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FULL LENGTH REVIEW

Platelet-rich plasma: a comparative and economical therapy for wound healing and tissue regeneration

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Abstract Rise in the incidences of chronic degenerative diseases with aging makes wound care a socio-economic burden and unceasingly necessitates a novel, economical, and efficient wound healing treatment. Platelets have a crucial role in hemostasis and thrombosis by modulating distinct mechanistic phases of wound healing, such as promoting and stabilizing the clot. Platelet-rich plasma (PRP) contains a high concentration of platelets than naïve plasma and has an autologous origin with no immunogenic adverse reactions. As a consequence, PRP has gained significant attention as a therapeutic to augment the healing process. Since the past few decades, a robust volume of research and clinical trials have been performed to exploit extensive role of PRP in wound healing/tissue regeneration. Despite these rigorous studies and their application in diversified medical fields, efficacy of PRP-based therapies is continuously questioned owing to the paucity of large samplesizes, controlled clinical trials, and standard protocols. This review systematically delineates the process of wound healing and involvement of platelets in tissue repair mechanisms. Additionally, emphasis is laid on PRP, its preparation methods, handling, classification,application in wound healing, and PRP as regenerative therapeutics combined with biomaterials and mesenchymal stem cells (MSCs).

Keywords Wound healing · Platelet · Platelet-rich plasma · Growth factors · Biomaterials · Mesenchymal stem cells

Abbreviations

PRP	Platelet-rich plasma
MSCs	Mesenchymal stem cells
GFs	Growth factors
PDGF	Platelet-derived growth factor
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
IGF	Insulin-like growth factor
VEGF	Vascular endothelial growth factor
TGF-β	Transforming growth factor-beta
KGF	Keratinocyte growth factor
HGF	Hepatocyte growth factor
TNF	Transforming growth factor
PEG	Poly (ethylene glycol)
CD	Cluster of differentiation
RANTES	Regulated on activation, normal T expressed, and secreted
PMPs	Platelet microparticles
PRF	Platelet-rich fibrin
RBCs	Red blood cells
WBC	White blood cells
PPP	Platelet-poor plasma

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DEAP	Dose of injected platelets, production efficiency, activation
ROS	Reactive oxygen species
PLA	Polylactic acid
RGD	Arginine-glycine-aspartic acid
SDF	Stromal cell-derived factor-1
IFN-γ	Interferon-gamma
MMPs	Matrix metalloproteinases

Introduction

Millennia of evolution have created our skin; it is the largest organ of the human body and contributes10% of the total body mass (Theoret 2009; Hanson et al. 2010; Maxson et al. 2012). Itis a highly adaptive, multifunctional organ that serves as a shield for internal organs and protects body from the onslaught of mechanical damage, microbial infections,andother environmental extremities. Additionally, any imbalance in the skin's structural, anatomical, and functional integrity may result in wound formation. Interestingly, wound healing is a dynamic physiological process that restores typical structure and function of damaged tissue (Shaw and Martin 2009). When tissue gets damaged, wide varieties of cells, growth factors, cytokines, and chemokines underneath the skin layers coordinate to stimulate and complete different steps of wound healing cascade viz. hemostasis, inflammation, angiogenesis, epithelization, and tissue remolding (Cristina De Oliveira Gonzalez et al. 2016) (Fig. 1). According to statistical data of Medicare retrospective analysis 2014, for all wounds, including acute and chronic wounds, it was observed that approximately 8.2 million Medicare beneficiaries had at least one type of wound or related infection. Medicare budget for all wound treatments (infection management) ranged from $28.1 billion to $96.8 billion; a significant portion was contributed by surgical wounds and diabetic ulcers as they were more expensive to treat (Sen et al. 2009; Nussbaum et al. 2018; Sen 2019). In 2014, globally, the annual cost required for global wound care was estimated to be $2.8 billion, which will hike up to $3.5 billion at the end of 2021. According to a market research study, due to advancing technology, expensive wound care procedures, and increasing geriatric population, wound closure and dressing market will expand to $15 billion and $22 billion by 2022 and 2024, respectively. In progressing biomedical research era, several methods such as conventional and advanced dressing, biomaterial-based matrices, growth factors (GFs), cell-based therapies, and nanotechnology procedures are used to overcome wound healing complications (Gimble et al. 2007; Engel et al. 2008; Mason and Dunnill 2008; Negut et al. 2018). However, due to the economic burden of wound healing procedures, there is a great demand for effective, economical, and side-effect-free healing strategies.

Interestingly, it has been found that the regenerative potential of stem cells and platelets (especially platelet-rich plasma (PRP)) can serve as an appropriate alternate method for wound healing. Platelets are anucleated blood components, they circulate for 7–10 days in blood, critically modulating hemostasis and thrombo-inflammation (Ni and Freedman 2003; Versteeg et al. 2013). They secrete ample cytoplasmic granules, lysosomal content, microparticles, and exosomes, that play a pivotal role in regulating wound healing signalling mechanisms (Blair and Flaumenhaft 2009; De Pascale et al. 2015a; Golebiewska and Poole 2015). PRP (an autologous biological product isolated from a patient's blood)has a high platelet concentration compared to naïve plasma. According to some previous studies, PRP has a copious number of growth factors and cytokines, and these factors promote proliferation, differentiation, and migration of cells such as fibroblast, epithelial, endothelial, and mesenchymal stem cells (MSCs) and are responsible for wound healing (Blair and Flaumenhaft 2009). Moreover, they are involved inhemostasis, angiogenesis, collagen synthesis, and revascularization of the damaged tissue. Clinical studies on different research models also substantiated the efficiency and efficacy of PRP in improving wound and tissue regeneration. This compilation highlights the process of wound healing, its phases, strategies used to cure wounds and reviews the involvement of platelet, its secretome, and autologous product (PRP) as a cost-effective, easy to handle regenerative method for wound healing/tissue regeneration.

Platelets in wound healing

One microlitre of human blood contains approximately 150,000–450,000 platelets (anucleate biconvex discoid cell fragments of diameter 2–3 μm and

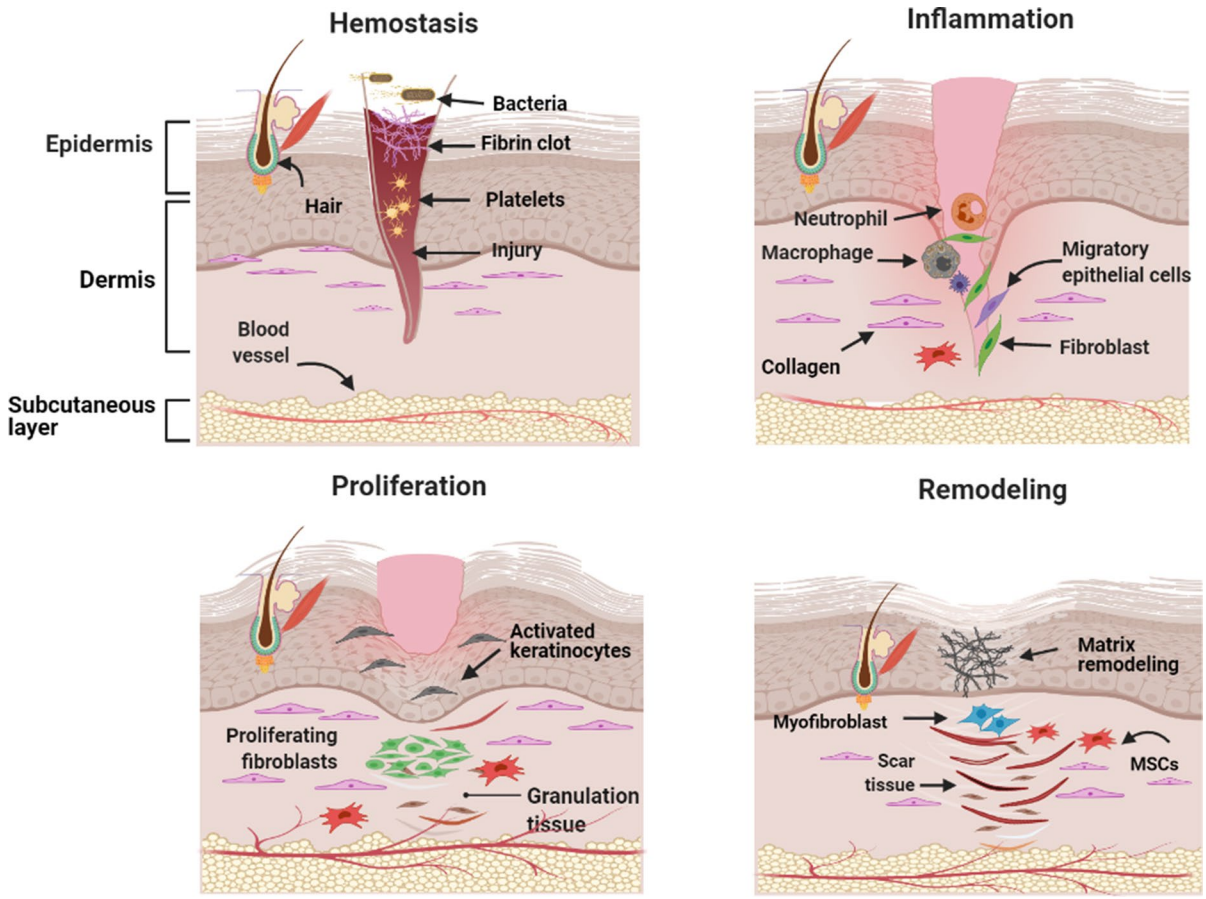

Fig. 1 The four phases of wound healing. It starts with hemostasis, where blood loss is prevented by platelet plug and fibrin matrix formation. The inflammation phase ensures the removal of dead cell debris and prevents further infection after neutrophil influx (stimulated by histamine release from the mast cell). Monocytes also get differentiated into macrophages to clear leftover dead cells and neutrophils around the wounded area. In the proliferative phase, various cascade culminates, such as keratinocytes migrate to seal the wound; angiogenesis starts for new blood vessel formation, and fibroblast triggers granulation tissue formation. Finally, fibroblast, blood vessels, MSCs, and myofibroblasts trigger tissue remolding, resulting in complete wound closure

0.5 µm thick) in circulation (Kaushansky 2005, 2008). Due to various cellular receptors on their surface, they are the first responder to a wound/tissue repair and play a critical role in wound healing mechanism (Harrison 2005; Rivera et al. 2009; Kauskot and Hoylaerts 2012). These receptor proteins bind to von Willebrand factor (vWF), thrombin, and fibrinogen, resulting in platelet plug formation and platelet morphological transition at the injury site.

Moreover, platelets also accommodate several secretory cytoplasmic and lysosomal granules, microparticles, and exosomes,which release various factors as platelets secretome (GFs, cytokines, adhesive molecules, chemokines, and other signalling molecules) that significantlyparticipatein wound repair mechanism (Anitua et al. 2004, 2006; Pietrzak and Eppley 2005; Fitch-Tewfik and Flaumenhaft 2013; Golebiewska and Poole 2015; Heijnen and van der Sluijs 2015). These secretomes regulate diverse biochemical, molecular, and cellular aspects of wound niche, such as inflammation, recruitment of neutrophils and macrophages, promoting angiogenesis, ECM formation, and tissue remodelling (Etulain et al. 2014; Burnouf et al. 2016a; Gresele et al. 2017; Etulain 2018; Nurden 2018; Everts et al. 2020). There are three types of platelet secretome: α-granules, dense granules, and lysosomal granules, approximately 50–80 granules are present in each platelet (Lacci

and Dardik 2010; Heijnen and van der Sluijs 2015; Sekhon and Sen Gupta 2018)(Pietrzak and Eppley 2005). After activation or programmed cell-death (apoptosis), platelet also shed some small evagination-mediated microparticles {platelet microparticles (PMPs)} of size 0.05–1 μm, also known as platelet dust or platelet-derived microvesicles (Varon and Shai 2015; Wojtukiewicz et al. 2017). They promote transfer of different platelet antigens viz CD41, CD61, CD62P, CXCR4, and PAR-1, to hematopoietic stem cell progenitor, and contain various proteinaceous wound healing factors like RANTES that stimulates multiple responses such as coagulation, inflammation,angiogenesis, neovascularization, and tissue regeneration (Janowska-Wieczorek et al. 2001; Ohtsuka et al. 2013). Apart from PMP, platelets also secrete exosomes by direct exocytosis; they are rich in various microRNAs and tetraspanin family of proteins. Some studies (in vitro and preclinical models) substantiate thatexosomes positively influence wound healing. However, detailed mechanism of platelet exosomes mediated wound recovery is still unclear, and it is one of the objectives of future research (Gawaz and Vogel 2013; Torreggiani et al. 2014; Rani et al. 2015; Guo et al. 2017).

Platelet rich plasma

PRP, also termed as autologous plasma, is rich in growth factors (PRGF), platelet-rich fibrin (PRF) matrix, and platelet concentrate. Haematologists introduced this concept in 1970 to describe elevated platelet level in a small amount of plasma, used initially to treat patients with thrombocytopenia (Pietrzak and Eppley 2005); (Jayadev et al. 2013). PRP has a high concentration of growth factors and cytokines that participate in various cellular, immune, and regenerative processes, such as wound healing and tissue regeneration, with sufficient tissue reparative efficacy (Currie et al. 2001; Kawase et al. 2003; Christgau et al. 2006; Banerjee et al. 2009; Lyras et al. 2010). In recent years, many controversies have arisen regarding the definition and nomenclature of PRP. Anitua and co-workers proposed definition of PRP as a vague and imprecise term because blood preparation differs in their production, resulting in variation in quantitative and qualitative characteristics of isolated PRP (Chicharro-Alcántara et al. 2018). All these complications stress the need for standard processing and preparation methods for PRP, which can compare different aspects of studies.

Preparation of PRP

Various systems can synthesize PRP in a reproducible manner, and its preparation procedures mainly rely on the type of device and instruction provided by the manufacturers (Table 1). Most of the devices obtain PRP with platelet concentrations higher than naïve plasma, but their platelet and leucocyte concentrations differ due to variability in isolation methods and centrifugation time. Hence, it is challenging to decide which preparatory kit is best and which is worst. All these systems generally operate on a small volume of blood and centrifugation principle. PRP is prepared through differential centrifugation, in which individual blood components are sedimented based on specific gravity (ratio of density of an object to reference's density) (Dhurat and Sukesh 2014). The procedure of PRP preparation usually includes three sequential steps. The blood of an individual is collected by venipuncture in a tube with an adequate anticoagulating agent (e.g., acid citrate dextrose and sodium citrate solution). It is followed by centrifugation at varying speeds of 100-3000 g, depending upon the device, PRP type, and purpose of extraction. After centrifugation, blood sample separates into three layers: bottom layer (RBC with leucocytes deposited immediately above), middle layer (contains PRP), and top layer (contains platelet-poor plasma (PPP) (Fig. 2). Usually, two centrifugation spins are applied; the first spin (hard spin) separates PRP from RBCs, while the second spin (soft spin) separates PRP from platelet-poor plasma (PPP) (Mishra et al. 2009; Dohan Ehrenfest et al. 2009; Lyras et al. 2010). Inducers of aggregation like bovine thrombin and 10% of calcium chloride are used for PRP's activation to stimulate degranulation, further releasing GFs. These activators increase platelet concentration up 3–5 times within 15 min as compared to native plasma (Mishra et al. 2009; Everts et al. 2012; Dhurat and Sukesh 2014; De Pascale et al. 2015b; Burnouf et al. 2016b).

After successful extraction of PRP from patient's blood, it is either used or stored. For storage of PRP, some scientists claim that in circulating blood PRP could not be preserved beyond 6 h of blood

Table 1 Devices used for PRP preparation (Gentile et al. 2010, 2017, 2020; Alves and Grimalt 2018)

S. No	Device	Company	Blood Collected	Anti-coagulant	Platelet Activator	Description
1	Angel®	Arthrex, Inc. Corporate Naples, Florida, USA	Syringe 40–180 mL	Acid citrate dextrose	10% (v/v) calcium gluconate	It is a closed technique, using software and programmed centrifugation to isolate PRP with a wide range of platelet concentrations from 3 to 18X compared to naïve plasma
2	Cascade® or Selphyl®	Musculoskeletal Transplant Foundation, Edison, New Jersey, USA	Tube 9 mL	Sodium citrate	$CaCl_2$	Pellet of activated PRP is prepared after centrifuging 18 ml of blood (9 ml in each tube) at 1100 g for 10 min
4	C-Punt®	Biomed Device, Modena MO, Italy	Syringe 60 mL	Sodium citrate	$CaCl_2$	A volume of 9 ml of PRP was harvested after centrifugation at 1200 rpm for 10 min
5	i-Stem® Preparation System	i-Stem, Biostems, Co., LTD., Seoul, Korea	Tube 20 mL	Sodium citrate	$CaCl_2$	After first centrifuging at 3000 rpm for 6 min, 1 ml of PPP and 2 ml of RBCs are removed. Suspension is again centrifuged at 3000 rpm for 3 min to obtain 15 ml of A-PRP
6	MAG-18®	DTS MG Co., Ltd., Seoul, Korea	Tube 19 mL	Sodium citrate	$CaCl_2$	The sample is collected and centrifuged twice, firstly at 3000 rpm for 6 min and secondly at 3400 rpm for 2 min to harvest 1.5 mL of PRP
8	Regenlab®	EnBudron b2, 1052 Le Mont-sur-Lausanne, Swiss	40 mL	Sodium citrate	Thrombin	Blood is collected in five ATS (autologous thrombin serum) Regen tubes (8 mL each). All tubes are centrifuged at 1500 g for 15 min at room temperature using the universal centrifuge (Regen Lab PRP-Centrig)
9	PRGF Endoret®	Biotechnology Institute (BTI)	Tube 9 mL	sodium citrate	$CaCl_2$	Sample is centrifuged at 270 g for 7 min

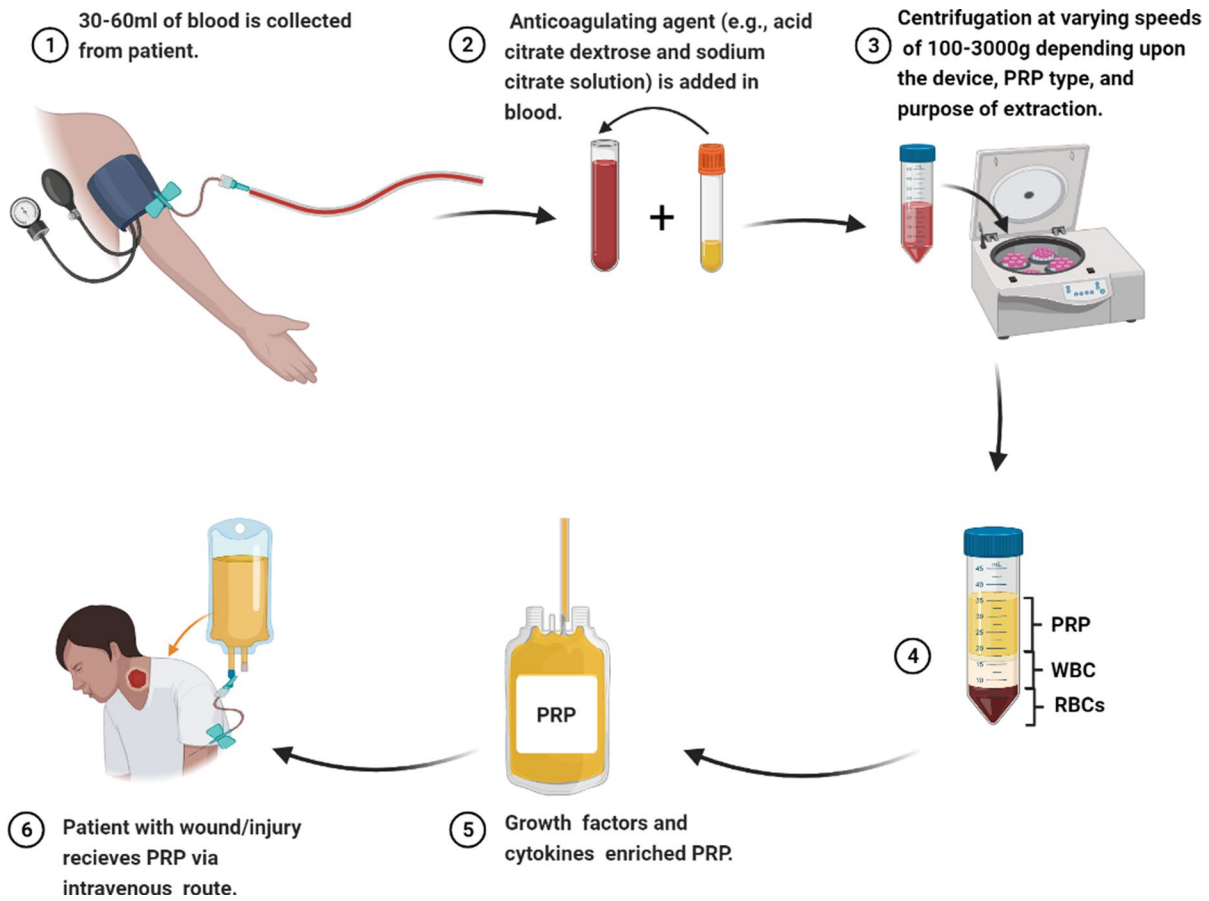

Fig. 2 Preparation of PRP for treatment

collection, while others observed that additives solution might enhance their stability, viability and enable their storage up to 7 h (Sweeney et al. 2006; Etulain 2018). Moreover, frozen PRP can be stored for longer. In some studies, frozen PRP was stockpiled with a 3-D scaffold (Lee and Blajchman 2001; Li et al. 2017). According to Shinga and co-workers, level of growth factors present in PRP reduce after 2 weeks of storage at room temperature. Whereas, in freeze-dried PRP, a baseline level of growth factors is maintained up to 8 weeks of storage. Therefore, PRP's freeze-dried form can be stored for an extended period with bioactivity and efficacy, a prerequisite for PRP's multiple applications in the same patient (Shiga et al. 2017).

Classification of PRP

Depending upon different parameters and their clinical applications, PRP is categorized into four distinct groups: activated PRP, non-activated PRP, leucocyte rich, and leucocyte poor. Activated PRP is prepared with the aid of $CaCl_2$ and with or without use of thrombin. They stimulate cytokine release from plateletgranules, while non-activated PRP synthesis includes platelet contact with intrinsic collagen and thrombin. The presence of leukocytes in PRP impedes bacterial growth and enhances soft tissue injury repair. In 2016, Magalon and co-workers postulated a DEAP classification of PRP based on dose of injected platelets, production efficiency, PRP activation, and

PRP purity (Magalon et al. 2016). Moreover, some studies categorized PRP; based onmethods used in their preparation (centrifugation and anti-coagulation), content, and composition of platelets, leucocytes, growth factors, and medical applications.

Ehrenfest and his colleagueproposed another way to classify PRP based on the presence and absence of leucocytes and fibrin.

The purest form of PRP: After activation, theyhave a low concentration of fibrin.

1. Leucocytes and PRP: This composition contains leucocytes with a low density of fibrin.
2. Pure-platelet-rich fibrin: They have a high density of fibrin network, but leucocytes are more or less absent.
3. Leucocyte and platelet-rich fibrin: This preparation has a high leucocyte concentration anda high fibrin network density.

3Growth factors present in PRP

PRP has a significant role in hemostasis, innate immunity, angiogenesis, stem cell migration, proliferation, and wound healing (Andia and Abate 2013; Shin et al. 2014; Anitua et al. 2016; Suthar et al. 2017a; Guszczyn et al. 2017). It contains many growth factors, cytokines, and chemokines, as they stimulate downstream signaling pathways required to synthesize proteins necessary for collagen, osteoid, and extracellular matrix formation(Jee et al. 2016) (Brissett and Hom 2003a) (Table 2). Platelets are a reservoir of more than 800 proteins,interacting with stem cells, fibroblast, endothelial and epithelial cells. PRP is a natural source of many growth factors (PDGF, IGF, VEGF, TGF-β), primarily stored in platelets α-granules (Anitua et al. 2004). The activating agents or stimuli like thrombin, $CaCl_2$, and collagen could trigger release of these growth factors (Fig. 3), which are further involved in crucial stages of wound healing and regenerative processes like chemotaxis, proliferation, differentiation, and angiogenesis (Bennett and Schultz 1993). In addition to these growth factors, PRP also contains some adhesive molecules such as fibronectin, vitronectin, fibrinogen, and sphingosine-1-phosphate. These are also essential for completing wound healing and bone formation process (Fernández-Barbero et al. 2006).

PRP as a regenerative therapeutic agent

Since year 1990, platelets derived products are efficiently been used in sub-fields of regenerative medicine. Over the past few years, PRP-based treatments are continuously in the limelightto curemultiple clinical challenges such as wound healing, skin and bone regeneration, ophthalmology, ulcer, burn, muscle repair, and others (De Pascale et al. 2015b; Burnouf et al. 2016b; Gresele et al. 2017). PRP influencesbone, tendon, and cartilage regeneration by modulating MSCsproliferation, chondrogenic differentiation, bone cell proliferation, and differentiation. It mobilizes circulating cells for tendon healing, matrix biosynthesis, and angiogenesis in acute tissue injury (Kajikawa et al. 2008; Lin et al. 2013; Kreuz et al. 2015). Reportedly, PRP is predominantly utilized in dermatology, especially in tissue regeneration, wound healing, acute and chronic ulcers, due to their impact on mitogenesis, angiogenesis, chemotaxis, type-I collagen synthesis, and proliferation and migration of keratinocytes, dermal fibroblast cells, and endothelial cells (Shin et al. 2014; Anitua et al. 2016; Guszczyn et al. 2017).

Application of PRP in wound healing

Advancing medical field is trying to trailblaze less invasive and cost-effective treatments (Lacci and Dardik 2010; Yung et al. 2017). Over the last few decades, PRP-based treatment had a potent impact in reducing economic cost of standard medical treatment and served as a potential competitor for replacing conventional therapies. PRP-based therapies supplement wound sites with a high concentration of GFs, cytokines, and chemokines, which play a crucial role in tissue repair (Glover 1992; Brissett and Hom 2003b; Jee et al. 2016). These factors also regulate inflammation, angiogenesis, synthesis of extracellular matrix, and newly formed tissue remodeling. An increased concentration of GFs also stimulates regeneration of epithelial and endothelial cells and synthesized collagen. For the first time, the PRP-based treatment method was used to treat chronic leg ulcers, which successfully resulted in vascularized connective tissue formation (Andia and Abate 2013; Suthar et al. 2017a). Besides humans, clinical studies have suggested that PRP-based treatment enhances wound healing in dogs, horses, and other animals (Carter

Table 2 Growth factors regulating wound healing process

S. No	Growth factor	Origin	Function	Future prospective
1	Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, keratinocytes, and muscle cells	It is the first growth factor that is secreted just after injury and regulates various cellular reactions throughout wound healing Promotes synthesis of TGF-β and IGF-1 It stimulates collagen synthesis and chemotaxis of macrophages and neutrophils 4. Increases hair growth. (Steed 2006; Graham et al. 2009; Takikawa et al. 2011; Shah et al. 2014)	The application of PDGF onsets wound healing. Therefore harnessing the effective use of PDGF in wound care increases its economic uses. The chemotaxis nature of PDGF would also be helpful in treating rare diseases
2	Epidermal growth factor (EGF)	Mainly secreted by platelets and cells like macrophages, fibroblast,and MSCs	Involved in proliferation, migration, and differentiation of epithelial cells and keratinocytes Promotes angiogenesis Stimulates hair cell proliferation and regeneration It also triggers epithelization of burn and granulation of wound. (Kim et al. 2010; Makki et al. 2013; Nanba et al. 2013; Lin et al. 2015; Takabayashi et al. 2016; Chicharro-Alcántara et al. 2018)	The application of EGF in wound enhances proliferation of healthy cells, facilitating wound repair

Table 2 (continued)

S. No	Growth factor	Origin	Function	Future prospective
3	Transforming growth factor-β (TGF-β)	Macrophages, T-lymphocytes, and keratinocytes	There are three isoforms of TGF-β; TGF-β1, -β2, -β3, having overlapping but unique function in wound healing TGF-β1 promotes angiogenesis, TGF-β2 and β3 are linked with scarring and fibrosis. They enhance fibroblast and myofibroblast differentiation, extracellular matrix deposition, wound contraction, and scar formation TGF-β triggers proliferation of undifferentiated MSCs, regulates mitogenesis of endothelial, fibroblast, and osteoblasts Inhibits proliferation (of macrophages and lymphocytes) and metalloproteins activity Regulates synthesis of collagen and secretion of collagenase. (Enoch et al. 2006; Le et al. 2012; Kofler and Simons 2016; Lamora et al. 2016; Etulain 2018)	The application of TGF-β stimulates key processes of wound healing such as angiogenesis, fibroblast proliferation, collagen synthesis and thus accelerate wound healing
4	Vascular endothelial growth factor (VEGF)	Platelets, keratinocytes, macrophages, and fibroblasts	It has a robust paracrine influence on endothelial cells and also promotes angiogenesis of wounds VEGF is a regulator of processes, such as vasculogenesis, lymphangiogenesis, and vascular permeability. (Werner and Grose 2003; Hsu and Chang 2004; Tammela et al. 2005; Hanft et al. 2008; Karayannopoulou et al. 2014; Shibuya 2015; Ferrara and Adamis 2016)	The VEGF promotes angiogenesis, which ensures a constant supply of oxygen at the site of injury. For instance, a decrease in the supply of oxygen drastically reduces the healing potential of the wound

Table 2 (continued)

S. No	Growth factor	Origin	Function	Future prospective
5	Fibroblast growth factor-2 (FGF-2)	Platelets, macrophages, mesenchymal cells, chondrocytes, and osteoblasts	Involved in re-epithelization, angiogenesis, and granulation tissue formation Indirectly stimulates the release of TGF-α Promotes fibroblast proliferation, collagen accumulation and accelerates granulation tissue formation. (Enoch et al. 2006; Niu et al. 2007; Xie et al. 2008; Shi et al. 2013; Shah et al. 2014; Maddaluno et al. 2017, Koike et al. 2020)	Previous reports has suggested that FGF-2 is effective in comorbidity such as diabetic cases in which wound healing processes get slow or decline
6	Insulin-like growth factor (IGF-1)	Platelets, plasma, epithelial cells, endothelial cells, fibroblasts, osteoblasts, and bone matrix	Mainly involved in inflammatory and proliferative phase of wound healing In combination with other growth factors like PDGF and EGF, it can exert a strong synergistic effect and promotes keratinocyte migration and tissue repair. (Reckenbeil et al. 2017; Yu et al. 2007)	Among all, IGF-1 significantly promotes wound healing as well as self-renewal and differentiation of cells. For a constant supply of new cells in a dysfunctional tissues, the role of IGF-1 becomes necessary
7	Hepatocyte growth factor (HGF)	Platelets and mesenchymal cells	Regulates cell growth, mortality, and morphogenesis in epithelial and endothelial cells Directly involved in epithelial repair, granulation tissue formation, and neovascularization In combination with VEGF, it exerts a robust cooperative effect that enhances angiogenesis at the injury site. (Conway et al. 2006; Anitua et al. 2005)	There is a direct effect of HGF on liver and kidney. HGF helps in the activation of VEGF and stimulates angiogenesis
8	Keratinocyte growth factor-2 (KGF-2), also described as fibroblast growth factor-10 (FGF-10)	Fibroblasts and MSCs	It is involved in remolding phase of wound healing: it induces migration and proliferation of keratinocytes Increases the proliferation of epithelial cells. (Enoch et al. 2006; Everts et al. 2020; Jimenez et al. 1999)	The fouth phase of wound healing lasts for 61 days to 2 years. In long run, the role of KGF-2 is very significant for proper healing of damage tissues

Table 2 (continued)

S. No	Growth factor	Origin	Function	Future prospective
9	Transforming growth factor (TNF)	Macrophages, mast cells, and T-lymphocytes	Regulates monocyte migration, fibroblast, proliferation, macrophage activation, and angiogenesis. (Giusti et al. 2020)	Transforming growth factor (TNF) activates macrophages which kill the microorganism and drastically reduce further infection

et al. 2003; Kimura et al. 2005; Lee et al. 2008; Sardari et al. 2011; CH et al. 2016; Suthar et al. 2017b). In chronic diseases such as diabetic ulcers, excess reactive oxygen species (ROS) are generated, resulting in an imbalance between pro-inflammatory and anti-inflammatory cytokines. PRP contains a high concentration of GFs and cytokines that maintain ROS levels and reduces wound recovery time (Lacci and Dardik 2010). Several studies have been performed to observe clinical effects of PRP-based therapies, majority of them showed a significant reduction in wound size without side-effects. Subcutaneous PRP administration in patients suffering from nonhealing ulcers demonstrated decreased wound size, pain, and inflammation. According to Babaei et al., after topical PRP application in 150 patients diagnosed with a diabetic foot ulcer, a significant granulation tissue formation, and early wound closure was observed (Babaei et al. 2017). In a study by Man et al., a quantitative improvement in human skin wound healing was also reported after using a cutaneous flap with autologous PRP (Man et al. 2001). Even AIDS patients suffering from crural ulcers showed increased neovascularization and re-epithelization after PRP and platelet application to achieve faster wound healing than other conventional methods (Cieslik-Bielecka et al. 2018).

The second intension wound (SIH) occurs when a significant tissue loss and edges cannot be brought together by granulation, contraction, and epithelization. It can be affected by a wide variety of factors, such as inadequate blood supply, previous infection, and systemic disease that result in imperfect wound healing (Schreml et al. 2010; Zaman Phull et al. 2018). For efficient closure, proper regulation of granulation tissue formation, angiogenesis, collagen synthesis, and epithelization is highly needed. Karayannopoulou et al. evaluated the effect of intra-lesional PRP administrationon SIH involving acute full-thickness skin defect in dogs. They observed improved tissue perfusion that uplifted granulation tissue formation and attracted nutrients and oxygen towards the wound, simultaneously accelerating collagen formation and wound healing process (Karayannopoulou et al. 2015). A full-thickness wound was treated with PRP in a study by Ostvar and co-workers on rabbits and other small research models. The PRP application increased vascular density, angiogenesis, granulation tissue formation, and healing rate compared to thestandard method (Ostvar et al. 2015). Some

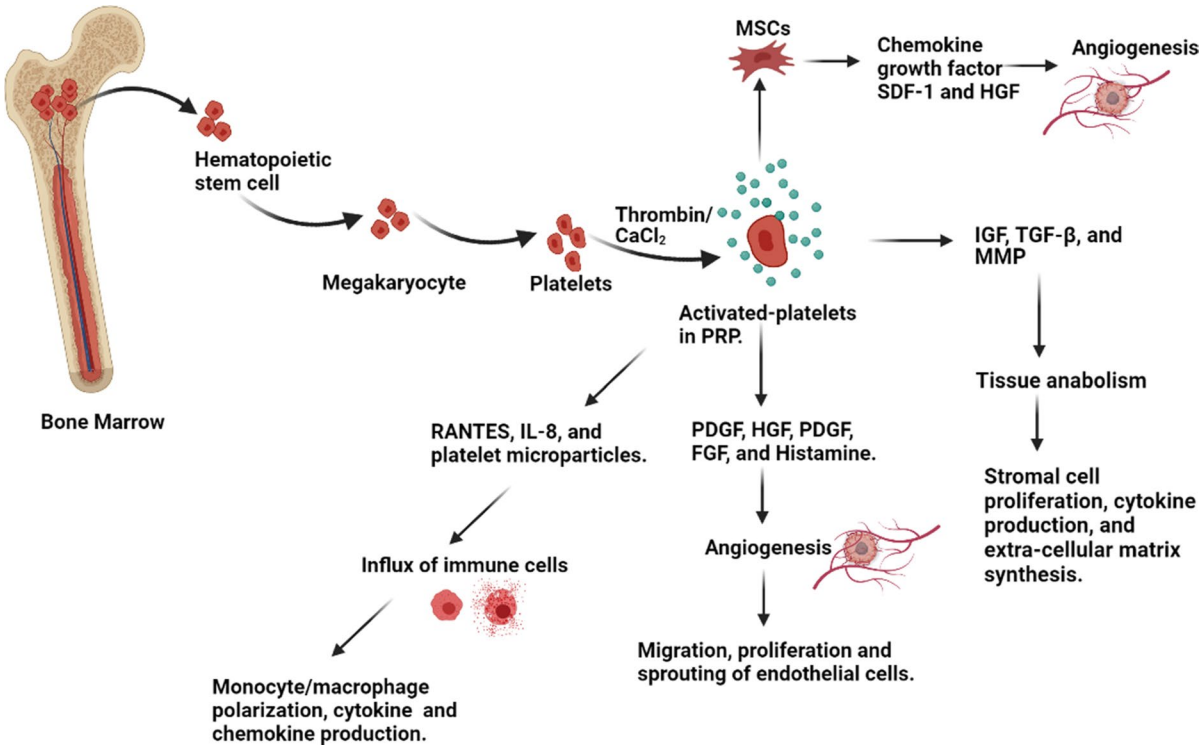

Fig. 3 Mechanistic role of PRP in tissue repair

studies have also mentioned PRP's synergistic effect combined with bone-morrow-derived mesenchymal stem cells (BM-MSCs) (Lian et al. 2014). This combination offers a suitable microenvironment for proliferation and differentiation for facilitated wound healing. In a study by Park et al., when wounded mice were treated with a combination of PRP and hydrogel, a marked improvement in wound healing was observed in comparison to control and PRP/hydrogel (Park et al. 2017).

Platelet inspired biomaterials

As previously discussed, platelet and their secretory molecules are used in wound healing procedures. But during their administration, various constraints have been observed, like prominent risk of contamination, low viability, and portability (Spinella et al. 2012, 2016; Lambert et al. 2013; Shin et al. 2014; Miron et al. 2017). These shortcomings limit the efficiency and efficacy of platelet-based therapies. Several biomaterial and nanotechnology procedures are considered to develop synthetic and non-synthetic platelet mimics to overcome these limitations. For designing platelet mimics, nanotechnology approaches are used in which polymer nanoparticles of polylactic acid (PLA) and poly-N-isopropyl acrylamide-co-acrylic acid (pNIPAm-AAc) are coated with fibrinogen (Fg) or Fg-mimetic Arginine-Glycine-Aspartic Acid (RGD) peptides. Also, surface of liposome was decorated with fibrinogen γ-chain dodecapeptide. These synthetical designs reduce bleeding in various injury models and are used in platelet-inspired drug delivery (Coller 1980; Takeoka et al. 2001, 2003; Bertram et al. 2009; Ravikumar et al. 2012; Modery-Pawlowski et al. 2013a, b; Anselmo et al. 2014; Brown et al. 2014; Shukla et al. 2017).

In some cases, these synthetic platelets are also loaded with some anti-infective agents and GFs (PDGF, VEGF, and others); they are released in spatio-temporally controlled manner during hemostasis to stimulate post-hemostasis wound healing mechanism. Even fibrin-coagulated PGFM, bFGF, and PDGF are incorporated in gelatine hydrogel; they collectively promote tissue and blood regeneration (Matsui and Tabata 2012; Leotot et al. 2013; Santo

et al. 2015; Mittermayr et al. 2016; Robinson et al. 2016). Furthermore, synthetic platelets integrated biomaterial matrix system was also used to develop multi-component technology, affecting different aspects of wound healing and assisting direct loading and delivery of platelet-relevant biomolecules. Some studies have demonstrated that recombinant FGF in combination with collagen sponge system reduces recovery and wound closure time. Tuneable hydrogel has been shown to regulate delivery of various cell secretory GFs and cytokines (e.g., interferon-γ and IL-4), resulting in macrophages transition to promotetissue regeneration (Yao et al. 2006; Spiller et al. 2015; Skardal et al. 2017). Even PEG-fibrin gel also secretes some muscle cell markers, for instance, α-smooth muscle actin, PDGF-β, NG2 proteoglycan, and angiopoietin-1 that assist the development of vascular structure in a wound area. For sustained degradation, release, and activation, PRP was encapsulated within enzyme-degradable hydrogel matrices to modulate wound healing mechanism. These combinations of polymer, synthetic platelets, and nanotechnology systems are administered via topical, intracavitary, or intravascular passage to interact with bleeding site and damaged tissue directly. These systems release several GFs and biomolecules to enhance wound healing (Zamora et al. 2013).

Synergism of PRP and MSCs in wound healing

Treatment of chronic and nonhealing wounds is a tedious and challenging task for the health sector as it involves replacing cutaneous lesions with new regenerative skin. Also, pre-existing strategies (bioengineered dressings and cell therapies) were not optimal for chronic wound treatment as these wounds persist as an unmet medical need. Wound care products should have a similar composition to normal skin, which constitutes a proper amalgamation of GFs, extracellular proteins, MSCs, fibroblast, and endothelial cells. Even presence of endogenous MSCs in skin and their involvement in various phases of wound healing substantiate the application of exogenous MSCs combined with other tissue repair therapies (Paquet-Fifield et al. 2009; Sellheyer and Krahl 2010). In the inflammatory phase, these cells prevent deleterious effects of inflammatory cytokines (TNF and IFN-γ) and secrete several antimicrobials factors to facilitate wound clearance via stimulating phagocytosis through immune cell and promote transition from inflammatory to proliferative phase in a chronic wound, otherwise which is hindered due to high level of inflammation (Robson et al. 2001; Ramasastry 2005; Velnar et al. 2009). Like PRP, MSCs also secrete numerous soluble factors (VEGF and SDF-1), growth factors and cytokines, micro-vesicles/exosomes with cytoprotective, proangiogenic, and anti-inflammatory properties. MSCs associated secretomes are adopted well in their niche, and their paracrine effect lasts for a more extended period post-engraftment (Yong et al. 2018)(Yiou et al. 2016). During proliferative and remodeling phase, MSCs release GFs like VEGF, bFGF, and KGF; they promote granulation, neovascularization, tissue epithelization, ECM organization, and mobilization of stem cells at the wound site (Clark 1993, 2001; Tonnesen et al. 2000; Mulder and Vande Berg 2002; Baum and Arpey 2006; Koellensperger et al. 2014; Marfia et al. 2015). A considerable number of completed clinical trials are available, which validate safety and efficacy of MSCs in stimulating regeneration of damaged tissues, including the skin. Based on genetic modification, pharmacological pre-conditioning, and use with biomaterial, robust studies have been performed to ameliorate viability, retention, and functionality of MSCs, but these approaches are pretty expensive and non-feasible to translate in humans (Sheykhhasan et al. 2015; Li et al. 2016; Frese et al. 2016).

Barbara Hersant and her colleague performed a studyto evaluaterole of a combination of MSCs and PRP in wound healing. According to their observations, this amalgamation is more efficient in promoting vascularization, proangiogenic potential, and tissue regeneration in wound as compared to individual treatment of PRP and MSCs (Hersant et al. 2019). After PRP treatment, MSCs secrete VEGF and SDF-1 in higher concentration, resulting in more significant vessel formation and endothelial cell migration. Moreover, PRP also serves as a clinical-grade adjuvant to elevate therapeutic efficacy of engrafted MSCs and increase its adaptability, paracrine effect, retention, and persistence at wound site and shields MSCs from oxidative damage (as cytoprotectant) by increasing oxygen consumption and ATP-linked respiration (Badiavas and Falanga 2003; Falanga et al. 2007; Yoshikawa et al. 2008; Dash et al. 2009; Lu et al. 2011; Martínez et al. 2016; Chen and Liao

2018; Samberg et al. 2019). Still, there is a scope for exploring different mechanisms that affect regenerative properties of MSCs to develop a more efficient protocol for tissue repair and other degenerative diseases.

Merit and demerits of using PRP based therapies

The prime advantage of using platelets as a regenerative agent in wound healing/tissue regeneration is that they can be prepared instantly and do not require any advanced preparation facilities. They are safe and natural due to their direct extraction from a patient's blood, and this method even demolishes probability of any adverse immune response and blood-born contaminations (Lyras et al. 2010) (Bianco et al. 2008).

There are as such no such demerits of platelet-based treatments. However, infection site morbidity, infection, and blood vessel injury were reported in some cases due to formation of tissue scars and calcification at injection site. Platelet and its secretomes and autologous PRPare generally injected intravenously; sometimes, it might damage arteries and veins, resulting in blood coagulation. Patients with ahistory of platelet dysfunctions syndromes, thrombocytopenia, hyper-fibrogenemia, hemodynamic instability, chronic heart disease, and cancerexperienceseveral complications during platelet-based treatment (Bianco et al. 2008).

Cost effectiveness of PRP and comparision with standard treatment

Through Meta-analysis using the Markov Mode, the cost of PRP in skin ulcers was calculated. The comparative result showed that the probability of healing was 56% using PRP and 31% with standard treatment. The associated costs were €5224 and €5133 respectively. The major benefit of PRP treatment is associated with reducing the average length of hospital stay which compensates for the normal cost of treatment. The incremental cost to achieve additional healing was €364, within a 48-week time of treatment. In an another comparative study, the cost of PRP treatment in 81 patients with ulcers demonstrated that the average length of stay with PRP was (11 ± 2.5 days) and cost € 785.25, whereas the standard treatment average length of stay in the hospital was 23.1 ± 1.5 days with cost € 1649.02. The overall study demonstrated that PRP therapy would significantly reduce the length of hospital stay and directly becomes economic. The major reason for the slightly high cost of PRP treatment is the procedure of PRP preparation. Scientists are exploring new approaches to reduce the cost of preparation of PRP so that a significant reduction in cost can be observed (Oliveira et al., 2020).

Meta-analysis for cost effectiveness of PRP therapy

The cost-effective comparison was done through meta-analysis (Fig. 4). A total of 27 published papers were found with the search term (Economic cost effectiveness PRP) term from the Pubmed database. Papers were screed, out of 27 papers, 7 paper was considered for analysis because the data and study were more relevant to our study. In one study, Linertová et.al observed that PRP treatment with the manual method was more effective and less costly compared to PRP treatment with the commercial kit and standard methods (Linertová et.al. 2021). The cost of PRP treatment with the manual method was significantly less but not as effective as PRP treatment with a commercial kit. According to Alcerro et al. (2019) when PRP was compared with Stem cells Therapy (SCT), the mean cost of PRP injection was $897, and for SCT injection, it was $3,100. It was also observed that about 36% of people preferred PRP whereas 24.5% accepted SCT. The cost-effectiveness of PRP therapy and hyaluronic acids (HA) was compared by Samuelson et al., it was observed that PRP injection was more effective and less economical as compared to HA (Samuelson et al. 2020). Randomized controlled clinical trials (RCTs) indicate that autologous PRP was associated with an increase in hair density when compared to placebo but the economic cost-effective measurement was not done (Dervishi et al. 2020). Bendich et al. also conducted RCTs for PRP, HA, and Saline groups, the result showed that the lowest total cost for HA and saline were $681.93 and $516.29 respectively. For PRP to be cost-effective, total treatment cost would have to be less than $3,703.03 and $1,192.08 for 6-month and 12-month outcomes respectively (Bendich et al. 2020). When PRP gel and gas dressing was compared by Uçar et al. 2020, the result showed PRP gel had a positive effect on the healing of stage II pressure ulcers with PRP

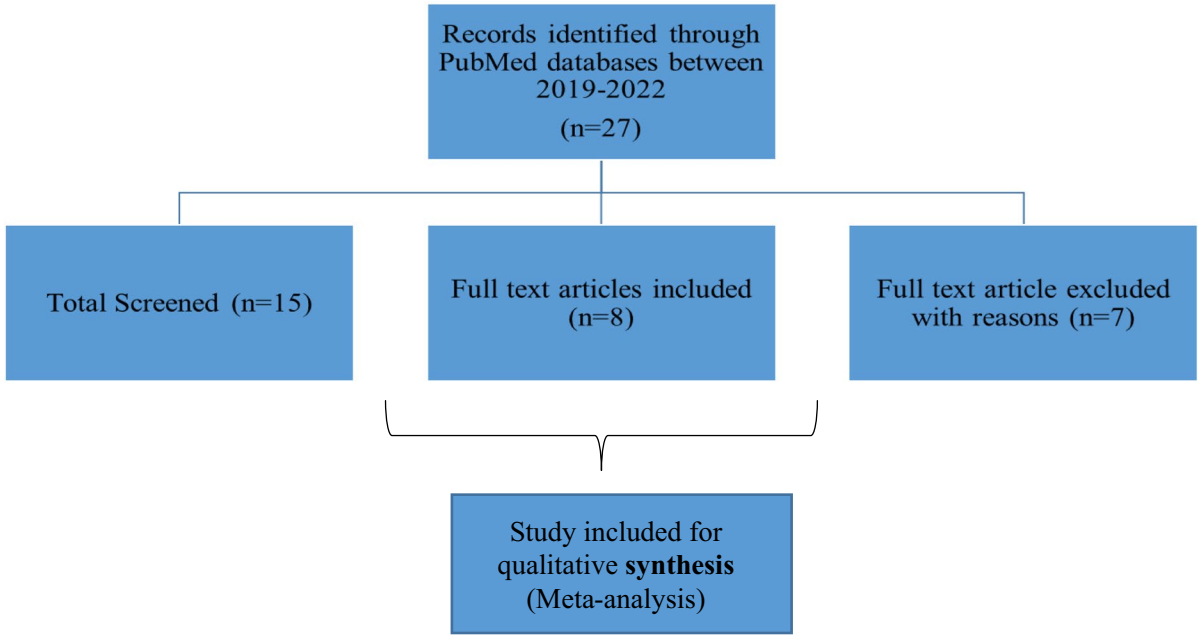

Fig. 4 Meta-analysis of cost effectiveness of PRP therapy

gel dressings. In addition, when evaluated in the long term, it was concluded that PRP gel is easily accessible and less costly than serum physiological dressing (Uçar et al. 2020). The overall analysis from different papers suggested that the PRP is therapeutically effective but more research are required to minimize the cost. Many studies have suggested that PRP treatment was cost-effective but need more clarity.

Future prospects and market value

The total market valuation of PRP therapy has reached US$ 370.78 million in 2021. The data also demonstrated that the market is projected to expand at a steady 6% compound annual growth rate (CAGR) through 2031. According to Future Market Insights (FMI) analysis on PRP, growth prospects will remain positive because of gaining traction in diverse medical procedures such as orthopaedic and neurological surgeries. In recent years, the application of PRP in regenerative therapies and surgical procedures has created prospects for intensive medical research. There was significant use of PRP therapy observed in COVID-19. The growth of PRP in the year 2021 was 8.8% [https://www.futuremarketinsights.com/reports/platelet-rich-plasma-market].

Conclusion

In wound healing, several intracellular, intercellular, and extracellular signaling mechanisms regulate distinct phases of healing. Some studies substantiate significant involvement of platelets and their related products such as PMPs and exosomes in wound healing phases. Due to these characteristics, PRP is continuously explored for its role in wound healing/tissue regeneration as they have higher platelet concentrations (Lacci and Dardik 2010; De Pascale et al. 2015b). Apart from natural platelets, robust research has been done to develop platelets' bio-mimics. An amalgamation of PRP-based components with synthetic biomaterials was also used to designs several biohydride systems (Oryan et al. 2016) (Salamanna et al. 2015). These approaches enhance wound healing, prompt site-specific delivery, and even regulate loaded drugs' release patterns. However, wide variability in preparation, composition, and concentration of these platelet products makes standardized correlation a tedious

task. In recent years, various clinical trials have been performed to evaluate the significance of platelet-based products; they showed several beneficial results in clinical conditions with minimal sideeffects. However, their efficacy as regenerative medicine is still in its infancy owing to a lack of accepted standard preparation protocol. For illustration, PRP-based therapy has shown its salutary role in many health complications, but their significance is continuously undermined. Metanalysis of clinical trials also showed a disparity in the results of these trials, which might be due to variation in preparation, activation, and administration procedure. Therefore, it is imperative to understand the mechanism of PRP in regeneration, step-wise preparation, long-term side effects, and anti-aggregating drug effects on PRP-based treatment. There is dearth of data that could substantiate long-term outcome of cutaneous wound healing with PRP application. Therefore, controlled studies with a significant sample size are highly needed to validate PRP's efficacy as regenerative medicine to treat wound healing. Despite these complications and controversies in PRP-based approaches, recent clinical trials show promising results of PRP application in dermatology, dentistry, ophthalmology, orthopedics, and other fields. Further insights can be made after completion of phase 3 and phase 4 trials. Therefore, PRP can serve as a potentform of therapeutic, solo, or in combination with other regenerative approaches for wound healing and tissue regeneration. Due to economic sufficiency, these therapies also have the potential to replace conventional treatments. Thus, it is essential to collect more consensus data obtained from various clinicaltrials and standardize application of its formulation as a potent regenerative therapy for wound healing/tissue regeneration.

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