provide guidance for the standardization of PRP therapy.

ACTIVE INGREDIENTS AND CLASSIFICATION OF PRP

Marx[5] defined PRP as plasma with a platelet count greater than 1 × 10^6 per microliter in. PRP is distinguished by its rich content of growth factors and other bioactives.[6–8] We list the sources and physiological roles of the aforementioned growth factors in Table 1. These growth factors are delivered intracellularly through α-granules, dense granules, or λ-granules.[23,24] This targeted delivery plays a crucial role in exerting anti-inflammatory and reparative effects. α-granules regulate early inflammation, promote macrophage polarization, and actively prevent inflammatory responses.[25] Dense granules predominantly contain bioactive agents such as serotonin, histamine, dopamine, calcium, and adenosine. These substances enhance membrane permeability and modulate inflammatory processes.[26,27] The orchestrated action of these components underscores the multifaceted therapeutic potential of PRP.

Different derivatives of PRP with varying properties can be obtained through distinct preparation schemes. Dohan Ehrenfest et al.[28] categorized PRP into four types based on the levels of leukocytes and fibrinogen within PRP: pure PRP or leukocyte-poor PRP (P-PRP), leukocyte-rich PRP (L-PRP), leukocyte-poor platelet-rich fibrin (P-PRF), and leukocyte-rich platelet-rich fibrin (L-PRF). Figure 1 schematically illustrates this classification, offering a visual representation of the various PRP types. The first two types can exist in liquid or activated

Table 1. Overview of active ingredients of PRP

Growth factors	Origins	Physiological effects
PDGF	Neuronal cells, astrocytes, oligodendrocytes, and vascular cells[9]	Induces stem cell differentiation, participates in neuroprotection, and promotes cell proliferation and migration[9,10]
TGF-β	B cells, T cells, dendritic cells, macrophages[11]	Promoting cell proliferation and differentiation, participating in tissue repair and fibrosis, and inhibiting the activation of immune cells[12,13]
VEGF	Production by endothelial cells, smooth muscle cells, platelets, neutrophils and macrophages[14]	In charge of angiogenesis and vascular repair, indirectly promoting tissue repair and neuroprotection[14]
IGF-1	Hepatic stellate cells, osteoblasts, fibroblasts, macrophages[15]	Promotes growth, cell differentiation and cell proliferation[16]
bFGF	Endothelial cells, bone cells[17,18]	Induction of neovascularization and neurotrophy[19,20]
EGF	Endothelial cells, vascular smooth muscle cells, neutrophils, macrophages[21]	Promoting wound healing and anti-inflammatory[22]

gel form, while the latter two can only exist in gel form.[22] In the peripheral nervous system, activated PRP gel can serve as a tissue engineering scaffold for connecting injured nerves, inducing damaged nerves to reconnect in the correct physiological structure.[29,30] Different PRP derivatives can meet various clinical and research needs.[31] We summarize the characteristics of these PRP derivatives in Table 2 to provide a reference basis for selecting more suitable treatment options in clinical practice. It is hoped that through further research and practice, PRP preparation methods can be further refined to provide better support and assurance for clinical treatment and research endeavors in the future.

PREPARATION OF PRP

The preparation methods of PRP are diverse, with common techniques including centrifugation, extraction of the buffy coat layer, and the use of commercial kits, among which centrifugation is the most commonly employed method.[37] Despite the widespread familiarity with the PRP preparation process, variations in blood collection volume, centrifugation conditions, and storage methods among different protocols may impact the quality and efficacy of PRP. Therefore, strict control over each step of the preparation process is necessary to ensure the attainment of high-quality PRP. We schematically illustrate the

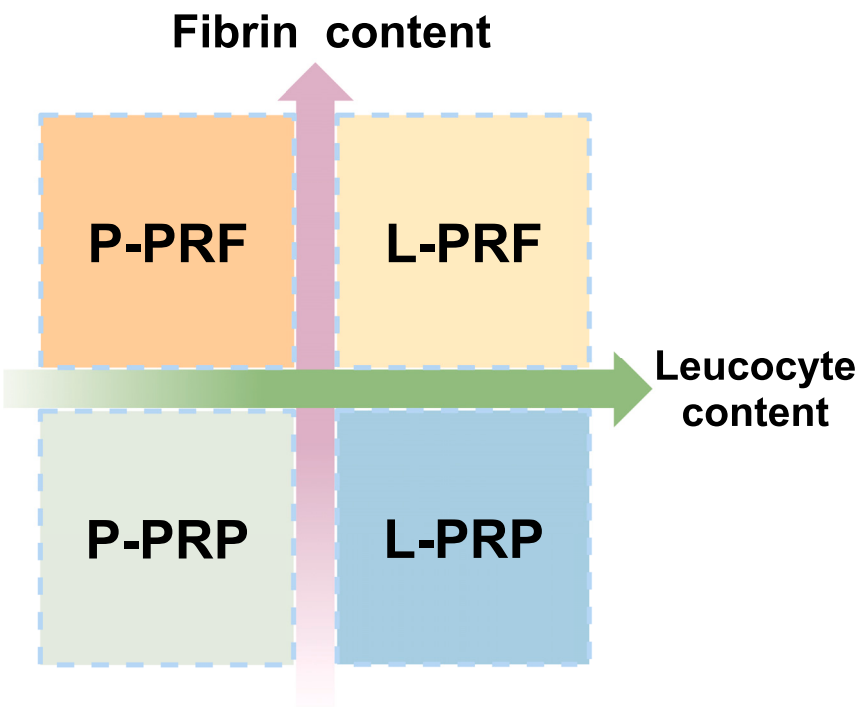

Figure 1. Platelet-rich plasma classification

Note: The Dohan Ehrenfest classification divides platelet-rich plasma into 4 categories based on leukocyte and fibrin content. (1) P-PRP: low fibrin content and no leukocytes or low leukocyte content after activation. (2) L-PRP: low fibrin content and relatively high leukocyte content after activation. (3) P-PRF: platelet-rich fibrin rich or platelet-rich fibrin poor in leukocytes. (4) L-PRF: high fibrin and leukocyte content after activation.

Table 2. Classification of PRP

Classification of PRP	Feature	Applications
P-PRP	Earliest to emerge, most widely used.[32]	With minimal adverse reactions, this product is highly utilized across different fields including tissue repair, anti-inflammation, and neuroprotection. Its primary applications are in orthopedics and dentistry, where it has shown significant benefits.[32]
L-PRP	The product contains a higher concentration of white blood cells, resulting in less loss of cytokines during the separation process.[33]	It is possible that P-PRP may exacerbate tissue inflammation and wound pain. However, due to its higher concentration of growth factors, the treatment outcomes may be superior to P-PRP.[31]
P-PRF	During centrifugation without the addition of anticoagulants, the resulting product contains fibrinogen. This product has the ability to sustain the release of cytokines over an extended period of time.[34]	Promoting tissue regeneration, improving skin elasticity, and reducing pigmentation deposition are the main functions of this product. It can also serve as a drug carrier for tissue engineering. It is primarily used in dermatology and oral surgery.[35]
L-PRF	Combines the advantages and disadvantages of L-PRP and P-PRF.[36]	The treatment efficacy may be superior to P-PRF, with a longer duration of effectiveness. However, there is also a risk of exacerbating inflammation.[35]

process of PRP preparation in Figure 2. Nevertheless, this is not the sole method for preparing PRP.

The diversity in preparation methods among researchers and institutions for obtaining PRPs results in varying platelet concentrations, and the content of growth factors and bioactive substances is crucial for treatment efficacy.[31] The current lack of comprehensive quantitative analysis hinders a thorough comparison of these methods beyond platelet concentrations.[38] Understanding the impact of these differences on growth factors and bioactive substances, and subsequently on treatment outcomes, is crucial.[39] By recognizing and addressing these discrepancies, practitioners can optimize results for patients or subjects. It is essential to recognize that any preparation method that aligns with the definition of PRP and demonstrates therapeutic benefits should be considered valid. Perfection in retaining all active therapeutic elements may not be achievable, making it crucial to prioritize efficacy over perfection in the selection of a preparation method.

PHYSIOLOGICAL ROLE AND MECHANISM OF PRP

PRP has a significant impact on gene expression, promoting cell proliferation, differentiation, and repair.[40,41] Its regulatory mechanisms include activating signaling pathways, regulating transcription factors, and controlling the cell cycle. By influencing intracellular signaling pathways, PRP can regulate the expression of multiple genes, thus affecting cell function and fate. Additionally, PRP can affect gene transcription and translation processes by regulating the expression and activity of transcription factors. Understanding the regulatory mechanisms of PRP on gene expression not only helps reveal its important role in regulating cell function but also provides a theoretical basis for its potential value in clinical applications. The following sections will elaborate on the process by which major growth factors regulating gene expression exert biological effects.

TGF-β FAMILY

The transforming growth factor β (TGF-β) family plays a crucial role in inhibiting inflammation and regulating cell cycle processes, including substances such as TGF-β1, TGF-β2, TGF-β3, bone morphogenetic proteins (BMPs), and activins.[42,43] TGF-β can bind to specific receptors on the cell membrane, known as TGFβR-I/II, which possess serine/threonine kinase activity.[44,45] Upon binding to TGF-β, TGFβR-II undergoes phosphorylation and activates TGFβR-I, forming a stable complex.[46,47] Activated TGFβR-I phosphorylates Smad2 and Smad3, with activated Smad3 further phosphorylating Smad4.[48] Phosphorylated Smad2/3/4 trimerizes and translocates into the nucleus to regulate the expression of target genes.[49,50]

TGF-β plays a crucial role in the anti-inflammatory effects of PRP. Yadav et al.[51] found that PRP exerts its biological effects by reducing the activity of nuclear factor κB (NF-κB), increasing the expression of growth factors such as TGF-β and vascular endothelial growth factor (VEGF). However, caution should be exercised in the use of PRP, as an excess of growth factors may interfere with tissue repair processes, leading to adverse reactions. Tsai WC et al.[52] revealed that high doses of TGF-β may promote fibrosis in injured muscles, affecting muscle regeneration. Combining TGF-β antagonists with PRP therapy can promote healing without negatively impacting muscle contractile properties and reducing the likelihood of muscle fibrosis. It is speculated that this may be related to the content and ratio of anti-inflammatory and pro-inflammatory factors in PRP, suggesting that excessive use of PRP may not achieve the desired therapeutic effects. Future quantitative studies are needed to evaluate the efficacy and safety of the active components in PRP.

VEGF FAMILY

This family comprises several members, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor.[53] VEGF is secreted to the target cell in an endocrine

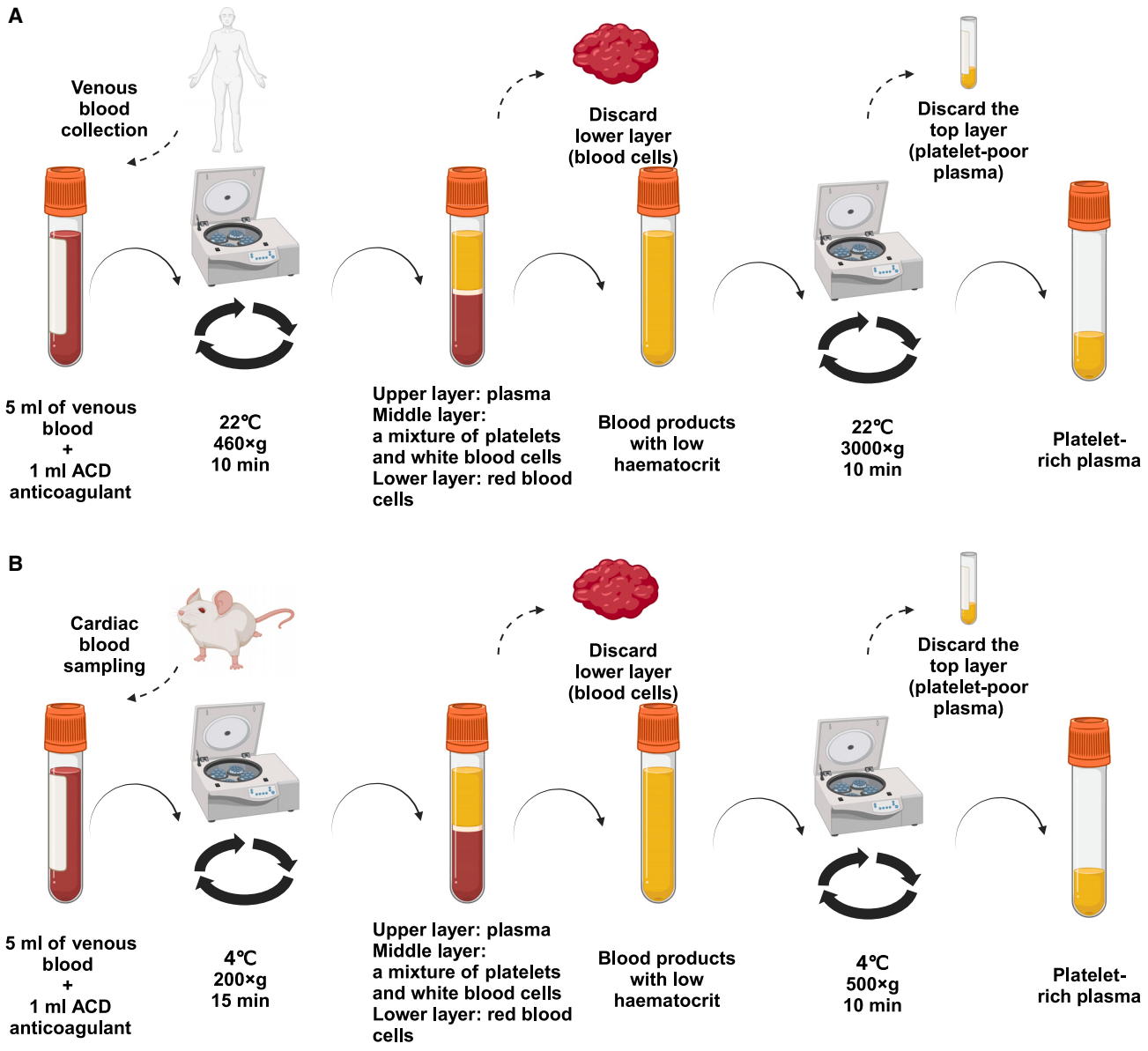

Figure 2. Pattern of preparation for rat/human PRP

Note: This procedure is a refinement of Landesberg's two-step centrifugation method.

(A) Demonstrates the process of preparing PRP in rats.

(B) Demonstrates the process of preparing PRP in humans.

or paracrine manner and forms a functional complex with VEGFR2.[54] This complex activates the cell membrane Gp protein, subsequently triggering phospholipase Cβ (PLCβ). PLC hydrolyzes phosphatidylinositol biphosphate (PIP2) into diacylglycerol (DAG) and 1,4,5-phosphoinositol triphosphate (IP3).[55] The activation of IP3-Ca^{2+} channels leads to the recruitment of protein kinase C (PKC) to the cell membrane, where it is subsequently activated by DAG. This cascade reaction influences gene expression, ultimately promoting the migration of vascular endothelial cells to injured vessels or the formation of new blood vessels.[56]

VEGF does not directly promote tissue repair and regeneration, but it can indirectly facilitate tissue regeneration, wound healing, and neuroprotection by supporting vascular reconstruction to provide nutrients to damaged tissues while removing toxins and metabolic waste produced by dying cells.[57] VEGF can inhibit the proliferation of microglial cells without increasing the infiltration of circulating macrophages, thereby limiting neuroinflammation.[58] Boisserand et al.[59] highlighted that neurons are rich in mitochondria, requiring significant oxygen consumption for oxidative respiration to maintain cellular metabolism; an adequate oxygen supply can effectively alleviate

neuroinflammation. Furthermore, it has been observed that VEGF in combination with other growth factors can enhance tissue repair and neuroprotection. However, the outcomes of VEGF administration may vary, depending on the timing and the physiological and pathological context. For instance, administering VEGF before ischemic injury may exert neuroprotective effects, whereas post-injury administration may pose a risk of exacerbating inflammation.[60] Therefore, further in-depth research on the timing of administration and treatment strategies is essential to overcome these limitations, improve therapeutic efficacy, and enhance patient survival rates.

PDGF FAMILY

The platelet-derived growth factor (PDGF) family plays a crucial role in tissue repair and fibrosis, consisting of various isoforms such as PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD.[61,62] During the wound healing process, fibroblasts are activated by PDGF secreted by these cells. This activation leads to the contraction of vascular smooth muscle, thereby reducing bleeding and scar tissue formation.[63] PDGF exerts its effects on target cells through paracrine or autocrine signaling and binds to tyrosine kinase receptors PDGFRa/b on the cell surface.[64,65] The intracellular signaling cascades triggered by PDGF involve phosphoinositide 3-kinase (PI3K), Ras protein-mitogen-activated kinase (Ras-MAPK), Src family kinases (Src), phospholipase Cγ (PLCγ), and the signal transducer and activator of transcription family (STATs). These signaling cascades promote the chemotaxis of fibroblasts and smooth muscle cells to the wound site, as well as the secretion of growth factors that are essential for tissue repair and regeneration.

PDGF cannot alter the process of tissue repair, but it can shorten the time required for tissue healing and also accelerate tissue fibrosis.[66] In cases of acute tissue injury resulting from trauma, chemical exposure, or extreme temperatures, an ischemic and hypoxic microenvironment is formed. Platelets are able to detect and respond to this altered microenvironment, releasing growth factors stored in α-granules to target cells. Of these growth factors, PDGF is particularly significant in promoting the proliferation and differentiation of mesenchymal stem cells (MSCs) in the vicinity of the injury, thus aiding in tissue repair.[67] In chronic injury repair, where sustained physicochemical injury factors or infection are at play, PRP has been observed to reduce the secretion of inflammatory cytokines interleukin (IL)-10 and tumor necrosis factor alpha (TNF-α) from macrophages in an anti-inflammatory manner. This is achieved through prostaglandin E2 or CD 40 L-dependent mechanisms,[68,69] ultimately mitigating inflammatory responses and expediting the regeneration of stubborn wounds.[70,71] Therefore, when selecting candidates for treatment, it is essential to consider not only whether the use of PRP can promote tissue repair but also whether it may induce fibrosis and affect the long-term function and normal morphology of the tissue.

IGF-1

Insulin growth factor (IGF)-1 is a crucial regulator of cell proliferation during the healing and regeneration of bone tissue, as well as in the central and peripheral nervous systems.[72,73] Research has established a positive correlation between IGF-1 levels and the proliferative capacity of cells.[74,75] Furthermore, in the initial stages of tissue repair, IGF-1 collaborates with TGF-β to enhance the recruitment and proliferation of MSCs.[76] At the molecular level, IGF-1 binds to IGFR-1/2, initiating the activation of the PI3K pathway.[77,78] This pathway results in the translocation of intracellular serine/threonine kinase (ATK) to the cell membrane, where it is further activated by PI3K. The activated ATK then enters the nucleus and promotes cell proliferation, ultimately leading to tissue repair and regeneration.[79]

Although IGF-1 plays a crucial role as a mediator of growth hormone action and is involved in controlling intermediary metabolism, tissue repair, and lifelong disease mechanisms, the powerful tissue repair function of PRP relies on the synergistic action of multiple growth factors, rather than the stimulating effect of a single or a few growth factors. Beitia M et al.[75] found that when studying the effect of different growth factors on cell proliferation, the stimulating effect of various growth factors alone (such as PDGF, TGF-β, VEGF, and IGF-1) in PRP-effective components was not as effective as using PRP. This result suggests the complexity of elucidating the impact on gene expression and regulatory mechanisms of PRP, and calls for more detailed experiments to study this complex interaction. In future research, it is necessary to further explore the interactions between PRP growth factors to reveal their potential mechanisms in tissue repair and disease treatment, providing more accurate and effective guidance for clinical applications.

APPLICATION OF PRP

The pursuit of identifying an effective therapeutic approach to promote injury repair has remained a critical focus for healthcare professionals. Since its inception in cardiothoracic surgery back in 1987, PRP has attracted considerable attention and has progressively found application in a wide array of medical fields, including oral and maxillofacial surgery, orthopedics, gynecology, and urology. A comprehensive examination of the current utilization of PRP across diverse clinical departments is meticulously detailed in Table 3. This comprehensive review endeavors to showcase significant studies that underscore the effectiveness of PRP in distinct clinical scenarios, thereby illuminating its potential as a valuable therapeutic modality.

ORTHOPEDIC

PRP has emerged as a widely utilized treatment modality within the field of orthopedics, capturing the attention of an increasing number of orthopedic surgeons due to its procedural ease and safety, coupled with its capacity to yield favorable therapeutic outcomes.[110,111] Numerous orthopedic conditions have shown promising responses to PRP therapy.

Osteoarthritis

Osteoarthritis, a chronic and progressive ailment affecting individuals across various age groups, is characterized by joint soft tissue degeneration, resulting in diminished protective effects, subsequent pain and impaired mobility.[112,113] While traditional

Table 3. The current status of PRP applications across various clinical departments

Departments	Diseases
Orthopedic	Osteoarthritis, tendinopathy of Achilles tendon, rotator cuff tear, peripheral nerve injury, fracture, etc.[80–82]
Pain medicine	Radiculopathy, lumbago, phantom limb pain, etc.[83–85]
Plastic surgery	Skin healing, autologous fat transplantation, cartilage rebuilding, etc.[86,87]
Urology	Erectile dysfunction, urethral stricture, hypospadias, prostatic hyperplasia, bladder contracture, peyronie disease, etc.[88–90]
Dermatology	Androgenetic alopecia, alopecia areata, alopecia cicatrisata, chronic vitiligo, chloasma, psoriasis, paronychia, acne scarring, skin aging, etc.[91–94]
Ophthalmology	Xerophthalmia, corneal ulcers, etc.[95,96]
Otorhinolaryngology, Head and Neck Surgery	Tympanic membrane perforation, sensorineural hearing loss, perforation of nasal septum, leakage of cerebrospinal, dyssomnia, atrophic rhinitis, cicatricial stenosis of larynx, tracheal stenosis, tonsillectomy, etc.[97,98]
Oral and maxillofacial surgery	Alveolar osteitis, gingivitis, periodontitis, osteonecrosis of jaw, oral implant, etc.[99,100]
Respiratory medicine	COPD, asthma, interstitial pulmonary fibrosis, etc.[101]
Gynecology	Intrauterine adhesion, premature ovarian failure, genital tract fistula, pelvic floor dysfunction, thin endometrium, repeated Implantation Failure, etc.[102–104]
General surgery	Anal fistula, etc.[105]
Cardiothoracic surgery	Coronary artery bypass grafting, sternotomy complications, bronchial fistula, myocardial injury, etc.[106–109]

treatments such as oral calcium gluconate or local dexamethasone injections have been employed, their efficacy has been inconsistent. Fadi Hassan et al.[114] analyzed 18 studies that examined the effectiveness of botulinum toxin type A, sodium bicarbonate, and calcium gluconate in treating osteoarthritis of the knee. Positive results emerged by 9 weeks and were sustained through the 3.5-year follow-up. The findings indicate that there is limited evidence supporting the efficacy of these treatments. Although joint replacement remains a highly effective intervention, its restricted indications, high costs, and potential complications render it unsuitable for all patients.[115] PRP therapy, on the other hand, focuses on restoring anatomical structures and physiological functions by promoting tissue repair and suppressing inflammation.[116] The consensus from the European Society of Sports Traumatology, Knee Surgery, and Arthroscopy (ESSKA) indicates that PRP is considered an effective treatment option for osteoarthritis based on a significant body of literature and expert opinions. PRP is also seen as a potential first-line injectable treatment for non-surgical management of knee osteoarthritis, primarily for Kellgren-Lawrence 5-point scale (KL) grades 1–3.[117] Kefan Zhang et al.[118] successfully created a rabbit osteoarthritis model by injecting papain into the knee joint. They then administered PRP through a single injection into the same knee joint to evaluate its therapeutic potential. At 8 weeks post-injection, H&E staining and immunohistochemical analysis revealed solid green staining of cartilage samples from rabbit knee joints. These findings were quantitatively compared using Pelletier scores, Mankin pathology scores, and ImageJ software. Results indicated significant differences in all three evaluation metrics between the rabbit osteoarthritis model and the blank control group before and after PRP injection. Notably, both animal models and clinical observations have demonstrated improved joint function and anatomical restoration following local PRP injections, highlighting its potential as an effective therapeutic approach.

Tendon and ligament injuries

Tendon and ligament injuries are a significant concern within the field of sports medicine due to the limited vascularity of these tissues, which hinders their ability to receive necessary nutrients for efficient healing.[119] As a result, the recovery process for these injuries can be protracted or even unattainable. Treatment options for tendon and ligament injuries typically involve conservative measures or surgical reconstruction.[120,121] PRP has emerged as a promising intervention, as it has demonstrated the ability to mitigate inflammation and stimulate the activation of stem cells, thereby initiating the repair of tendons and ligaments.[122] Giuseppe Messina et al.[123] conducted a comparison between the effectiveness of PRP intra-articular injections and rehabilitation in the management of posterior cruciate ligament injuries. Among the seven participants, a subset of three underwent stent immobilization for a duration of 20 days post-injury, after which they were treated with Nd-YAG laser therapy, known for its anti-inflammatory properties, complemented by a structured rehabilitation program. The remaining quartet was administered autologous PRP injections in the immediate aftermath of the injury, followed by Nd-YAG laser therapy and a rehabilitation regimen initiated seven days post-stent immobilization. Throughout the rehabilitation process, a licensed physiotherapist conducted daily assessments of the subjects' mobility and recovery progress. The outcomes demonstrated that subjects who received PRP injections exhibited a more rapid restoration of joint mobility, muscle strength, and gait pattern normalization and were able to return to physical activities at an earlier stage compared to the control group. Both treatment modalities resulted in patients returning to normal activities, suggesting the potential benefits of PRP injections in expediting recovery for individuals with such injuries.

Peripheral nerve injuries

Repairing peripheral nerve injuries, such as those involving the radial, ulnar, and median nerves, can be highly complex. Even in cases where successful nerve regeneration occurs, full functional recovery may not be guaranteed.[124] Yaqiong Zhu et al.[125] examined the impact of continuous ultrasound-guided PRP injection and low-dose ultrashort wave therapy on peripheral nerve regeneration in a crush injury model. The researchers conducted comprehensive assessments, including neurological, electrophysiological, and morphological evaluations of muscles, to assess the regenerative effects of this combined treatment. The findings of the study reveal a significant synergistic effect between PRP and low-dose ultrasonic therapy in promoting the accelerated regeneration of peripheral nerves. Such research has demonstrated the potential of neurotrophic factors in PRP for enhancing nerve regeneration.

PAIN MEDICINE

The intricacies of pain mechanisms necessitate a varied approach to treatment, particularly when addressing different pain locations.[126] PRP finds primary application in pain medicine for the management of radiculopathy, a condition characterized by tingling and numbness in the limbs resulting from compressed nerve roots around the cervical or lumbar spine.[127,128] Treatment modalities for radiculopathy encompass techniques such as bracing, physical therapy, and neural closure therapy. Notably, these treatments share common traits, including extended treatment durations and uncertain efficacy. Saurabh Kataria et al.[129] recently completed a systematic review of 10 articles focusing on the use of PRP for treating pain related to lumbar disc herniation. In the analysis of the seven studies encompassed in the review, no statistically significant disparities were observed in visual analog scale (VAS) at the 1st, 3rd, and 7th month milestones following PRP treatment when juxtaposed with the outcomes of the local hormone injection cohort (with p values of 0.57, 0.36, and 0.75, respectively). Research conducted by Sathish Muthu et al.[130] indicates that there may not be a significant difference in the VAS at specific time points between the treatment group and the control group (saline injection), possibly due to insufficient sample size. Koji Akeda et al.[131] emphasize the importance of conducting larger-scale studies to confirm the clinical efficacy of PRP in treating discogenic low back pain. In a study conducted by Sunil H. Shetty et al.,[132] the effects of local injections of steroids, PRP, and placebo on chronic plantar pain were examined. Results showed that all three methods of injection effectively improved plantar pain and function at 18 months. Steroids demonstrated superior efficacy within the first month of treatment, while PRP showed better pain improvement between 6 and 18 months compared to steroids and placebo. These findings suggest that PRP may be a promising treatment option for chronic plantar pain over a longer duration.

PLASTIC SURGERY

The use of PRP in the field of plastic surgery has been a significant advancement in therapeutic techniques. Research has shown that PRP has a multitude of benefits, including its ability to promote wound healing due to its antibacterial, anti-inflammatory, and cell regeneration properties.[71,133,134] Incorporating 19 clinical studies on PRP for treating skin ulcers, Hong OuYang et al.[135] observed that PRP application can enhance ulcer healing rates and expedite the recovery process. The study found that patients with DFUs achieved complete healing after treatment, with meta-analysis indicating that PRP use led to significantly higher healing rates ($p < 0.001$) and shorter healing times ($p < 0.001$), while not significantly reducing ulcer size ($p = 0.08$). However, further clinical data are imperative to substantiate the efficacy of this treatment modality. Additionally, establishing a standardized preparation protocol for PRP is crucial to ensuring consistency and reliability in its application. Ningjie Chen et al.[136] investigated the use of PRP by both elderly and young individuals in treating ischemic necrosis-induced skin tissue injury in mice. Their results showed that both sources of PRP had reparative effects, with the PRP from young individuals demonstrating a superior therapeutic effect compared to that from elderly individuals. This study highlights the potential of PRP therapy in treating skin tissue injuries, with age playing a factor in its efficacy. Furthermore, PRP has shown positive effects in promoting healing during profile reconstruction procedures, such as autologous fat transplantation commonly used in plastic surgery for soft tissue reconstruction. Autologous fat grafting in combination with PRP has shown promising results in improving fat graft survival rates. A retrospective review conducted by Picard et al.[137] examined a total of 11 clinical studies in humans and 7 studies in animals. Nine out of the 18 studies reported a statistically significant increase in fat graft survival when PRP was used in combination with autologous fat grafting. These findings suggest that PRP may have a beneficial impact on plastic surgery.

UROLOGY

PRP application in urology faces several challenges, including ambiguous patient inclusion criteria, small study sizes, and the absence of standardized treatment protocols. Nonetheless, it holds promise for addressing specific conditions. (1) Erectile dysfunction (ED) presents a significant burden for male patients, causing both psychological and physiological distress.[138] While current ED treatments encompass psychotherapy, pharmacotherapy, and vacuum pump-assisted therapy, their efficacy may vary due to individual differences.[139] Yino Wu et al.[140] examined the therapeutic potential of PRP in treating ED caused by cavernous nerve crush injury in rats. The results of their investigation showed that PRP significantly enhanced erectile function following a bilateral cavernous nerve injury. This finding suggests that PRP may hold promise as a potential therapeutic intervention for individuals with similar conditions. (2) Peyronie's disease, an acquired form of cavernous fibrosis of the penis, presents with penile pain and deformity, often accompanied by ED.[141] While the condition is self-limiting, symptomatic relief can be achieved through the use of oral painkillers or penile injection of collagenase clostridium histolyticum (CCH).[142] A Schirmann et al.[143] showed that PRP treatment may reduce penile curvature and improve subjective sensation in Peyronie's disease. No side effects

were noted during the study. The mean penile curvature angle was 28.6° (p = 0.007) at three months post-treatment. Erection perception scores showed significant improvement, rising from a preoperative mean of 10.67 with increases of 5 points at months 1 and 6 (p = 0.01 and p = 0.036) and 7 points at month 3 (p = 0.04). However, the existing studies are limited by insufficient sample sizes and the absence of control groups, thus failing to provide robust evidence supporting the efficacy of PRP as a reliable treatment. Future research should focus on expanding sample sizes and conducting long-term observations to establish a more conclusive understanding of the therapeutic efficacy of PRP in Peyronie's disease.

DERMATOLOGY

The field of dermatology has eagerly embraced the transformative potential of PRP for cell regeneration.[144] PRP, with its robust functional capabilities, has become a focal point in addressing various dermatologic disorders. (1)Androgenetic alopecia, a hereditary condition characterized by hair follicle hypersensitivity to dihydrotestosterone (DHT), presents as frontal or top-of-head alopecia in males and generalized hair thinning in females.[145,146] Traditionally, the treatment for this condition has centered on either stimulating follicular cells or suppressing androgen levels. However, long-term efficacy has been hampered by challenges such as extended medication periods and poor adherence.[147] In a comprehensive analysis of 64 randomized controlled clinical trials, Alireza Jafarzadeh et al.[148] demonstrated the significant efficacy of PRP in improving androgenetic alopecia. Three months of monthly intradermal PRP injections led to an average increase of 33.6 hairs in the treated area, while the placebo area saw a decrease of 3.2 hairs. The PRP-treated group experienced a significant increase in hair density, with 45.9 more hairs per square centimeter compared to a decrease of 3.8 hairs per square centimeter in the placebo group. Additionally, terminal hair density rose by 40.1 hairs per square centimeter in the PRP group, showing a significant difference from the control group. However, there was no significant change in the density of cuirass hairs compared to the placebo group. (2) Vitiligo, characterized by depigmented plaques due to abnormal melanocyte destruction, often leads to varying degrees of psychological distress, significantly impacting the patient's quality of life.[149] Xinju Wang et al.[150] examined the treatment landscape for refractory vitiligo, highlighting the challenges faced in achieving successful outcomes. The authors noted the limited effectiveness of various medications commonly utilized in refractory cases. This suboptimal response could be attributed to the reduced presence of follicular sebaceous follicles and perifocal melanocytes in refractory lesions. Further research and innovative therapeutic approaches may be necessary to address these complexities and improve treatment efficacy in refractory vitiligo cases. Soheir Abdel-Hamid et al.[151] conducted a study on the therapeutic efficacy of PRP for the treatment of vitiligo. They utilized the Vitiligo Area Scoring Index to clinically assess each individual. The study findings revealed that PRP treatment induced pigmentation in vitiligo patients with fewer side effects compared to fractional erbium-YAG laser.

OTORHINOLARYNGOLOGY, HEAD AND NECK SURGERY

PRP is of particular interest to otolaryngologists due to its simple preparation, various delivery modes, and minimal side effects.[152] (1) Tympanic membrane perforation stands as a prevalent outcome of ear trauma, often with varying degrees of hearing impairment, with severe cases reaching thresholds exceeding 60 dBL.[153] While such perforations are self-limiting, their natural healing process is often hindered by factors such as size, cause of injury, and potential infection.[154] Mahmoud F. Mandour et al.[155] explored the efficacy of PRP in treating 320 patients with medium-sized tympanic membrane perforations was explored. Consequently, the use of PRP was deemed to significantly enhance the success rate of tympanic membrane, closure with no reported complications. (2) Sensorineural hearing loss, characterized by high-frequency impairment, not only impacts patients' quality of life but also imposes a significant burden on public healthcare.[156] Currently, cochlear implantation remains the only effective treatment for this type of hearing loss.[157] In a comparative study conducted by Mahmoud Shawky, 50 patients with sensorineural deafness received 6 intratympanic steroid injections, while another 50 patients received 2 weekly PRP injections.[158] Among those treated with PRP, 39 individuals experienced notable enhancements in hearing and speech discrimination abilities. (3) Olfactory disorders encompass a range of conditions, including hyposmia, olfactory abnormalities, and olfactory loss.[159,160] Conventional treatments aimed at improving olfactory nerve function through neurotrophic drugs or addressing underlying causes with antiviral medications have shown limited therapeutic efficacy.[161,162] AlRajhi et al.[163] analyzed four clinical trials focusing on olfactory dysfunction resulting from PRP treatment. Their findings suggest that PRP could be a promising treatment for COVID-19-induced olfactory dysfunction. Nevertheless, further extensive studies are imperative to explore and validate the efficacy of PRP in managing olfactory dysfunction post COVID-19. (4) Vocal cord scarring, often stemming from tracheal intubation during general anesthesia or traumatic injuries, can significantly impact articulatory and ventilatory function.[164] In a prospective trial led by Benjamin van der Woerd et al., the safety of PRP as an injectable therapy for vocal fold scarring and atrophy was evaluated.[98] The study found that all patients tolerated the treatment well, and there was improvement in the patients' Voice Handicap Index-10 (VHI-10) and Voice Fatigue Index (VFI) questionnaire results post-treatment. These findings suggest promising results in the use of PRP for vocal cord scarring.

ORAL AND MAXILLOFACIAL SURGERY

PRP is a valuable tool in the realm of oral and maxillofacial surgery, showcasing promising therapeutic results owing to its robust soft-tissue regenerative and anti-inflammatory properties.[165] While PRP can be utilized across a wide spectrum of oral and maxillofacial procedures to enhance treatment outcomes, its primary application lies in addressing specific disorders. (1) Effective wound healing post-extraction is a paramount concern for oral and maxillofacial surgeons, as it not only diminishes the risk of oral infections but also contributes to the overall

enhancement of patients' quality of life.[166] Periodontitis and alveolar osteitis are common post-surgical complications, often presenting in symptoms such as periodontal swelling and pain, which, if left unaddressed, may lead to bacteremia as a result of bacterial invasion into the circulatory system from the surgical site. Eshghpour et al.[167] reported that rinsing the operative area with PRP led to reduced periodontal swelling, lower visual pain scale scores compared to pre-treatment levels, and significantly superior outcomes. (2) Peri-implant diseases encompass two distinct categories: peri-implant mucositis and peri-implantitis. The former affects the mucosal tissue surrounding the implant without impacting the bone tissue, while the latter extends to both the mucosal tissue and leads to bone atrophy.[168,169] Conventional treatment methods for peri-implant disease involve pharmacological anti-infection measures or surgical debridement, often entailing significant patient discomfort. Boora et al.[170,171] demonstrated that injecting PRP at the time of implant placement resulted in reduced loss of peri-implant mucosal and bone tissue at 1- and 3-month post-surgery compared to a control group without PRP, suggesting its potential in preventing the development of peri-implant disease.

GYNECOLOGY

PRP has garnered increasing attention in the field of obstetrics and gynecology in recent years. While its adoption in clinical practice remains limited, numerous studies have explored its potential applications. (1) Intrauterine adhesions (IUAs) can lead to symptoms such as low menstrual flow, amenorrhea, infertility, and recurrent miscarriages.[172] Conventional treatments, such as hysteroscopic mucosal detachment, often result in recurrent issues.[173,174] Ruonan Tang et al.[175] reviewed 10 clinical studies examining the benefits of PRP therapy for IUA. The analysis focused on various outcome measures, such as endometrial thickness, menstrual volume, clinical pregnancy rate, and live birth rate. PRP administration enhanced clinical pregnancy rates ($p = 0.006$) but did not significantly reduce the miscarriage rate ($p = 0.40$). The researchers concluded that autologous PRP is a promising treatment for IUA, though the limited sample size underscores the need for cautious interpretation of the results. (2) For premature ovarian failure, which manifests as ovarian hypoplasia or failure before the age of 40, hormone replacement therapy is a common approach, despite potential long-term adverse effects.[176] The research conducted by Máté Éliás et al.[177] highlights the positive impact of PRP treatment on fertility parameters in women with diminished ovarian reserve. Fourteen studies indicated that PRP treatment resulted in an average increase of 0.81 oocytes ($p = 0.002$). Ten studies found that in 616 patients, post-treatment embryo counts were 0.91 embryos higher than baseline ($p = 0.001$). A total of 19 studies, involving 1,800 patients, reported that 323 achieved biochemical pregnancies. (3) Genital tract fistula, an abnormal connection between the genital tract and adjacent lumens in female patients, can arise from developmental malformations, pelvic floor surgery, or radiotherapy for malignant tumors. This condition encompasses rectovaginal and vesicovaginal fistulas.[178,179] Traditional treatments involve electrocautery or surgical closure, which may cause significant pain and carry the risk of recurrence.[180] However, Hermann et al.[181] found that fistula scraping followed by PRP injection resulted in complete closure with reduced patient discomfort. This research indicates that PRP could potentially serve as a beneficial and innovative therapy for genital tract fistulas. The promising results of this study warrant continued investigation into the potential uses of PRP in managing genital tract fistulas for improved patient outcomes.

DISCUSSION

PRP is a rapidly emerging therapeutic technology that holds significant promise in various medical applications. However, despite increasing understanding of its mechanisms and benefits, numerous issues still require further investigation. In this article, we aim to provide a comprehensive overview of the advantages and limitations associated with the use of PRP.

The advantages of PRP

(1) It is derived from autologous blood, providing a stable source with a high yield. Typically, 30 cc of venous blood yields 3–5 cc of PRP.[182] While the yield can be influenced by factors such as blood collection and centrifugation methods, storage conditions, and choice of anticoagulant, the product source generally incurs lower economic costs compared to alternative treatments.

(2) PRP has a wide range of applications. Current literature indicates that over ten clinical departments have implemented its clinical application, while numerous others have conducted basic research and animal experiments. Given that cell injury is a common pathophysiological basis for many diseases, promoting cell repair or regeneration through PRP presents an effective approach for treating various conditions.

(3) PRP is relatively easy to prepare and minimally invasive.[99] Small quantities can be obtained by drawing venous blood with a collection needle, while larger quantities can be obtained using a platelet single-collection separation device, which reduces blood component wastage and minimizes patient harm. These characteristics make PRP a compelling option for various medical applications.

(4) PRP is well-known for its minimal side effects, making it a promising therapeutic option. As a blood product derived from the patient's own blood, it typically does not trigger immune responses, rendering it reusable in multiple treatments. Instances of serious adverse reactions associated with PRP across different clinical applications have been rare thus far. Reported side effects primarily revolve around localized reactions following injection, including mild discomfort and burning sensations.[183] While there is a potential risk of infection, this can be mitigated through adherence to strict aseptic protocols.

(5) PRP is a versatile treatment option for a variety of conditions, with different methods of administration tailored to specific diseases. Its therapeutic benefits can be utilized through local injection, intravenous injection, subcutaneous injection, intramuscular injection, and nebulized inhalation across a wide range of clinical disciplines.[184–188] Additionally, PRP can be used as a carrier for tissue

engineering, and can be activated and combined with other materials in biogel form to serve various functions.[189]

(6) PRP contains numerous growth factors, but the short half-life and instability of a single growth factor limit its clinical usefulness.[190] Therefore, combination therapy involving multiple growth factors can extend their activity within target cells and enhance therapeutic effectiveness through synergistic effects.

The limitations of PRP

(1) The absence of a standardized preparation process has led to a wide range of methods being reported in the literature, resulting in significant variations in the composition of PRP.[191] This diversity in preparation methods poses challenges for effective comparison and evaluation of different studies. Moreover, even when PRP is obtained using the same preparation method, its therapeutic efficacy can vary due to differences in activation methods. The absence of standardized guidelines for PRP therapy presents significant hurdles.

(2) The lack of comprehensive *in vivo* pharmacological studies has left critical aspects such as appropriate concentration, dosage, mode of administration, and frequency of administration largely unknown, thereby complicating the standardization of clinical study designs.[192] Consequently, the evaluation of real study outcomes becomes more complex.

(3) The long-term prognosis of PRP therapy remains uncertain.[84] While numerous clinical studies have focused on assessing the effectiveness of PRP in treating various conditions, only a limited number have investigated the long-term effects of treatment. It has been observed that the ameliorative effects of PRP on pain may diminish over time, underscoring the need for further research in this area. Addressing these challenges is crucial for enhancing the understanding and application of PRP therapy in clinical settings.

(4) In evaluating the existing studies on PRP treatment, several key issues emerge that limit the generalizability and reliability of the findings. Firstly, many studies involve small sample sizes, which restrict the applicability of the results and affect their statistical significance.[193] Secondly, the absence or improper establishment of control groups can lead to biased interpretations of results, affecting our understanding and confidence in the effectiveness of PRP.[194] Furthermore, many clinical studies feature short follow-up periods, limiting our ability to comprehensively evaluate the long-term effects and safety of PRP treatment. Short-term studies may fail to capture all potential outcomes and side effects, particularly concerning long-term efficacy and improvements in patients' quality of life. To enhance the scientific rigor and clinical applicability of future research, it is essential to employ larger sample sizes, establish appropriate control groups, and extend follow-up periods, thereby offering more comprehensive and accurate data on PRP treatment effects and safety. Such research design improvements will help elevate the level of evidence and provide a stronger scientific foundation for clinical decision-making.

The contraindications and adverse effects of PRP

(1) PRP therapy is generally low-risk, but adverse reactions can occur. Anna Arita et al.[195] reviewed adverse events associated with PRP use up to January 2024, noting risks like postoperative infection, blindness, inflammation, allergic reactions, and nodule development. We suspect these may stem from possible bacterial contamination during PRP preparation. We must also recognize that there may be unrecognized adverse effects. Thus, it's crucial to avoid blindly expanding PRP indications and overstating its therapeutic benefits. We will focus on two common adverse reactions: (1) Infection is one of the most frequently reported issues after PRP injection.[196] While localized infections and leg ulcers can occur, Alazzeh MS et al.[197] found that PRP injections do not significantly increase the risk of joint infection. We speculate that discrepancies between these findings may stem from bacterial contamination during PRP preparation, as well as differences in injection sites. (2) Visual disturbances have also been reported in some patients after PRP treatment. A study by Kar Wai Alvin Lee et al. indicated that while rare, such disturbances can occur soon after the procedure or within a few days, with delayed onset possible up to two weeks.[198] This underscores the importance of extended postoperative monitoring.

(2) As PRP relies on growth factors and platelets for its effects, individuals with coagulation disorders, such as those with coronary artery disease or cerebral infarction, may face an increased risk of vascular obstruction post-treatment.[199] Moreover, individual differences can affect PRP's efficacy; for instance, nicotine and alcohol addiction can elevate blood viscosity and cause platelet aggregation.[200] Such patients should be assessed for heightened risk of adverse effects before undergoing PRP therapy.

The cost of PRP

(1) Although the upfront costs of PRP are relatively high, typically ranging from several hundred to several thousand dollars, this price encompasses the processes of blood collection, centrifugation, and injection.[201] The treatment duration is relatively short, usually lasting 1–2 h, with a quick recovery time that allows patients to return to normal activities within a few days and experience pain relief and functional improvement within weeks.[202] In the long term, the effects of PRP therapy are sustained, potentially reducing the need for subsequent medical interventions and thereby lowering overall healthcare costs. Ranjan Verma et al.[203] indicates that PRP has a higher probability of promoting skin ulcer healing compared to standard treatments and significantly reduces patient hospitalization times, thereby accelerating the recovery process. Over time, PRP may decrease the need for repeat injections and surgeries, further lowering

long-term healthcare utilization costs. Additionally, PRP outperforms standard treatments in terms of functional recovery, pain relief, and overall satisfaction, particularly regarding pain management and functional outcomes, leading to improved long-term satisfaction. Given that PRP utilizes autologous blood products, it carries a relatively low risk of side effects and reduces reliance on external medications.

(2) In comparison, alternative treatment options such as physical therapy and surgery vary in cost. While physical therapy may have lower individual session costs, the cumulative expenses can equal or exceed those of PRP due to the necessity for multiple sessions. Surgical procedures tend to incur higher costs, involve longer recovery times, and may necessitate ongoing medication or repeated treatments. Therefore, while alternative therapies might appear more cost-effective in the short term, PRP may offer greater long-term financial benefits due to its enduring effects.

(3) In summary, PRP demonstrates clear advantages in treatment and recovery times while potentially offering better long-term outcomes, despite its higher initial costs. Alternative treatment options may provide flexibility and cost benefits, but they generally involve longer treatment and recovery periods. Consequently, these factors render PRP a cost-effective and effective treatment option for clinicians and policymakers alike.

The indications of PRP

To ensure the efficacy and safety of PRP, physicians must carefully assess individual patient factors and indications for its use. Patient selection and a tailored treatment approach are vital in PRP therapy, necessitating a personalized plan to maximize therapeutic efficacy and patient satisfaction.

(1) Age and overall health are critical considerations, as physiological responses and healing capacities vary significantly across age groups. Additionally, comorbidities or chronic diseases can impact PRP's effectiveness. A study by Verónica Salgado-Pacheco et al.[204] found that younger, healthier patients experienced shorter healing times with PRP for complex wounds.

(2) The nature and severity of the condition also matter. Most PRP used in clinical practice is derived from autologous blood components, and the preparation process for mild injuries can impose additional trauma and financial strain. For severe injuries, it remains unclear whether PRP retains its therapeutic effects due to changes in blood composition from loss or stress, and preparation may worsen the original condition. Research by Angelo Boffa et al.[205] indicates that higher platelet concentrations lead to better outcomes in knee osteoarthritis treatment.

(3) Before undergoing PRP, it is crucial to conduct a comprehensive assessment of the patient's risk factors. These factors include, but are not limited to, allergy history, bleeding tendencies, and other potential health issues. By carefully understanding the patient's medical history and current condition, the physician can identify risks that may lead to unnecessary adverse reactions during the treatment process. PRP should only be considered after a thorough evaluation and confirmation that the patient is in a safe health state, which will help maximize the treatment's effectiveness while minimizing the incidence of complications.

The ethical issues of PRP

(1) Patients should only decide to undergo PRP after fully comprehending the procedure, its benefits, potential risks, and alternative options. A study by Justin Tiao et al.[206] revealed that most patients lack a comprehensive understanding of PRP prior to treatment, which may lead to less cost-effective medical decisions.

(2) PRP is often marketed with exaggerated claims of its regenerative properties, which can create unrealistic patient expectations. Healthcare providers have an ethical obligation to manage these expectations by presenting accurate information about the variability of PRP's efficacy and the supporting evidence.[207] This approach prevents overpromotion and helps patients maintain realistic treatment outcome expectations.

(3) The promotion of PRPs must prioritize responsible, evidence-based statements that do not exploit patients' vulnerabilities or desperation for a cure. Regulation is essential to ensure ethical marketing practices and adherence to established guidelines. Research by Augustus D. Mazzocca et al.[208] indicates that PRP varies significantly based on preparation methods and individual differences, with even batches from the same person showing considerable discrepancies in growth factor content and platelet concentration. Thus, the therapeutic effects of PRP should not be overstated in promotional materials.

(4) The evidence base for PRP is still developing, with no consensus on its efficacy for certain applications. Healthcare providers must stay updated on the latest research and effectively communicate this evolving evidence to patients, ensuring treatment decisions are informed by the most reliable information. Our study suggests that while PRP shows promising therapeutic benefits across various conditions, its use should not be expanded indiscriminately. PRP should be approached cautiously, following adequate preclinical studies and rationalization to prevent unnecessary physical and economic harm to patients.

How to improve the utilization of PRP

To achieve standardization in PRP, a series of specific recommendations and guidelines are proposed.

(1) It is essential to establish consensus guidelines for PRP preparation, which should include a unified protocol detailing key parameters such as centrifugation speed, duration, and the use of anticoagulants.

(2) Developing standardized treatment algorithms for PRP injection techniques, including injection sites and needle depth, will enhance the accuracy and efficacy of treatments. Implementing standardized follow-up protocols is also crucial for monitoring patient outcomes, identifying

potential adverse reactions, and adjusting treatment strategies based on patient responses.

(3) Regular quality control procedures should be instituted to assess PRP quality, including evaluating platelet concentration, purity, and other relevant parameters, ensuring consistency and reliability in treatment outcomes. Rigorous quality control measures are vital for maintaining safety standards, meeting regulatory requirements, and fostering clinician and patient confidence in PRP.

(4) Patient assessment and communication are also critical; prior to treatment, healthcare providers should evaluate the patient's health status, considering potential issues such as cardiovascular disease or infections that may impact PRP efficacy. Clear and comprehensive communication with patients regarding expected outcomes, potential risks, and the experimental nature of PRP is necessary to manage their expectations effectively.

CONCLUSION

In summary, PRP has found application across a wide array of medical disciplines, including orthopedics, plastic surgery, pain management, urology, dermatology, ophthalmology, otorhinolaryngology, head and neck surgery, oral and maxillofacial surgery, gynecology, among others. The physiological effects and mechanisms of action of PRP have been increasingly clarified, revealing its neuroprotective and regenerative properties, as well as its ability to promote tissue repair, wound healing, and hemostasis. These effects are thought to stem from the regulation of cellular functions by growth factors such as IGF-1, PDGF, VEGF, and TGF-β. PRP is relatively noninvasive and has shown a favorable safety profile, with high patient satisfaction reported due to perceived significant benefits. Despite its widespread use, current clinical studies on PRP have yielded low-grade evidence, and its precise physiological function and mechanism of action remain incompletely understood. Further research, including investigations into treatment protocols and long-term patient outcomes, is crucial to standardize PRP's application across various clinical disciplines.

FUTURE DIRECTIONS

PRP holds significant promise, yet many questions remain unanswered, necessitating further investigation. The complexities of PRP preparation, variability in therapeutic regimens, and lack of long-term efficacy data highlight the need for a deeper understanding of PRP's role in clinical medicine. Optimizing PRP preparation methods is essential, as the variability in current practices can adversely affect therapeutic outcomes. Standardized treatment protocols must be established to guide clinicians, ensuring consistency and improving the reliability of PRP results. Moreover, large-scale randomized controlled trials are crucial for rigorously assessing the efficacy and safety of PRP across various diseases. These studies will not only confirm PRP's effectiveness but also uncover any potential risks. Expanding PRP's applications will require dedicated research into its long-term effects and the durability of its regenerative properties. Additionally, exploring PRP's use in diverse medical fields, from orthopedics to dermatology, demands a comprehensive understanding of its mechanisms of action and further basic research into the physiological interactions of its multiple bioactive components.

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AUTHOR CONTRIBUTIONS

Zhixin Zhang: conceptualization, visualization, writing – original draft; P.L.: writing – original draft, writing – review & editing; Zhiyu Zhang: writing – original draft, visualization; X.X.: visualization, writing – original draft; L.W.: visualization, writing – original draft; Y.J.: conceptualization, writing – original draft; C.Z.: conceptualization, writing – original draft; H.Z.: conceptualization, writing – original draft; S.L.: writing – review & editing; W.S.: writing – review & editing; S.Y.: conceptualization, funding acquisition, writing – review & editing; F.W.: conceptualization, funding acquisition, writing – review & editing.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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