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The mechanism of action of platelet-rich plasma for knee osteoarthritis: a systematic review

Mecanismo de acción del plasma rico en plaquetas en osteoartrosis de rodilla: una revisión sistemática

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Abstract

Background: *Platelet-rich plasma (PRP) is a biological intra-articular therapy that has shown good clinical outcomes in patients with knee osteoarthritis (OA) and has been widely studied from in vitro to pre-clinical animal models. We aimed to synthesize non-clinical evidence regarding the different effects related to PRP.* **Methods:** *A systematic literature review was conducted in the MEDLINE, EMBASE, and Google Scholar databases in December 2020. Studies were included if they were non-clinical basic science publications describing the effect of PRP treatment, studies focused on knee OA, and articles reporting the use of PRP or a similar platelet-derived product. Included articles were assessed and categorized based on the effect or the mechanism of the action described. The main findings of each study were obtained and analyzed.* **Results:** *A total of 41 articles were included to review the outcomes of interest. The most frequently reported mechanism was the modulation of genes involved in synthesizing and degrading the cartilage extracellular matrix (ECM), followed by ECM morphological analysis, inflammation, and cell proliferation. PRP preparations with low and high content of leukocytes were equally reported.* **Conclusions:** *The studies reviewed provide evidence for several ways in which PRP can act once it is present in the intra-articular environment. The vast majority of data support a beneficial effect of PRP therapy, especially for leukocyte-poor PRP formulations. The evidence collected gives us a clue as to what the mechanism of action could be. However, the great heterogeneity in the study formulations and models implies further investigation.*

Keywords: *Platelet-rich plasma. Knee osteoarthritis. Cartilage. Anti-inflammatory. Systematic review.*

Resumen

Objetivo: *El plasma rico en plaquetas (PRP) es una terapia biológica intraarticular que ha mostrado buenos resultados en pacientes con osteoartrosis (OA) de rodilla y se ha estudiado en ensayos in vitro hasta modelos animales. Nuestro objetivo fue sintetizar la evidencia no clínica sobre los diferentes efectos con los que se ha relacionado el PRP.* **Métodos:** *Se realizó una revisión sistemática de la literatura en las bases de datos MEDLINE, EMBASE y Google Scholar en diciembre de 2020. Se incluyeron publicaciones de ciencia básica no clínicas, que describieran el efecto del tratamiento con PRP, enfocados en la OA de rodilla y que reportaran el uso del PRP o un producto derivado de plaquetas similar. Los artículos incluidos se evaluaron y categorizaron según el efecto o mecanismo de acción descrito.* **Resultados:** *Se incluyeron un total de 41 artículos para su revisión. El mecanismo reportado con más frecuencia fue la modulación de genes implicados en la síntesis y degradación de la*

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matriz extracelular del cartílago (MEC), seguido del análisis morfológico de la MEC, inflamación y proliferación celular. Se hizo énfasis acerca de si las formulaciones de PRP tenían bajo o alto contenido de leucocitos. **Conclusiones:** *Los estudios revisados proporcionan evidencia de varias formas en las que el PRP puede actuar dentro del ambiente intraarticular. La gran mayoría respaldan un efecto benéfico de la terapia con PRP, especialmente para aquellas formulaciones de PRP bajas en leucocitos. Sin embargo, la gran heterogeneidad en las formulaciones y modelos de los estudios implica una mayor investigación.*

Palabras clave: *Plasma rico en plaquetas. Osteoartrosis de rodilla. Cartílago. Antiinflamatorio. Revisión sistemática.*

Introduction

Osteoarthritis (OA) of the knee is a progressive disease involving the cartilage from the tibia, femur, patella, and surrounding periarticular tissues[1]. Knee OA is associated with pain and functional loss that can significantly impair quality of life and is considered one of the leading causes of disability in the adult population[2]. Due to the increase in population longevity and a greater number of overweight and obese individuals, OA has become a major cause of medical attention over the past 60 years worldwide[3,4].

This disease alters every component of the tissues involved, from the molecular to the cellular and extracellular levels. OA is biochemically mediated and ultimately causes the structural and functional failure of the joint[5]. Knee OA is characterized by articular cartilage damage due to its progressive and degenerative nature. Because the cartilage is avascular and cells have low mitotic activity, it has limited healing potential once injured and eventually leads to irreversible damage[6]. Therefore, the articular cartilage's pathological processes represent a difficult clinical challenge for orthopedic surgeons.

To date, there is no cure for OA, and there is no effective pharmacological agent that can halt or reverse the existing damage. A variety of modalities have been used in the treatment of knee OA, including both conservative and surgical methods. Conservative modalities include non-pharmacological approaches (such as exercise and lifestyle modification)[7,8]. They also include pharmacological agents, such as analgesics (nonsteroidal anti-inflammatory drugs), topical agents, supplements such as chondroitin sulfate and glucosamine, and different intra-articular injections with corticosteroid-hyaluronic acid viscosupplementation[9-13]. In cases of severe pain, opioids have also been prescribed[14]. On the other hand, although effective, surgical options such as arthroscopy, osteotomy, and arthroplasty are often associated with serious complications.

Development in biological research has highlighted the importance of autologous platelet-rich plasma (PRP) for the treatment of a wide range of musculoskeletal pathologies[15]. The rationale for using PRP is that platelets are mainly responsible for hemostasis and wound-healing processes, and much of this leading activity is because once they are activated, they undergo degranulation and release a wide variety of bioactive proteins[16,17]. Because of the many molecules that platelets hold, PRP has been proposed to have many therapeutic mechanisms in knee OA, including anti-inflammatory effects, proteoglycan synthesis, cartilage matrix protection, and proliferation[18]. There are also reports suggesting distinct mechanisms of action between different PRP formulations[19,20]. These differences are mainly attributed to the number of leukocytes present in the PRP; thus, they can be classified as leukocyte-poor PRP (LP-PRP) or leukocyte-rich PRP (LR-PRP)[21].

Despite PRP being widely evaluated in multiple clinical trials and multiple efforts being focused on evaluating the responses of different tissues and cell types involved in knee OA pathogenesis, there is still no consensus on the mechanism of action and changes that PRP could produce. This study aims to systematically review the basic science evidence for the role of PRP in various aspects of the pathological process of knee OA, attempting to summarize the mechanisms of the actions described in the current literature.

Material and methods

Literature search and eligibility criteria

A systematic literature review was conducted in the MEDLINE, EMBASE, and Google Scholar databases until January 2021 to find original articles reporting the effect of PRP in different knee OA models following PRISMA guidelines for systematic reviews. The search terms included "platelet-rich plasma," "platelet lysate," "platelet growth factors," "platelet releasate," "osteoarthrit*," "knee osteoarthritis," "effect," and "mechanism." Examples of the search strategy are provided as supplementary material. Studies were included if they fulfilled the following criteria: they were (1) primary non-clinical basic science publications (including studies based on animal models), (2) articles describing the effect of PRP treatment, (3) studies focused on knee

OA, and (4) articles reporting the use of PRP or a similar concentrated platelet product (e.g., autologous protein solution, plasma rich in growth factors, platelet-rich fibrin, autologous conditioned plasma) with a platelet count higher than baseline.

Study selection process

The search results were reviewed for duplicates according to the inclusion criteria to determine articles that would be included in the final information extraction. Four reviewers, working as independent pairs, screened the titles, abstracts, and full text of manuscripts for eligibility in two screening phases. At phase one, titles, and abstracts were reviewed to exclude irrelevant studies; additionally, all studies had to be approved by at least one of the reviewers to be included in the full-text phase. At phase two, full-text articles were reviewed to determine the relevance of the studies. Disagreements were resolved by consensus with a third author. The same criteria were used for both screening phases. The chance-adjusted agreement was quantified using the kappa statistic, and consensus resolved disagreements. We used the Distiller Systematic Review Software (DistillerSR, Evidence Partners) to manage the screening process.

Data collection

Data were extracted in duplicate by two independent authors using an electronic spreadsheet, and data were reviewed and compared to reach a consensus with a third author. Included articles were assessed and categorized based on the effect or the mechanism of action described. Single articles were included in more than one category if they reported more than one mechanism of action for PRP. Following the information reported by the included studies, the different classifications developed in the data collection process were: apoptosis/cell death, anti-inflammatory effect, proliferation/cell viability, modulation of extracellular matrix (ECM) based on gene expression, and modulation of ECM based on histomorphological analysis. The key findings and conclusions from each included study were obtained in aggregate with articles of the same category.

Quality assessment

We used the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) Risk of Bias tool[22] to evaluate methodological quality by assessing ten items related to different types of bias (selection, performance, detection, attrition, reporting, and others). Each item of this tool is an answer to a specific question to determine the presence (high), absence (low), or undetermined (unclear) risk of bias on every animal model intervention study. The quality of *in vitro* studies could not be evaluated due to their high heterogeneity regarding the reporting of methodological designs and results.

Synthesis of results

The relevant findings and conclusions from each included study were abstracted and analyzed in agreement with articles of the same assigned category and listed in different tables according to established categories. Furthermore, the results presented have been derived by interpreting common and consistent mechanisms within each category.

Results

Search strategy and study selection

The initial search strategy yielded 1572 records, of which 41 studies met the inclusion criteria and were included in the systematic review. Figure 1 displays the flowchart of the study selection process. The categories into which each identified main mechanism of action were classified and the relevant outcomes of each study are further described.

Quality assessment

Fourteen studies reported the use of an animal model intervention. After applying the SYRCLE's risk of bias tool, we detected at least one domain at high risk of bias, indicating a low methodological quality for these records. All the studies had a high risk of bias for sequence generation, blinding, and random animal selection for outcome assessment. On the other hand, a low risk of bias was determined for incomplete outcome data, selective outcome reporting, and other sources of bias. The complete quality assessment is shown in Table 1.

Main mechanisms of action identified

Apoptosis/cell death

In vitro studies

Chondrocyte apoptotic events are decreased in cells treated with pro-inflammatory stimuli and further

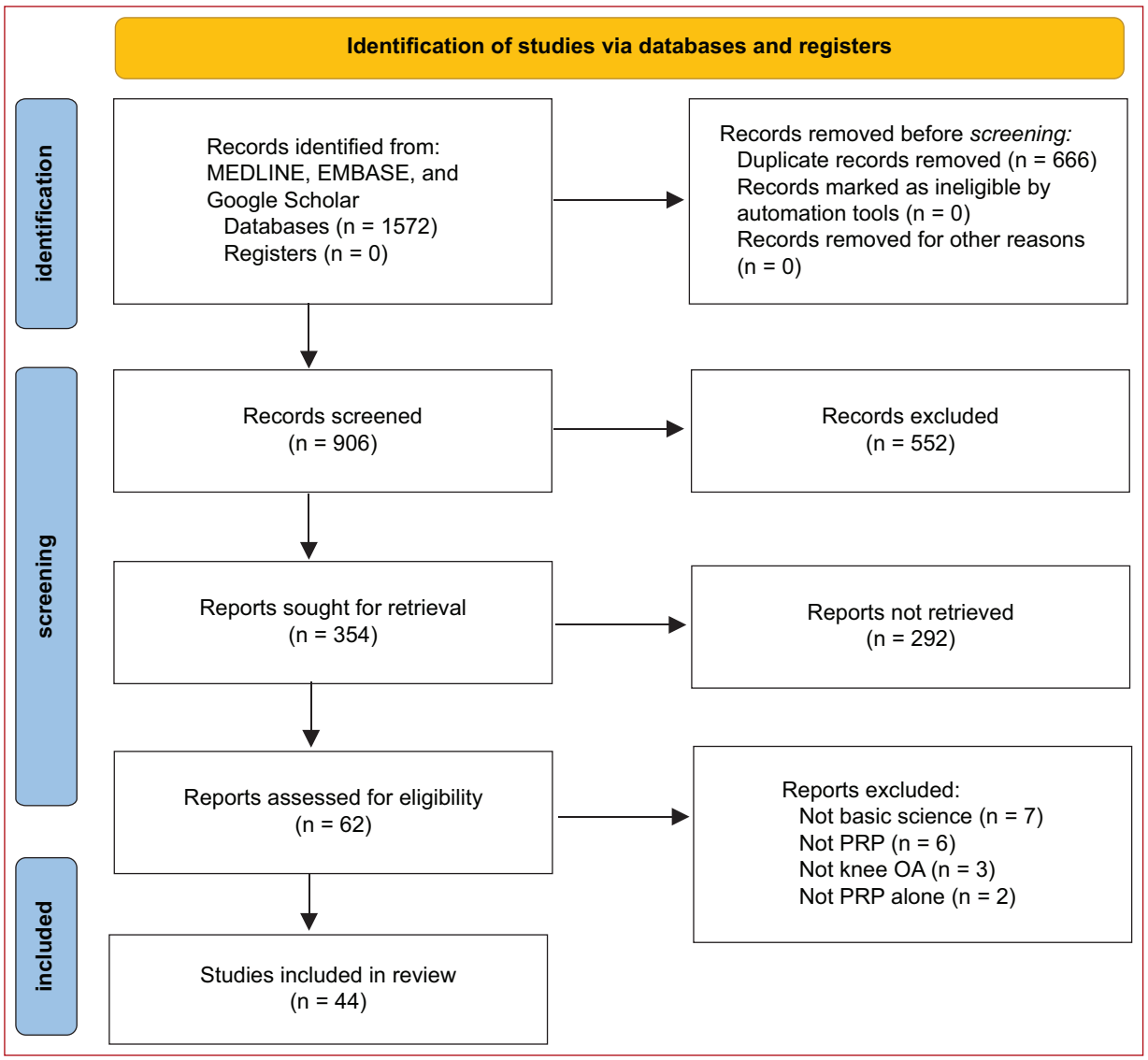

Figure 1. Flow chart of the study selection process.

challenged with LR-PRP[23-25]. In IL-1β-induced chondrocyte apoptosis, the presence of LR-PRP decreases the expression of the pro-apoptotic Bax and caspase-3 while increasing the expression of the anti-apoptotic Bcl-2 and PARP mediators[23]. In human fibroblast-like synoviocytes *in vitro*, treatment with LR-PRP significantly increase cell death compared with LP-PRP and controls (Table 2)[26].

In vivo studies

In a model of chemically induced OA in nude rats, the injection of LR-PRP did not significantly decrease the presence of apoptotic chondrocytes; however, when the injection of LR-PRP was combined with muscle-derived stem cells, apoptosis was significantly reduced (Table 2)[27].

Proliferation

In vitro studies

Most studies reporting the effect of PRP over cellular proliferation used human chondrocytes, although primary cultures of rabbit, rat, and porcine chondrocytes were also tested. All studies reported a proliferative effect of either LP-PRP or LR-PRP. This proliferative effect of PRP over chondrocytes was confirmed at the tissue level as well[28,29]. Some of these studies

Table 1. Quality analysis using the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) tool for studies reporting the use of animal models to evaluate the effect of PRP in knee OA

Author, year	Model of study	1	2	3	4	5	6	7	8	9	10
Araya et al., 2020[53]	Rat model of induced knee OA	H	L	H	U	H	H	L	L	L	L
Asjid et al., 2019[29]	Rat model of induced knee OA	H	L	L	L	H	H	L	L	L	L
Chouhan et al., 2019[76]	Guinea pig model of weight-induced knee OA	H	L	L	U	H	H	L	L	L	L
Liu et al., 2019[25]	Rabbit model of induced knee OA	H	L	H	L	H	H	U	L	L	L
Khatab et al., 2018[77]	Mice model of collagenase-induced OA	H	L	L	L	H	H	L	L	L	L
Bozynski et al., 2016[49]	Canine model of anterior cruciate ligament-induced OA	H	L	L	L	H	H	L	L	L	L
Hermeto et al., 2016[54]	Rabbit model of induced OA	H	U	L	U	H	H	L	L	L	L
Yin et al., 2016[47]	Synovial fluid from New Zealand rabbits with induced OA	H	L	L	L	H	H	L	L	L	L
Yun et al., 2016[48]	Canine model of induced OA by cranial cruciate ligament transection	H	L	L	L	H	H	U	L	L	L
Zhou et al., 2016[51]	Monosodium iodoacetate rodent model of osteoarthritis	H	L	L	H	H	H	L	L	L	L
Kazemi and Fakhrjou, 2015[57]	Canine model of acute articular cartilage injury of the knee	H	L	L	L	H	H	L	L	L	L
Almasry et al., 2014[52]	Rat model of surgically induced OA	H	L	L	U	H	H	L	L	L	L
Liu et al., 2014[46]	Surgically created cartilage defect in adult rabbits	H	L	L	L	H	H	L	L	L	L
Mifune et al., 2013[27]	Injection of muscle-derived stem cells and PRP in knees of nude rats	H	L	L	U	H	H	L	L	L	L

PRP: platelet-rich plasma; OA: osteoarthritis; H: high risk of bias; L: low risk of bias; U: unclear risk of bias.
1. Selection bias, Sequence generation
2. Selection bias, Baseline characteristics
3. Selection bias, Allocation concealment
4. Performance bias, Random housing
5. Performance bias, Blinding
6. Detection bias, Random outcome assessment
7. Detection bias, Blinding
8. Attrition bias, Incomplete outcome data
9. Reporting bias, Selective outcome reporting
10. Other sources of bias.

evaluated the dose-dependency of PRP on chondrocyte proliferation; supplementations from 5% to 25% were reported, showing a dose-dependency proliferation as PRP concentration increases. However, it seems that no further proliferative stimulation occurred above 10% PRP supplementation[23,30-32]. In some cases, the proliferative effect has prevailed despite chondrocytes being cultured under pro-inflammatory conditions, as represented by *in vitro* models of knee OA (Table 3)[25,28,33,34].

In vivo studies

The use of LR-PRP in different rat models of knee OA promoted proliferation of normal chondrocytes[29] and muscle-derived stem cells related to chondral repair (Table 3)[27].

Inflammation

In vitro studies

At the cellular level, PRP reduced gene expression of pro-inflammatory markers such IL-1β, COX-2, IL-6, IL-8, and IL-18 in chondrocytes after they were subjected to a pro-inflammatory stimulus[33-35]. Conversely, a more recent report indicated that LP-PRP was not able to inhibit TNF-α-induced inflammation, with an upregulated COX-2, prostaglandin E synthase, IL-1β, and IL-17 gene expression[36]. In primary cultures of synoviocytes, it was observed that LR-PRP, but not LP-PRP

Table 2. Studies reporting the effect of PRP on apoptosis/cell death

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
In vitro studies					
Liu et al., 2019[25]	Primary culture of IL-1β-induced OA rabbit chondrocytes	ND	LR-PRP	ND	LR-PRP inhibited the apoptosis rate induced by IL-1β
Moussa et al., 2017[32]	Primary culture of human OA chondrocytes	12	LR-PRP	ND	5%, 10%, and 20% LR-PRP significantly decreased the apoptotic ratios of OA chondrocytes by 37.63%, 37.97%, and 38.65%, respectively
Carmona et al., 2016[24]	Culture of horse cartilage explants challenged with lipopolysaccharide (LPS)	6	LR-PRP and LP-PRP	Calcium gluconate	No chondrocytes in apoptosis were detected in explants treated with LR-PRP (50%) + LPS and LP-PRP (50%) + LPS Apoptotic chondrocytes were detected in explants treated with LPS, LR-PRP (25%) + LPS, and LP-PRP (25%) + LPS
Yang et al., 2016[23]	Primary culture of rat chondrocytes treated with IL-1β	3	LR-PRP	$CaCl_2$	LR-PRP reduces the number of IL-1β-induced apoptotic cells (anexin V positive cells)
Braun et al., 2014[26]	Culture of human type B fibroblast-like synoviocytes cell line	4	LR-PRP and LP-PRP	No activation	LR-PRP produces a higher percentage of cell death (5%) at 96 h versus LP-PRP, PPP, and control (<1%)
In vivo studies					
Mifune et al., 2013[27]	Injection of muscle-derived stem cells and PRP in knees of nude rats	36	LR-PRP	$CaCl_2$	Injection of LR-PRP did not significantly decrease apoptotic chondrocytes regarding control. Injection of LR-PRP and stem cells combined significantly reduced apoptosis

PRP: platelet-rich plasma; LR: leukocyte-rich; LP: leukocyte-poor; OA: osteoarthritis; ND: no data.

formulations, induced the expression of IL-1β and IL-8 pro-inflammatory cytokines, which was directly related to the presence of leukocytes[37,38]. Earlier, results from synovial cells from OA suggested that LP-PRP might restore hyaluronic acid concentrations but did not modify the IL-1β-induced synthesis of VEGF, matrix metalloproteinase-1 (MMP-1), and MMP-3[39]. LR-PRP showed inhibition of IL-1β pro-inflammatory effects in tridimensional cultures of human chondrocytes[40] and human cartilage and horse cartilage explants[24,41], with an additional reduction in IL-1β-induced nitric oxide production[40,41]. At the protein level, both LR-PRP and LP-PRP high supplementation (50%) have been shown to induce greater production of TNF-α in culture supernatants of horse cartilage and synovial explants[42-44]. In contrast, the co-culture of human cartilage and synovial explants in the presence of LP-PRP decreased the presence of TNF-α but not IL-6 (Table 4)[45].

In vivo studies

Different animal models have shown that LP-PRP injections reduced the presence of IL-1β in synovial fluid[46,47], suggesting that LP-PRP can inhibit the activation of the nuclear factor-kappa B (NF-κB) pathway *in vivo*[47]. Canine models of induced OA reported that the use of LR-PRP and LP-PRP ameliorate the degenerative process[48,49] showing that LR-PRP could reduce the presence of IL-1β, TNF-α, COX-2, INF-γ, and iNOS positive cells (Table 4)[48].

Modulation of ECM based on histomorphologic analysis

In vitro studies

Both LR-PRP and LP-PRP have been tested in explants models of OA, showing an overall better surface remodeling[24,28,50]. However, when explants were challenged with a pro-inflammatory stimulus, LP-PRP had the best therapeutic profile, with higher type II collagen and proteoglycan deposition and fewer surface fissuring (Table 5)[24,28].

In vivo studies

Mice and rat models of induced OA have revealed positive results after interventions with PRP formulations. Particularly, LP-PRP formulations presented a

Table 3. Studies reporting the effect of PRP on proliferation

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
In vitro studies					
Rikkers et al., 2020[36]	Primary culture of human OA chondrocytes	5	LP-PRP	ND	Chondrocyte proliferation but not migration was significantly increased with 20% LP-PRP supplementation
Liu et al., 2019[25]	Primary culture of IL-1β-induced OA rabbit chondrocytes	ND	LR-PRP	ND	LR-PRP promoted chondrocytes proliferation significantly after treatment with IL-1β as compared with inflammation control (IL-1β only)
Simental-Mendía et al., 2018[28]	OA human cartilage explants treated with IL-1β	10	LP-PRP	Calcium gluconate	There were significantly higher chondrocytes in IL-1β/LP-PRP treatment than IL-1β control at 28 days
Durant et al., 2017[78]	Cell line of human chondrocytes treated with corticosteroids and local anesthetics	8	LR-PRP	ND	The addition of LR-PRP to corticosteroids and local anesthetics resulted in significantly improved viability and proliferation of chondrocytes relative to the agent alone
Jeyakumar et al., 2017[31]	Primary culture of human OA chondrocytes	6	LP-PRP	ND	Supplementation with 10% LP-PRP showed a similar proliferation rate to that of 10% fetal calf serum supplementation
Moussa et al., 2017[32]	Primary culture of human OA chondrocytes	12	LR-PRP	ND	Increased dose-dependent proliferation rate after supplementation with 5%, 10%, and 20% LR-PRP
Russo et al., 2016[79]	Primary culture of human OA chondrocytes treated with IL-1β	10	LR-PRP	Freeze/thaw cycles	Higher proliferation rate in chondrocytes cultured in the media containing LR-PRP compared to the cultures with hyaluronic acid alone
Yang et al., 2016[23]	Primary culture of rat chondrocytes treated with IL-1β	3	LR-PRP	$CaCl_2$	Supplementation with 10% LR-PRP resulted in significantly increased chondrocyte viability compared with the 25% LR-PRP at 24 and 48 h
Zhou et al., 2016[51]	Primary culture of rat chondrocytes	6	LP-PRP	ND	Chondrocytes co-cultured with platelets showed increased proliferation of chondrocytes via the ERK/CDK1/cyclin B1 signaling pathway induced by BMP7 production
Cavallo et al., 2014[60]	Primary culture of human chondrocytes	10	LR-PRP and LP-PRP	$CaCl_2$	Supplementation with 10% and 20% of LP-PRP induced greater cell proliferation than LR-PRP and PPP
Chen et al., 2014[33]	Primary culture of human OA chondrocytes treated with IL-1β and TNF-α	5	LR-PRP	Bovine thrombin	Chondrocytes triggered by IL-1β+TNF-α showed a reduced cell number. This was significantly restored by LR-PRP and LR-PRP+HA
Wu et al., 2011[34]	Human chondrocyte cell line (hPi) treated with IL-1β and TNF-α	ND	LP-PRP	Bovine thrombin	Treatment with IL-1β+TNF-α decreased chondrocyte proliferation but was strongly rescued by LP-PRP. This rescue was enhanced when combined with collagen
Akeda et al., 2006[30]	Culture of porcine chondrocytes in alginate beads	8	LP-PRP	Thrombin/ CaCl2	Supplementation with 10% LP-PRP significantly increased chondrocytes proliferation compared to FBS and PPP groups.
Choi, 1980[80]	Primary culture of rabbit chondrocytes	ND	LP-PRP	Freeze/ thaw cycles	The presence of LP-PRP increases cellular growth, represented by an increment in DNA concentration (150% over control)
In vitro studies					
Asjid et al., 2019[29]	Rat model of knee OA	16	LR-PRP	$CaCl_2$	A significantly higher number of normal chondrocytes after LR-PRP treatment
Mifune et al., 2013[27]	Injection of muscle-derived stem cells and PRP in knees of nude rats	36	LR-PRP	$CaCl_2$	The addition of LR-PRP promoted the proliferation of muscle-derived stem cells expressing BMP-4 and sFlt1 for chondral repair

PRP: platelet-rich plasma; LR: leukocyte-rich; LP: leukocyte-poor; OA: osteoarthritis; ND: no data.

Table 4. Studies reporting the effect of PRP on inflammation

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
In vitro studies					
Mariani et al., 2020[38]	Primary culture of OA human synovial fibroblasts	10	LR-PRP LP-PRP	$CaCl_2$	IL-1β and IL-8 gene expression were significantly enhanced by LR-PRP compared with LP-PRP. No difference among preparations was found in IL-6 and IL-10 gene expression
Rikkers et al., 2020[36]	Primary culture of human OA chondrocytes	5	LP-PRP	ND	LP-PRP was not able to inhibit TNF-α-induced inflammation. COX 2, prostaglandin E synthase, and IL-17 were significantly upregulated.
Carmona et al., 2016[24]	Culture of horse cartilage explants challenged with lipopolysaccharide (LPS)	6	LR-PRP and LP-PRP	Calcium gluconate	Expression of IL-1β was upregulated in an LP-PRP dose-dependent manner The activated LR-PRP (25 and 50%) and LP-PRP (25%) significantly decreased the expression of NF-κB
Assirelli et al., 2015[37]	Primary culture of human OA synoviocytes	7	LR-PRP and LP-PRP	$CaCl_2$	LR-PRP induced IL-1β and IL-8 gene expression. There is no difference between different PRP formulations (LR-PRP, LP-PRP, or PPP) in the expression of VEGF, IL-6, IL-10, and TNF-α
Osterman et al., 2015[41]	Co-culture of human OA cartilage and synovial membrane explants treated with IL-1β	9	LR-PRP and LP-PRP	ND	Both PRP preparations decreased IL-1β-induced VEGF gene expression in synovial explants and decreased IL-1β-induced nitric oxide production in cartilage and synovial explants
Ríos et al., 2015[44]	Culture of horse cartilage explants challenge with lipopolysaccharide (LPS)	6	LR-PRP and LP-PRP	Calcium gluconate	Treatment with LR-PRP and LP-PRP (50%) produces more TNF-α. PRP formulations, as well as LPS, increased IL-4 synthesis in cartilage. Only the LR-PRP (50%) notably increased the presence of IL-1ra
Ríos et al., 2015[42]	Culture of horse synovial membrane explants challenge with lipopolysaccharide (LPS)	6	LR-PRP and LP-PRP	Calcium gluconate	Both the LR-PRP and LP-PRP (25%) induced a smaller concentration of TNF-α. The LP-PRP increased anti-inflammatory IL-4, and LR-PRP produced higher levels of IL-1ra
Ríos et al., 2015[43]	Culture of horse synovial membrane explants	6	LR-PRP and LP-PRP	Calcium gluconate	The LR-PRP induced greater production of IL-1ra and IL-4. Both LR-PRP and LP-PRP at 50% induced greater liberation of TNF-α
Wang et al., 2015[35]	Primary culture of human OA chondrocytes and meniscocytes treated with FN-fragments	43	LP-PRP	Freeze-dried powder	The addition of LP-PRP to 30-kDa FN-f-stimulated chondrocytes and meniscocytes importantly decreased the release of IL-8 as well as IL-8 and IL-6 gene expression
Chen et al., 2014[33]	Primary culture of human OA chondrocytes treated with IL-1β and TNF-α	5	LR-PRP	Bovine thrombin	The gene expression of IL-1β and COX-2 is decreased by LR-PRP in chondrocytes treated with IL-1β + TNF-α; greater effect with LR-PRP+hyaluronic acid. LP-PRP significantly decreased gene expression of IL-1β, IL-1α, IL-6, IL-8, and IL-18; greater effect with LR-PRP+hyaluronic acid
Sundman et al., 2014[45]	Co-culture of human cartilage and synovial membrane explants	21	LP-PRP	$CaCl_2$/ thrombin	Treatment with LP-PRP or hyaluronic acid decreased the presence of TNF-α in culture media
van Buul et al., 2011[40]	Tridimensional culture of human chondrocytes in alginate beads treated with IL-1β	3	LR-PRP	$CaCl_2$	LR-PRP (10%) reduced PTGS2 gene expression and NF-κB activation induced by IL-1β. LR-PRP was not able to counteract the IL-1β-induced NO production

(Continues)

Table 4. Studies reporting the effect of PRP on inflammation *(Continued)*

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
Wu et al., 2011[34]	Stable human chondrocyte cell line (hPi) treated with IL-1β and TNF-α	ND	LP-PRP	Bovine thrombin	LP-PRP significantly decreases IL-1β+TNF-α-induced gene expression of IL-1β and COX-2 in the presence of matrix collagen (Type I+Type II)
Anitua et al., 2007[39]	Primary culture of human OA synoviocytes treated with IL-1β	10	LP-PRP	$CaCl_2$	LP-PRP did not modify the IL-1β-induced synthesis of VEGF by synovial fibroblasts. The increase was IL-1β-dependent
In vivo studies					
Bozynski et al., 2016[49]	Canine model of anterior cruciate ligament-induced OA	9	LP-PRP	$CaCl_2$/ thrombin	One LP-PRP application after the anterior cruciate ligament resection is sufficient to decrease the concentration of IL-8 monocyte chemoattractant protein-1 (MCP-1) and keratinocyte-derived chemoattractant (KC) over time (1-7 weeks)
Yin et al., 2016[47]	Synovial fluid from New Zealand rabbits with induced OA	50	LR-PRP and LP-PRP	ND	Higher concentration of IL-1β and PEG2 on the synovial fluid from rabbits treated with injections of LR-PRP against controls and rabbits treated with LP-PRP. LP-PRP can inhibit the activation of the NF-κB pathway *in vivo*
Yun et al., 2016[48]	Canine model of induced OA by cranial cruciate ligament transection	24	LR-PRP	ND	Treatment with injections of LR-PRP decreased the presence of IL-1β, TNF-α, COX-2, INF-γ, and iNOS positive cells. The greater effect is when LR-PRP is combined with stem cells
Liu et al., 2014[46]	Surgically created cartilage defect in adult rabbits	30	LP-PRP	$CaCl_2$	Treatment with LP-PRP significantly decreased the presence of IL-1β in synovial fluid against control and hyaluronic acid

PRP: platelet-rich plasma; LR: leukocyte-rich; LP: leukocyte-poor; OA: osteoarthritis; ND: no data.

better cartilage surface restoration, with the presence of proteoglycan and type II collagen, in a greater thickness of hyaline-like cartilage[27,51-53]. Nevertheless, others have observed no significant differences between LR-PRP and LP-PRP when assessing the degenerative process of tissues[53]. Furthermore, rabbit models of induced OA have also reported less severe cartilage damage with LR-PRP[25,47]; however, one of them concluded that LP-PRP demonstrated a less severe cartilage loss[47]. In studies where OA was chemically- or surgically-induced, the controls and the LR-PRP treated models did not show significant macroscopical differences from each other. The only models that showed improvement were the ones where the sample was treated with LP-PRP, revealing better cartilage structure and smoothness of the articular surface[27,47,51,54,55]. It is important to mention that the combination of any of the tested PRP formulations with MSC or hydrogel microspheres improved the effect of PRP in the cartilage quality, suggesting a preventive effect against OA progression[48,54,55]. On the other hand, no significant articular cartilage surface remodeling was found using LP-PRP in guinea pigs with early knee OA[56]. In canine models of surgically induced OA, LR-PRP showed improved Mankin and O'Driscoll scores with higher cellularity and tissue organization (Table 5)[48,57].

Modulation of ECM based on molecular analysis

In vitro studies

Data from different explant-based (cartilage and synovial membrane) models of OA suggest an overall anabolic and anti-inflammatory effect of both LR-PRP and LP-PRP[24,28,41,44,45,50,58]. PRP formulations were capable of reducing the gene expression of some proteinases (specifically, MMP-13, disintegrin, and metalloproteinase with thrombospondin motifs-4 [ADAMTS-4], and ADAMTS-5) and increased gene expression of ECM-related components (ACAN, Type II collagen, SOX9, and HAS-2), thus reversing the pro-inflammatory

Table 5. Studies reporting the effect of PRP on modulation of extracellular matrix based on histomorphologic analysis

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
In vitro studies					
Simental-Mendía et al., 2018[28]	OA human cartilage explants treated with IL-1β	10	LP-PRP	Calcium gluconate	Higher Type II collagen deposition and less Type I collagen deposition after IL-1β+LP-PRP treatments. Improved Mankin score and cartilage surface remodeling with IL-1β+LP-PRP treatments compared to controls
Carmona et al., 2016[24]	Culture of horse cartilage explants challenged with lipopolysaccharide LPS	6	LR-PRP and LP-PRP	Calcium gluconate	Cartilage explants treated with 25% LP-PRP and 50% LR-PRP had better necrosis scores and lower fibrillation/fissuring scores. 25% LP-PRP and LR-PRP had similar cluster formation, significantly lower cell loss, and better general histology. 25% LP-PRP presented the best therapeutic profile
In vitro studies					
Araya et al., 2020[53]	Rat model of induced knee OA	36	Pure PRP LP-PRP LR-PRP	Freeze/thaw cycles	Inflammatory scores were significantly lower in the pure-PRP group than those in the control group. The degenerative process was significantly recovered by pure-PRP
Lui et al., 2019[25]	Rabbit model of induced knee OA	ND	LR-PRP	ND	Higher type II collagen deposition after LR-PRP treatment in IL-1β-induced OA compared with IL-1β control. Reversed cartilage degeneration, a smoother cartilage surface, and better chondrocyte arrangement by LR-PRP
Chouhan et al., 2019[76]	Guinea pig model of weight-induced knee OA	36	LP-PRP	$CaCl_2$	Better articular cartilage scores (mild degenerative process) with multiple LP-PRP injections. Less synovial inflammation with single and multiple LP-PRP injections than a control group
Asjid et al., 2019[29]	Rat model of induced knee OA	16	LR-PRP	$CaCl_2$	Uncalcified cartilage thickness was significantly greater in the group treated with LR-PRP compared with no intervention control
Khatab et al., 2018[77]	Mice model of collagenase-induced OA	36	LR-PRP	$CaCl_2$	PRP injected knees had thinner synovial membrane and had less cartilage damage. The presence of inflammatory cells was negatively associated with synovial membrane thickness
Hermeto et al., 2016[54]	Rabbit model of induced OA treated with PRP and MSC	24	LP-PRP	Calcium gluconate	No significant differences in histological evaluations between one PRP application and untreated controls. Improved macroscopic and histological examinations revealed (tissue repair) in the PRP and MSC-treated group
Yin et al., 2016[47]	Synovial fluid from New Zealand rabbits with induced OA	50	LR-PRP and LP-PRP	ND	LP-PRP had a better gross morphological assessment score than the LR-PRP group. Marked reduction in the severity of cartilage loss with LR-PRP compared with that of the control. The cartilage height in samples from the LP-PRP group seemed to be higher than the control and LR-PRP groups
Yun et al., 2016[48] Kazemi and	Canine model of induced OA by cranial cruciate ligament transection	24	LR-PRP and LP-PRP	ND	Better Mankin score with LR-PRP, the effect was augmented with a combination of MSC. Cartilage thickness was higher than the control group. The more favorable effect on the articular surface was examined when LP-PRP was combined with MSC
Fakhrjou, 2015[57]	Canine model of acute articular cartilage injury of the knee treated with implantation of LR-PRP	18	LR-PRP	Calcium gluconate	Better histological score (O'Driscoll) between LR-PRP and control groups. Formation of better reparative tissue in the LR-PRP treated group. Higher cellularity and organization of repair tissue compared to the control group
Zhou et al., 2015[51]	Monosodium iodoacetate rodent model of OA	24	LP-PRP	ND	Joints transplanted with LP-PRP-treated chondrocytes exhibited smooth articular cartilage surfaces, increased expression of type II collagen, and the highest proteoglycan deposition

(Continues)

Table 5. Studies reporting the effect of PRP on modulation of extracellular matrix based on histomorphologic analysis *(Continued)*.

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
Almasry et al., 2014[52]	Rat model of surgically induced OA	45	LP-PRP	$CaCl_2$	Better histological score (OARSI) with LP-PRP than control specimens. Return of the regular histological features after LP-PRP injection in the synovial membrane
Chen et al., 2014[33]	Anterior cruciate ligament transection-induced OA in mice	5	LR-PRP	Bovine thrombin	Slight cartilage surface damage recovering in the LR-PRP group. The meniscus and cartilage surface structure was better recovered when combined with hyaluronic acid. Positive-stained regions of type II collagen similar to healthy cartilage were detected in PRP and PRP + hyaluronic acid groups

PRP: platelet-rich plasma; LR: leukocyte-rich; LP: leukocyte-poor; OA: osteoarthritis; ND: no data.

and ECM-degrading effect induced by different cytokines (IL-1β, TNF-α, and lipopolysaccharide). Other reports indicate that the action of IL-1β increases the gene expression of metalloproteinases (mainly MMP-1 and MPP-13) which are then downregulated by any of the PRP preparations no matter the model of study lymphocyte concentration or activation method[23,33,39,40,59]. In studies reporting the modulation of ADAMTS genes, both PRP preparations significantly decreased ADAMTS-4 when the model was challenged with LPS[24]. Similar behavior was observed when the model was treated with IL-1β, increasing the ADAMTS-4 gene expression, which was downregulated with LR-PRP and LP-PRP preparations. Furthermore, both PRP preparations were able to reduce the levels of ADAMTS-5 mRNA in animal- or human-derived cartilage samples[24,40,41,51].

On the other hand, an equine cartilage explant model challenged with IL-1β reported an increase in ADAMTS-4 gene expression in the presence of LR-PRP but not LP-PRP[58]. In the case of the natural inhibitors (tissue inhibitors of metalloproteinases [TIMPs]) of enzymes degrading ECM, LR-PRP preparations were shown to increase TIMP-1 gene expression in chondrocytes and synovial fibroblasts[19,23,38]; however, in cartilage and synovial explants, no significant modulation of gene expression was observed[28,41]. No relevant differences were found for other TIMPs (Table 6).

The addition of LR-PRP and LP-PRP shows a recovery of the expression of SOX9, COL II, and ACAN previously inhibited by IL-1β and TNF-α[23,33,34]. Notably, the combination of any PRP with hyaluronic acid or mesenchymal stem cells represents a synergistic effect in increasing gene expression of SOX9, Type II collagen, and ACAN[33]. The genes that code for the main components of the cartilage ECM, such as Type II collagen and ACAN, even the transcription factor SOX9, are generally downregulated by the effect of IL-1β and TNF-α. However, mRNA expression is partially recovered in the presence of either LR-PRP or LP-PRP in human chondrocytes or cartilage explants[28,34,36,40]. However, it has been reported that LP-PRP yielded a higher type II collagen and ACAN gene expression compared with LR-PRP primary cultures of human chondrocytes[19]. It is important to remark that the gene expression of ACAN increased when specimens were treated with any PRP preparation with no variation in the results between the activation method and origin of the samples[34,40,41,45,51]. Moreover, conflicting results were reported for type I collagen gene expression. While downregulation was observed in human cartilage explants and monolayer chondrocytesh LR-PRP and LP-PRP[24,31], cartilage and synovial co-culture model indicated overexpression of type I collagen with LR-PRP (Table 6)[45].

In vivo studies

Only one study reported gene expression analysis in an OA animal model (canine). LR-PRP increased gene expression of aggrecan and SOX9 compared to non-intervened controls (Table 6)[48].

Discussion

After reviewing the compiled information, we can certainly say that the PRP preparations activate a cascade of reactions that involves mediators of the inflammatory response, cell proliferation, anabolism, and catabolism. The preparation of LP-PRP is the one that shows a more generalized positive response. We were able to identify the

Table 6. Studies reporting the effect of PRP on modulation of extracellular matrix based on molecular analysis

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
In vitro studies					
Mariani et al., 2020[38]	Primary culture of OA human synovial fibroblasts	10	LR-PRP and LP-PRP	$CaCl_2$	Both preparations similarly induced MMP13, TIMP3, and TIMP4 mRNA expression. TIMP1 expression was significantly increased by LR-PRP
Rikkers et al., 2020[36]	Primary culture of human OA chondrocytes	5	LP-PRP	ND	Col II and ACAN were significantly downregulated in inflamed chondrocytes on the addition of LP-PRP
Simental-Mendía et al., 2018[28]	OA human cartilage explants treated with IL-1β	10	LP-PRP	Calcium gluconate	Treatment with LP-PRP decreased the expression of MMP13, ADAMTS5, and IL-1β; and increased expression of Col II, ACAN, and SOX9 after 28 days of culture
Yang et al., 2018[23]	Primary culture of rat chondrocytes treated with IL-1β	ND	LR-PRP and LP-PRP	Thrombin	Increased ACAN and Col II expression and decreased expression of MMP13 and ADMTS5 after treatment with PRP preparations
Jeyakumar et al., 2017[31]	Primary culture of human OA chondrocytes	6	LP-PRP	ND	Downregulation of Col I and MMP3 mRNA; upregulation of Col II and MMP13 mRNA (MMP13 downregulated under hypoxia, 1% O_2)
Moussa et al., 2017[32]	Primary culture of human OA chondrocytes	12	LR-PRP	ND	Dose-dependent (5%, 10%, and 20% of LR-PRP) downregulation of MMP3, MMP13, ADAMTS5, IL-6, and COX2 mRNA; dose-dependent (5%, 10%, and 20% of LR-PRP) upregulation of Col II, ACAN, and TGF-β
Carmona et al., 2016[24]	Culture of horse cartilage explants challenged with lipopolysaccharide	6	LR-PRP and LP-PRP	Calcium gluconate	Both PRP preparations significantly decreased LPS-induced NF-κB, MMP-13, ADAMTS-4, and Col I mRNA expression. Col II mRNA expression does not recover after PRP treatment. Both PRP increases COMP mRNA expression at 25% concentration Activated 25% of LR-PRP presented the best therapeutic effect
Russo et al., 2016[79]	Primary culture of human OA chondrocytes treated with IL-1β	10	LR-PRP	Freeze/thaw cycles	Increased GAG production above control but no different from hyaluronic acid treatment. Combination with hyaluronic acid significantly increased GAG production
Yang et al., 2016[23]	Primary culture of rat chondrocytes treated with IL-1β	3	LR-PRP	$CaCl_2$	Decreased IL-1β-induced MMP-1 and MMP-13 mRNA and protein expression and slightly increased mRNA and protein expression of MMP-3 and MMP-9. Increased mRNA and protein expression of SOX9, Col II, and TIMP-1 in IL-1β-treated chondrocytes

(Continues)

Table 6. Studies reporting the effect of PRP on modulation of extracellular matrix based on molecular analysis *(Continued)*

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
Assirelli et al., 2015[37]	Primary culture of human OA synoviocytes	7	LR-PRP and LP-PRP	$CaCl_2$	LR-PRP decreased TIMP-4 and HGF and significantly induced FGF-2 expression compared to LP-PRP and PPP. LR-PRP and LP-PRP downregulate MMP-13 expression. TIMP-1 and TIMP-3 expression were not significantly modified
Osterman et al., 2015[41]	Co-culture of human OA cartilage and synovial membrane explants treated with IL-1β	9	LR-PRP and LP-PRP	ND	Both treatments decreased IL-1β-induced ADAMTS-5 and TIMP-1 expression in cartilage and synovial and decreased VEGF expression in synovial. ACAN and Col I expression increases with both PRP treatments in IL-1β-challenged cartilage and synovial, respectively
Ríos et al., 2015[42]	Culture of horse synovial membrane explants challenged with lipopolysaccharide (LPS)	6	LR-PRP and LP-PRP	Calcium gluconate	Explants treated with 25% LR-PRP increased IL-1ra and decreased HA production. Explants treated with 50% LP-PRP increased IL-4 and HA production. The 25% and 50% LR-PRP and 50% LP-PRP presented the best anabolic and anti-inflammatory effects
Sakata et al., 2015[81]	Primary culture of cells isolated from human cartilage, synovial membrane, and anterior cruciate ligament	12	LR-PRP	Freeze/thaw cycles	Activated LP-PRP induces superficial zone protein (lubricin) production in the three types of culture. Ten times in synovial cells, 4-5 times in chondrocytes, and no significant changes in ligament-derived cells
Wang et al., 2015[35]	Primary culture of human OA chondrocytes and meniscocytes treated with FN-fragments	24	LP-PRP	Freeze-dried powder	LP-PRP treatment decreases the 30-kDa FN-fragments-induced expression of MMPs, including MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13
Zhou et al., 2015[51]	Primary culture of rat chondrocytes		LP-PRP	ND	LP-PRP treated chondrocytes had a higher Col II and ACAN mRNA expression and decreased MMP-13 and ADAMTS-5 mRNA levels. The catabolic and metabolic activity of chondrocytes is influenced by platelet-derived mediators TXA2, TGF-β, and ADP
Cavallo et al., 2014[19]	Primary culture of human chondrocytes		LR-PRP and LP-PRP	$CaCl_2$	Higher Col II and ACAN gene expression with LP-PRP and PPP than with LR-PRP treatment. VEGF and FGF-2 were highly expressed with LR-PRP. TGF-β and MMP-13 gene expression were similar in all PRP preparations. HA production and HAS-2, TIMP-1, and IL-10 gene expression were upregulated by LR-PRP. All PRP increased lubricin production
Chen et al., 2014[33]	Primary culture of human OA chondrocytes treated with IL-1β and TNF-α	5	LR-PRP	Bovine thrombin	LR-PRP recovers the expression of SOX9, Col II, and ACAN in IL-1β and TNF-α-treated chondrocytes. A higher effect when LR-PRP and hyaluronic acid are combined. The opposite phenomenon is shown with the expression of IL-1β, COX2, MMP-1, and MMP-3

(Continues)

Table 6. Studies reporting the effect of PRP on modulation of extracellular matrix based on molecular analysis *(Continued)*

Author, year	Model of study	Sample size, n	PRP used	Method of activation	Relevant outcomes
Sundman et al., 2014[45]	Co-culture of human cartilage and synovial membrane explants	21	LR-PRP	$CaCl_2$ / thrombin	LR-PRP increased ACAN and Col I gene expression against HA in cartilage. No differences in Col II and MMP-13 expression between groups. LR-PRP increased MMP-13 and HAS-2 gene expression against HA and control in synovial. No differences in TNF-α and MMP-1 expression between groups
Matuska et al., 2013[50]	Culture of bovine cartilage explants treated with IL-1α and TNF-α	4	LR-PRP	Lysis at 4°C	LR-PRP significantly decreases GAG and collagen release in explants treated with the combination of IL-1α and TNF-α
Kisiday et al., 2012[58]	Culture of equine cartilage explants treated with IL-1β	5	LR-PRP and LP-PRP	No activation	LP-PRP promoted the highest protein and proteoglycan synthesis Protein and proteoglycan synthesis is the same as any PRP in the presence of IL-1β. LR-PRP increased ADAMTS-4 expression with or without IL-1β, which did not occur with LP-PRP
van Buul et al., 201[40]	Tridimensional culture of human chondrocytes in alginate beads treated with IL-1β	3	LR-PRP	$CaCl_2$	LR-PRP and IL-1β did not influence the GAG content LR-PRP diminished IL-1β-induced inhibition of Col II and ACAN and reduced IL-1β-induced increase of ADAMTS-4 and PTGS2. LR-PRP did not modify ADAMTS-5 expression and IL-1β-induced MMP-13 expression
Woodell-May et al., 2011[59]	Primary culture of human chondrocytes treated with IL-1β and TNF-α	10	LR-PRP	Polyacrylamide beads	MMP-13 production stimulated in chondrocytes by IL-1β or TNF-α was reduced by LR-PRP
Wu et al., 2011[34]	Stable human chondrocyte cell line (hPi) treated with IL-1β and TNF-α	ND	LP-PRP	Bovine thrombin	The addition of LP-PRP recovered IL-1β and TNF-α-induced inhibition of SOX9, Col II, and ACAN gene expression and reduced the increase of IL-1β, COX-2, and MMP-2. Better results with the addition of a collagen matrix
Saito et al., 2009[55]	Tridimensional culture of rabbit chondrocytes in alginate beads	33	LR-PRP	Thrombin	The production of GAG and proteoglycan core protein expression increases with LR-PRP. Col II expression was not modified with LR-PRP
Anitua et al., 2007[39]	Primary culture of human synovial fibroblasts treated with IL-1β	10	LP-PRP	$CaCl_2$	The production of hyaluronic acid increases with LP-PRP but not with PPP. LP-PRP did not modify the rise in MMP-1, MMP-3, and VEGF
Akeda et al., 2006[30]	Primary culture of porcine chondrocytes	8	LP-PRP	Thrombin	LP-PRP increases proteoglycan and collagen synthesis when compared with platelet-poor plasma and control
In vivo studies Yun et al., 2016[48]	Canine model of induced OA by cranial cruciate ligament transection	24	LR-PRP	ND	Treatment with LR-PRP increases GAG, total collagen concentration, and ACAN and SOX9 mRNA expression concerning non-treated control. Combination with MSC increased the concentration and expression of these components

PRP: platelet-rich plasma; LR: leukocyte-rich; LP: leukocyte-poor; OA: osteoarthritis; ND: no data.

most commonly reported mechanisms in different models of study for knee OA, evaluating PRP formulations. Nevertheless, it is not entirely clear if there is a main pathway through which PRP exerts its therapeutic effect.

The great variety of methodologies used to form the PRP preparations and the different study models that have been used complicates reaching a consensus regarding the effect that each type of PRP can have and its implication in the progression of knee OA. It is worth mentioning that almost every PRP preparation reported by the revised articles describes a similar effect on the generated models for knee OA, which indicates that the activation method or the additional substances used with the PRP may have a secondary role.

Although still controversial, current evidence from clinical research indicates that LP-PRP formulations may represent a better therapeutic option for knee OA, considering the number of adverse reactions, improvement in clinical scores, and recommendations from different investigations[21,60-62]. The data found in basic science research suggests that both LR-PRP and LP-PRP promote a positive response in the treatment of knee OA. Likewise, pre-clinical evidence suggests that LP-PRP formulations have more advantages and a better therapeutic profile than LR-PRP.

Various systematic reviews and meta-analyses of clinical trials have reported a therapeutic effect of PRP that can last for several months, even up to a year[61,63]. This means that, even though the injected autologous concentrate remains only for a few days, the large number of active biomolecules that are released produce changes that result in a long-lasting therapeutic effect. Therefore, intra-articular injections of PRP might be considered as a disease-modifying effects therapy. Furthermore, a clinical superiority of PRP injections over other intra-articular therapies such as hyaluronic acid has been described[64,65]. Despite the above, the controversy regarding the use of PRP also lies in the results of some well-conducted controlled clinical trials. It was recently reported that PRP injections had no therapeutic effect over placebo injections[66]. However, the reported mean change in pain score in both groups at 12 months was greater than the clinically minimally important difference in knee OA (1.37)[67]. This could indicate that both interventions produced a positive therapeutic effect with no difference between thems. This information requires further analysis as it has previously been reported that placebo injections in knee OA produce a therapeutic effect[66,68,69]. Therefore, it would be important to consider this “placebo effect” when evaluating other injected therapies for the treatment of OA.

One of the main attributes that have been described for PRP therapy is its anti-inflammatory effect. Chronic inflammation is a characteristic that prevails in the microenvironment of a knee with OA. Therefore, it is beneficial that new treatments counteract or stop the degenerative effects caused by a persistent inflammatory process. It is thought that inflammation plays an important role in the development and progression of knee OA. The synovial membrane mainly contributes to the synthesis of pro-inflammatory cytokines such as IL-1β and TNF-α, which subsequently stimulate the production of enzymes that degrade the ECM of cartilage (MMPs and ADAMTSs)[70,71]. A characteristic in the progress and establishment of OA is the affection of cartilage homeostasis, which produces an imbalance between the formation and degradation of the ECM. PRP therapy has gained much attention due to reports indicating a plausible anti-inflammatory effect mainly attributed to the great production of growth factors blocking the effect of IL-1β and TNF-α, which leads to an anti-catabolic state. It has been described that the deleterious effect of IL-1β and TNF-α is through activation of different cascades such as the NF-κB signaling pathway, which then activates the expression of many catabolic genes in chondrocytes[40,72]. In part, the anti-inflammatory and hence, the anti-catabolic effect of PRP (especially LP-PRP formulations) might be a consequence of blocking the NF-κB translocation, avoiding the expression of catabolic genes.

Nonetheless, as OA progresses, so does the damage to the tissues involved in the joint, primarily the cartilage. In this regard, several investigations have attempted to evaluate, macroscopically and histomorphologically, the effect of PRP formulations. Reports have used different approximations to this end, from cartilage explants through several animal models of induced OA. The effects of PRP on cell proliferation and ECM formation could lead to restoring cartilage damage in the early stages of OA. Recent evidence has suggested that PRP therapy is clinically more effective in patients with mild or moderate knee OA[73,74]. It is very difficult for PRP to restore the damage generated in the cartilage or synovium in people with more severe OA. As reported in most animal models, PRP has a protective and cartilage formation effect against the pro-inflammatory stimulus, preventing articular cartilage from further degeneration. Analysis from human synovial fluid revealed that injections of LR-PRP did not induce significant changes in pro and anti-inflammatory cytokines; a deleterious effect was attributed to leukocytes[75].

Some limitations should be acknowledged in this review. The quality of all studies included could not be formally evaluated since *in vitro* studies presented a wide variety of methodological designs and parameters evaluated. The quality of the *in vivo* studies is questionable since the vast majority had a high risk of bias in at least one of the domains evaluated. In general, the evidence presented here can be considered to lack high quality, so the results must be viewed with caution. We tried to systematically collect and evaluate all the scientific information on this subject. Although some studies agreed to report the effects of PRP on a particular characteristic, the elements evaluated were different on many occasions, which made it difficult to reach a consensus. Further high-quality research on this topic is necessary.

We now know a little more about how PRP can act in a joint with OA. The need to use standardized PRP formulations is essential to be able to compare results and reach conclusions. *In vitro* studies provide us with information about molecular mechanisms. Studies in animal models indicate the effect these mechanisms can have, bearing in mind the extrapolation that all this may have on humans.

Although PRP therapy may be far from representing a cure for OA, it can represent an alternative to stop or slow the progression of the disease. Furthermore, if this is combined with changes in the lifestyle and diet of the patient, the chances of improvement in their quality of life would be markedly increased.

Conclusions

Based on the analyzed results, it is certain that the PRP preparations on any sample challenged with a pro-inflammatory stimulus reduced cell apoptosis and improved chondrocyte proliferation, leading to an improvement of the quality of cartilage restoration. On the ECM, the results showed that the PRP preparations had a contrary effect to the ones challenged with the pro-inflammatory cytokines (mainly IL-1β and TNF-α), which means that it reduces the expression of enzymes that degrade the cartilage ECM, including MMPs and ADAMTSs. Importantly, the expression of genes related to the formation of cartilage ECM is increased by the PRP preparations (Type II collagen and ACAN). The histology of the reviewed samples of all trials included was very heterogeneous, as the results varied from one study to another. However, most of the reviewed literature reported a better quality of cartilage when the model was treated with LP-PRP. It seems that LP-PRP is the one that presents the best therapeutic profile at the cellular and molecular level, which coincides with what is reported in clinical studies.

Every time, we better understand the mechanism of action of PRP. However, it still requires further study in each of the aspects involved in the pathogenesis of OA, in addition to a greater effort aimed at reducing the great variability in PRP formulations.

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Conflicts of interests

The authors state that they have no conflict of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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