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RELATIONSHIP BETWEEN PRP THERAPY AND INFLAMMATORY SIGNALING CONCERNING HEPATOCYTES REGENERATION

Muddasir Hassan Abbasi[1*], Adil Farooq[1], Muhammad Babar khawar[2] & Nadeem Sheikh[3]
[1]Department of Zoology, University of Okara, Pakistan
[2]*Department of Zoology, University of Narowal, Pakistan*
[3]Department of Zoology, University of the Punjab, Lahore-Pakistan

Article Info

*Corresponding Author
Email ID: muddygcs@gmail.com

Abstract

In plasma fluid that more than 200,000–900,000 platelets/microliter suspended plasma. Platelets are the chief promoters of the body due to comprising a large number of growth factors PDGF, TGF, VEGF, IGF, support in the regeneration/proliferation. In platelet-rich plasma number of platelets at least 1000000 platelets/µl also containing enzymes biological active molecules active ions (Ca, Mg, Cu, Zn, etc.). Platelets containing fluid is used as regenerative medicine in different fields of medical sciences orthopedic, dermatology, plastic surgery, diabetic wound healing dentist, antibacterial activity with gram +ve, -ve pathogens, and gynecological infections. The liver performs many key biochemical and secretory functions. In hepatic cell abnormality cause any type of chronic disease ischemia/reperfusion injury, liver cirrhosis, and cholestatic liver. Platelets have an anti-apoptotic marker which increases the damage portion. The manifestation of mRNA genes TGF-β, α-SMA, and hepatic compacted by platelets NF-κB and hepatic IL-8. TNF-,cytokines and PG, are released by Kupffer cells which take part in liver regeneration. IL-1, 6, interferons, and HGF, distressing hepatic regeneration, and IL-6 emission amplified subsequently in hepatectomy.

Keywords
Platelets drive growth factors (PDGF), Kupffer Cells (KCs), hepatic stellate cell (HSC).

1. Introduction

PRP is that consisted of more than 200,000 – 900,000 platelets/μl (microliter) suspended plasma. Now a day it is reported to be extensively used for therapeutic drives i.e. tissue repairing, orthopedics, dermatology, musculoskeletal regeneration, etc. (Zahn *et al*., 2020). During the process of healing, platelets activate in the body and release multiple growth factors (GFs) which accelerates the healing phenomenon (Dhillon *et al*., 2012). Prominent GFs consist of platelet-derived growth factor (PDGF), transforming growth factor (TGF-β1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF-1). Many studies recognized that the process of liver regeneration occurs by platelet growth factors (Hesami *et al*., 2014). PRP also acting an active part in the provocation response by producing and releasing a diversity of inflammatory intermediaries, including cytokines such as TGF-, IL-1 (Interleukin), CD40L, and chemokines. (Galliera *et al*., 2012). Platelets carry significant growth factors, and their interaction with protein factors (PFs) such as fibronectin and vitronectin is accountable for the remedial interaction and regenerative biochemical processes such as chemotaxis, cell propagation, tissue debris eradication, and angiogenesis (Tiwari & Bhargava, 2013). Approximately 150,000 to 350,000/microliter (µl) normal platelet counts in the blood whereas PRP is commonly defined as at least 1,000,000 platelet/µl adjourned in plasma (Wasterlain *et al*., 2016). Fibrin, and enzymes, active ions (Ca+, Mg+, Mn+, Cu+, Zn+, etc), membrane-associated receptors, and biologically active molecules are key constituents in PRP include a variety of growth factors, leukocytes. There are three overlapping phases of wound healing, and it is typically divided into the following three phases: (i) hemostasis/inflammation, (ii) cell proliferation, and (iii) remodeling, these phases impart role in cell regulation, cytokines, and progression factors that can act directly over the responsible cells for their release, nearby cells, or even distant cells (Chicharro-Alcántara *et al*., 2018; Jee *et al*., 2016; Zielins *et al*., 2014). PRP is constantly being used in regenerative medicine for chronic wound healing (Mehta & Watson, 2008). It decreases postoperative infection, pain, blood loss, and an increase in bone and wound healing (Waters & Roberts, 2004). The metabolic disorders and several pathophysiological conditions can disrupt the normal wound healing process and in resulting delayed the wound and take maximum time for healing (Markova & Mostow, 2012; Wu *et al*., 2010). Wound healing process control by various GFs, cytokines, integrin, keratins, matrix-metalloproteinase, chemokines, and extracellular macromolecules will assist in the therapeutic process (Chicharro-Alcántara *et al*., 2018). GFs are vital in wound healing because each growth factor has many roles in wound healing and binds to unique receptors on target

cells. (De La Mata, 2013; Roubelakis *et al*., 2014). PDGF, EGF, FGF, IGF, VEGF, TGF, HGF, and KGF are among the several GFs recognized to be intricate in wound therapy (Grazul-Bilska *et al*., 2003).

Table 1: Growth factors and their functions with references**.**

TGF-β	i)Stimulates mesenchymal stem cells proliferation ii)Proliferation of macrophage and lymphocyte; iii)Regulates endothelial, fibroblastic, and osteoblastic cell mitogenesis	(De Pascale *et al*., 2015)
PDGF	i) Stimulates many metabolic processes like protein ii) Migration and proliferation of endothelial cells iii) Stimulate the production of IGF-1 iv) Production of TGF-β which initiate the collagen synthesis	(Chicharro-Alcántara *et al*., 2018; Lynch *et al*., 1987)
EGF	i) DNA synthesis and cell proliferation ii) Promotes chemotaxis of endothelial cells iii) Promotes the angiogenesis	(Bertrand-Duchesne *et al*., 2010; Girdler *et al*., 1995)
FGF	i) Re-epithelialization, angiogenesis, and granulation tissue formation by FGF. ii) New blood vessels formation from the established vasculature	(Wasterlain *et al*., 2013; Waters & Roberts, 2004; Xie *et al*., 2008)
IGF	i) inflammatory and proliferative role ii) IGF-1 secretes by fibroblasts which employ autocrine effects iii) keratinocytes migration promotion and enhancing tissue repair by combination with IGF	(Chicharro-Alcántara *et al*., 2018)
VEGF	i) Strong paracrine effect during wound healing ii) Significant regulators of physiological and pathological vasculogenic, lymphangiogenesis, and vascular permeability	(Tammela *et al*., 2005)
HGF	i) The Main protagonist in the directive of cell growth, tissue formation, neovascularization ii) HGF and VEGF both have a synergistic effect during wound healing	(Anitua *et al*., 2005; Conway *et al*., 2006)
KGF	Accelerate the healing process during venous ulcer	(Enoch *et al*., 2006)

2. Role of PRP in hepatic Inflammation

The liver is the body's principal organ for metabolism, detoxification, and secretory processes, transcription it susceptible to a variety of diseases. Because there is now no effective treatment for these illnesses, experts are working to develop new drugs. During the fetal stage, the liver is a hematological organ, and entirely grown liver cells generate thrombopoietin, which stimulates platelet synthesis in the bone

marrow (Hesami *et al*., 2014). Hepatic abnormalities mediate several pathogenic symptoms, containing, hepatic stellate cell (HSC) propagation, pro-inflammatory cytokine construction, and protein confession in the extracellular matrix (ECM), leading to the regression of liver fibrosis (Salem *et al*., 2018). Although liver fibrosis was previously thought to be an incurable condition, new evidence suggests that such chronic fibrosis could be curable. New treatments for liver cirrhosis have been discovered, according to these recent studies (Yu *et al*., 2017). Marx *et al*. reported that platelet-rich plasma (PRP), an allogeneic product rich in growth factors that may be obtained from a blood sample by centrifuging the platelet-rich supernatant (Lee *et al*., 2013). Moreover, platelets play a significant part in inhibiting the evolution of hepatic fibrosis both *in vitro* and *in vivo*, and platelet transfusion-induced growth factor increase can improve hepatic function in patients with CLD and cirrhosis (Maruyama *et al*., 2013). The liver is a hematological organ, and its advanced hepatocytes release thrombopoietin, which can determine thrombocytes' synthesis in the bone marrow, during the fetal period. The Thrombocyte's synthesis in the bone marrow then its issues are abundant with no effective therapies; nonetheless, the exploration for innovative medications continues. Though, few studies have considered the liaison between hematic components, that is, platelets and liver rejuvenation (Hesami *et al*., 2014). Platelets include a variety of GFs and proteins that are required for hemostasis and Platelets have anti-fibrotic and pro-proliferative properties in the liver (Hiyama *et al*., 1981).

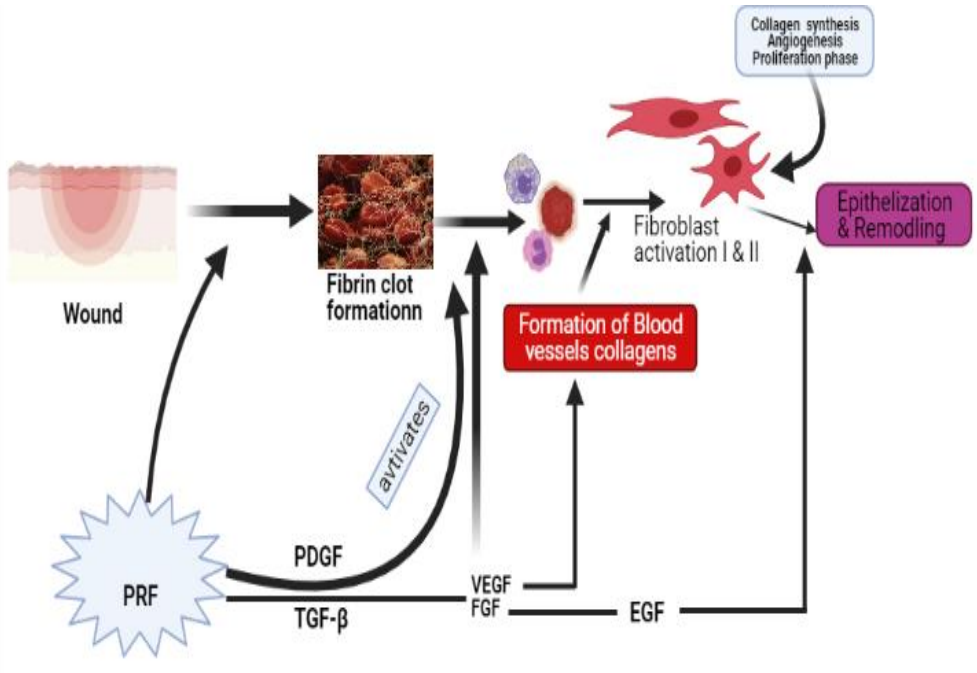

Figure 1: Process of Wound healing. PRF; platelet-rich fibrinogen, PDGF; Platelet drive growth factors, mechanism of the directive in wound healing.

Some clinical studies have demonstrated platelet accretion in the liver under certain pathologic surroundings, such as ischemia/reperfusion damage (Khandoga *et al*., 2003; Pak *et al*., 2010), liver cirrhosis, cholestatic liver, and viral hepatitis (Hesami *et al*., 2014). In response to various types of liver damage, liver regeneration is an effective and well-regulated process in which leftover liver cells proliferate to restore the afflicted organ's original proportion (Michalopoulos & DeFrances, 1997). Hepatocytes accomplish one or more cell divisions throughout this time while maintaining all regular cellular processes. The stimulating phase and the advancement phase of hepatocyte mitosis are two successive biochemical mechanisms in which the actions of numerous cytokines and growth factors are arranged (Murata *et al*., 2014). Platelets have been found in several studies to stimulate liver regeneration due to the presence of Alpha granules, dense granules, and lysosomal granules (Murata *et al*., 2014; Murata *et al*., 2007). Direct platelet-hepatocyte contact may be significant in the proclamation of soluble molecules from the platelets; the furthermost significant mediator is IGF-1, which is found in human platelets and has a proliferative impact, and hepatocyte growth factor (HGF) containing platelets instigate hepatic mitosis, which leads to liver regeneration, and hepatocyte generated mitogen signaling for another benevolent of hepatic cells, and each mediator determine the downstream processes that relocation hepatocytes from an inactive state to the cell cycle (Nakamura *et al*., 1989; Ohkohchi *et al*., 2012; Ozaki, 2008).Platelets have an imperative role in both in vitro and in vivo liver fibrosis and expand a hepatic purpose in individuals with CLD and cirrhosis (Maruyama *et al*., 2013). TGF-β, α-SMA, and hepatic hydroxyproline, NF-B, and hepatic cytokine were shown to have highly concentrated mRNA expression in PRP. Furthermore, PRP has a substantial rise in the anti-apoptotic indicator Bcl-2 for use in liver regeneration, and liver regeneration/recovery is a challenging procedure. (Gilgenkrantz & de l'Hortet, 2011). The surface maker for platelet stimulation is a CD62P initiate in platelet granules. It is also useful in distinguishing early bleeding and clotting problems triggered through liver cirrhosis (Xianghong *et al*., 2013). On the other hand, Inflammation, cancer, and an immunological response are some of the adverse reactions of platelet degranulation (Murata *et al*., 2014). In 2006 Lesurtel *et al* stated that platelets have proliferating effects in liver regeneration and In critical and chronic liver disease platelets are abnormal in number and conventionally have been supposed to contribute to impairment (Hugenholtz *et al*., 2009; Lesurtel *et al*., 2006). PRP treatment pulls down liver enzymes while increasing albumin levels, suggesting hepatocytes rejuvenation, decrease of injury, and

better hepatocytes function (Mafi *et al*., 2016). According to Neveen Salem and his colleagues, Platelet therapy offers anti-fibrotic, anti-apoptotic, and anti-inflammatory properties, and it has the potential to open the way for the creation of novel medicines. PRP might be utilized as a supplement to reduce the deleterious effects of hepatotoxicants (Salem *et al*., 2018). TNF/NF-B, IL-6/STAT3, PI3K/Akt, HGF/HFG receptor (cMet), and extracellular indication synchronized kinase 1/2 (ERK1/2) are all significant paths in hepatocytes regeneration and repossession. (Chen *et al*., 2013). Under thrombocytosis environments, a considerable increase in hepatic levels of HGF and IGF-1, as well as early and strong phosphorylation of Akt and signal transducer and stimulator of transcription-3 (STAT3), is generated (Murata, Matsuo, *et al*., 2008; Murata *et al*., 2007). Murata, Soichiro, *et al*. reported that TPO, (thrombopoietin) is a potent stimulus that assists in hepatic cell proliferation and is regulated by the development of MK and platelet production (Murata, Matsuo, *et al*., 2008; Wolber & Jelkmann, 2002). TPO boosted marginal platelets and encouraged liver regeneration, including improving fibrosis in the peri-portal areas and boosting the liver cells-proliferating cell nuclear antigen (PCNA) labeling index and mitotic index in the cirrhotic liver (Murata, Hashimoto, *et al*., 2008). TPO, which is generated at a consistent rate in the liver and kidney, is the most significant GF in the directive of megakaryocyte enlargement and platelet construction, and TPO mRNA levels in the liver were considerably diminished in patients with liver cirrhosis (Witters *et al*., 2008). Patients with hepatofugal portal blood flow had diminished TPO levels (Sezai *et al*., 1998). TPO improved the platelet count in liver fibrosis (Kurokawa & Ohkohchi, 2017). In patients with cirrhosis, IP3 synthesis in response to thrombin ready is much reduced in platelets, whereas cytosolic calcium is elevated, and aggregation calcium is the last common route in platelets, leading to platelet hypofunction (Witters *et al*., 2008). In dense bodies, there is a diminution in ATP and serotonin (5HT), as well as a decrease in PF4 (platelet factor 4), thromboglobulin (BTG), and P-selectin, and plasma levels of BTG and PF4 are testified to be raised to platelet count (Witters *et al*., 2008). Serotonin (5-hydroxytryptamine, 5-HT) has synergistic activity as a neurotransmitter as well as a hormone with a variety of extraneous neuronal activities. It is a potent mitogen that distresses tissue remodeling. Platelets transport them and release 95 percent of the serotonin contained in blood at the site of damage; it is a powerful mitogenic and stimulates hepatocytic mitosis. M. Lesurtel and colleagues discovered that platelet-derived serotonin (PDGFS, with EGFS) had a role in the early stimulation of Kupffer cells (KCs), which create responsive oxygen species, in the inception of liver regeneration (Bilzer *et al*., 2006; Jaeschke, 2006; Lesurtel *et al*., 2006). Moreover, serotonin agonists' appearance that serotonin may work

downstream of platelet and leukocyte interfaces with endothelial cells or hepatocytes (Marcos *et al*., 2004). The local liver macrophages, Kupffer cells (KC), were the first to identify this non-parenchymal cell type. KC accounts for around 35% of non-parenchymal liver cells (Phillips, 1987; Wake, 1980). KC function is diminished in the absence of platelets and leukocytes, resulting in ischemic liver injury (Sindram *et al*., 2001). Kupffer cells, which account for ≥ 82% of all tissue macrophages in the body, function in opposition to gastrointestinal microbes, with microbial debris, and endotoxins (Bilzer *et al*., 2006). Platelets are a predominantly ironic source of chemokines, and they assist in the anticipation of liver fibrosis and the elevation of liver rejuvenation following hepatectomy. Following ischemia, KCs harvest a large number of pro and anti-inflammatory mediators, as well as TNF, and cytokine (Charo & Ransohoff, 2006; Pak *et al*., 2010). HGF, IL-1, IL-6, and interferons all affect hepatic rejuvenation, with IL-6 invention increasing after hepatectomy (Rai *et al*., 1996). Furthermore, P-selectin impacts platelet and leukocyte recruitment, as well as platelet-dependent leukocyte recruitment, signifying that P-selectin is associated with cholestatic liver damage. which may open the mode for more tailored therapy approaches to protect the liver in situations when bile flow is impeded (Laschke *et al*., 2008). Platelets secreted IL-6, which boosted LSEC proliferation and DNA synthesis in hepatocytes (Kawasaki *et al*., 2010). In epidemiologic hepatitis, the cytotoxic-T lymphocyte (CTL) reaction remains a strong prognosticator of liver impairment. Platelet reduction or activation inhibitors limit CTL dispersion in the hepatic cells of mice. Because they stimulate reciprocal recruitment, platelet-CTL interactions are supposed to be important in hepatic microcirculation Surprisingly, thrombocyte-derived serotonin has been hypothesized to mediate liver injury via microcirculation variations in a lymphocytic choriomeningitis virus infection model (Ripoche, 2011). Nearly 80% of HCCs are found in the context of chronic liver injury caused by other diseases such as chronic infections and drunk liver disease (Farazi & DePinho, 2006). Such as the cells collect chromosomal abnormalities and genetic and epigenetic alterations, the dysplasia in regenerative nodules leads to HCC in the cirrhotic liver, finally resulting in massive amplification of cytoprotective and proliferative signals. Many pathways have been considered to be significant in HCC, including Ras/MAPK, PIK3CA/AKT, and Wnt/-catenin signaling (Villanueva *et al*., 2007). β-Catenin, the main effector of Wnt signaling, is generally recognized as an oncogene due to its widespread effects in a range of malignancies, comprising 20% -40% of all HCCs (Monga, 2011). β-Catenin is also exclusively associated with FOXO during a cell's changed redox state to control the production of genes involved in oxidative stress signaling, which could be impaired if β-catenin is absent (Essers *et al*., 2005). Hepatocytes

lacking β-catenin are unable to adjust toward oxidative trauma caused by DEN-induced genotoxic damage plus prolonged through inflammation and excitation of Kupffer and stellate cells, leading to death and fibrosis (Oseini & Roberts, 2009; Stock *et al*., 2007; Zhang *et al*., 2005). PDGFRα activation may be caused by PDGFs generated by numerous inflammatory and persistent non-parenchymal cells in the liver (Wong *et al*., 1994). PDGFR is an identified PIK3CA/Akt pathway upstream effector (Hunter, 2000). Because of EGFR's importance in HCC, its reduced levels of β-cat in livers are intriguing; yet, this upriver effector of PIK3CA has been demonstrated to be a mark of Wnt/-catenin signaling (Tan *et al*., 2005). Correspondingly, the HGF receptor c-Met is known to boost the PIK3CA pathway and is crucial in HCC, although it was shown to be a Wnt signaling target and was down-regulated of β-cat in livers. (Boon *et al*., 2002).

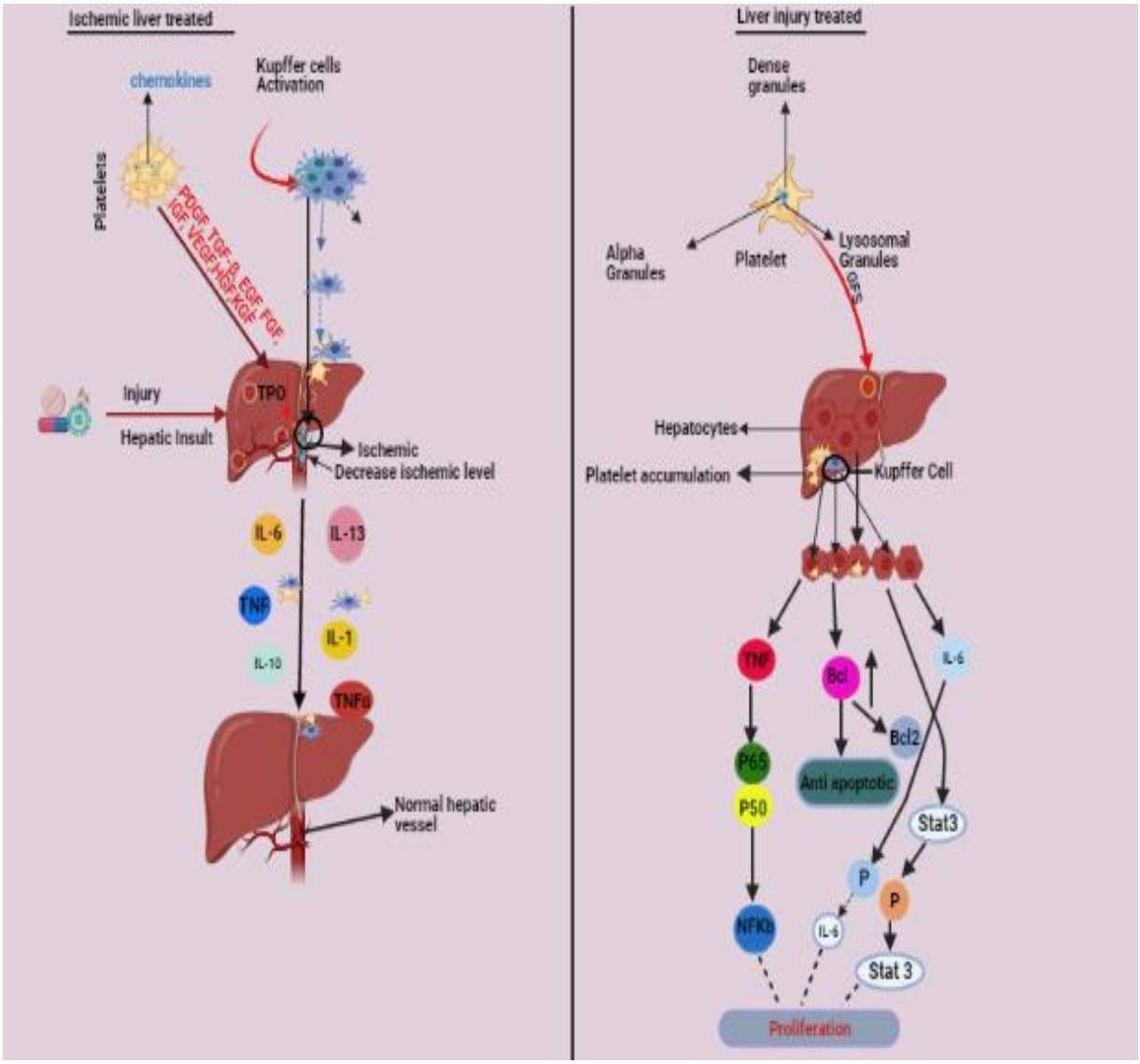

Figure 2: Shows how proliferation completed after any injury in the liver and the ischemic condition is going to normal after being treated with Platelet and taking part in the signaling pathway for proliferation**.**

3. Conclusion

Platelets' clinical applications have been thoroughly investigated and documented. Platelets and their growth factors, known as PDGFs, are the primary components of every well-prepared PRP preparation. PRP administration might be an important component of liver regeneration treatment. PDGFs are anti-inflammatory and promote compact mRNA expression, and they play a crucial role in cell regulation**.**

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