CELLULAR THERAPY AND REGENERATIVE MEDICINE

Review

Platelet rich plasma for facial rejuvenation: an overview of systematic reviews

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Background - Platelet-rich plasma (PRP) as a non-surgical therapy for facial rejuvenation is increasingly adopted. This article aims to review the literature and critically appraise the available evidence regarding the efficacy and safety of PRP for facial rejuvenation.

Material and methods - An overview of systematic reviews (SRs) of PRP use for facial rejuvenation. The methodological quality of the SRs was assessed using the AMSTAR-2 checklist; quality of the evidence from the trials included in each SR was appraised following the GRADE approach.

Results - Thirteen SRs published between 2015 and 2023, reporting data from 114 overlapping reports, based on 28 individual primary studies (18 uncontrolled reports), were included in this umbrella review. Eight primary studies evaluated PRP in combination with other treatments (laser therapy, fat grafting, hyaluronic acid, basic fibroblast growth factor), and 20 PRP monotherapy. Most of the included primary studies were uncontrolled, and meta-analysis for outcomes related to facial rejuvenation was conducted in only 1 of the 13 SRs, showing that patients treated with PRP as an adjunct treatment have increased satisfaction over controls without PRP (mean difference, 0.63; 95% confidence intervals (CIs) 0.25/1; p=0-001; low certainty of evidence due to risk of bias (ROB) and inconsistency). No other quantitative data were available from the SRs, although 4 SRs concluded in a descriptive way reveal that PRP combined with laser therapy increased subject satisfaction and skin elasticity, and decreased the erythema index (very low certainty of evidence due to imprecision, unsystematic clinical observations, and ROB). The occurrence of adverse events was a predefined outcome in only 2 SRs (15%). Almost all the SRs demonstrated poor compliance with the AMSTAR 2 items, and the confidence in the results of SRs was graded as low or critically low in 12 of the 13 SRs.

Discussion - The available evidence is insufficient to suggest firm conclusions about the use of PRP, alone or in combination with other treatments, in promoting facial rejuvenation.

Keywords: *platelet-rich plasma, facial rejuvenation, umbrella review, systematic review, meta-analysis.*

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INTRODUCTION

A significant advance that has emerged in the last two decades in the field of transfusion medicine regards the development of blood components for non-transfusion use, in particular, platelet-rich plasma (PRP)-based technologies. Platelet-rich plasma (PRP) has been used in different non-transfusion indications due to its role in tissue regeneration and healing[1-5]. Besides platelets, PRP contains some inflammatory cells (i.e., monocytes and polymorphonuclear neutrophils) and large amounts of proteins, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF) and adhesion molecules (i.e., fibrin, fibronectin and vitronectin).

Such growth factors and cells have been shown to promote cell recruitment, proliferation and angiogenesis, which may be implicated in tissue regeneration and healing, and have been extensively studied in humans in a wide range of clinical situations in areas such as orthopedics, sport medicine and dentistry[6-10]. An area, which has received increasing attention in recent years, is that of PRP use in dermatology. Several trials and SRs evaluated the use of PRP for the treatment of alopecia, acne scars, chronic wounds and vitiligo[11-14]. Moreover, the use of PRP in cosmetics and skin care is receiving increasing attention.

PRP has been evaluated in the field of aesthetic dermatology, and several clinical studies and systematic reviews (SRs) on the use of PRP as non-invasive skin and facial rejuvenation method have been published in the last years[15-21]. However, their conclusions show the extensive heterogeneity among studies in terms of design, conduct, lack of standardization in outcome measures, and reporting. The current study is an overview of systematic reviews, also called umbrella review, review of (systematic) reviews, and "meta-review". Umbrella reviews provide an overview of multiple systematic reviews on a given research question, taking in consideration the SR as the object of the analysis rather than the primary study[22,23].

The current overview is aimed to reappraise the validity of the conclusions of the SRs and meta-analyses related to PRP use for non-surgical treatment of skin aging and facial rejuvenation. The decision to perform this overview is because PRP is increasingly adopted as non-surgical treatment of the signs of skin aging, and for this reason new data from recently published clinical trials, SRs and meta-analyses are available. Increasing the number of studies can improve precision of effect estimates, allowing additional comparisons or subgroup analyses to be performed. In this umbrella review, we have also applied new review methods such as the AMSTAR-2 tool, and a GRADE assessment, with the aim of enhancing the existing results in terms of the certainty of the review's findings[24,25].

MATERIALS AND METHODS

The protocol of this overview of reviews has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023486477. The results are reported according to the PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions[26].

Review question/objective

The aim of this umbrella review is to evaluate the efficacy and safety of PRP injection as facial rejuvenation treatment, either as monotherapy or in combination with other treatment modalities.

Inclusion and exclusion criteria

We considered for inclusion in this overview SRs that comprised randomized controlled trials (RCTs) and non-RCTs (i.e., prospective and retrospective comparative cohort studies, and non-comparative studies such as case-control studies and case-series) assessing the safety and efficacy of PRP for facial rejuvenation. Traditional reviews with no clear methodological approach were excluded from this umbrella review. SRs evaluating other use of PRP were excluded unless they also reported data on PRP use for facial rejuvenation that could be evaluated separately.

Intervention and outcomes

Treatment with PRP for facial rejuvenation, either as monotherapy or in combination was compared to any control. In all primary studies, PRP is used by injection; only one study evaluated topical PRP (with the addition of fractional laser technology). We included the following outcomes: patients, satisfaction scores, physician assessed outcomes, and adverse reactions.

Search strategy

The search was conducted from inception to November 2023 in the following databases: MEDLINE (through

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PubMed), medRxiv and bioRxiv, Embase, Epistemonikos, and Cochrane library. The searches were carried-out without languages restriction using Medical Subjects Heading: ("Platelet rich plasma/PRP") AND ("systematic review" OR "meta-analysis") AND ("treatment" OR "therapy") AND ("Facial rejuvenation" OR "Skin rejuvenation"). Furthermore, we checked the reference lists of the most relevant manuscripts (original studies and reviews) to identify potentially eligible studies not captured by the electronic literature search.

Study selection and data extraction

All titles were screened by two assessors (MC and IP). Eligibility assessment was based on the title or abstract and on the full text if required. Full texts of possibly eligible articles were obtained and assessed independently by two reviewers (MC and FM). Both reviewers compared the identified articles. The two assessors also independently extracted quantitative and qualitative data from each selected study, with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (IP). Findings are presented in tabular format with supporting text. Tabulation of results include: first author name and year of publication, clinical setting (e.g., outpatients and hospitalized patients, number of RCTs and non-RCTs included in the SR, intervention and control group, the outcomes assessed, and the main conclusion of the review as reported by authors.

Assessment of methodological quality and overlap in systematic reviews

We used the AMSTAR-2 critical appraisal checklist for SRs, a tool that evaluates both quantitative and qualitative reviews[24]. The tool is suitable for reviews including randomised and non-randomised studies. It includes 16 domains (7 considered critical) relating to the research question, review design, search strategy, study selection, data extraction, justification for excluded studies, description of included studies, risk of bias, sources of funding, meta-analysis, heterogeneity, publication bias, and conflicts of interest (see footnote of **Table II** for details of each question). Two review authors (MC, FM) independently assessed the quality of evidence in the included reviews and the methodological quality of the SRs. We resolved discrepancies through discussion or, if needed, through a third review author (IP). We did not exclude reviews based on AMSTAR 2 ratings, but considered the ratings in interpretation of our results. We rated overall confidence in the results of the review according to Shea *et al.*[24], as follows:

- high, no or one non-critical weakness;
- moderate, more than one non-critical weakness but no critical flaws;
- low, one critical flaw with or without non-critical weaknesses;
- critically low, more than one critical flaw with or without non-critical weaknesses.

Methods to describe and quantify the overlap in overviews of reviews have been described, and for the current overview, we have narratively discussed it and applied the corrected covered area (CCA) index, calculated as follows[27]: $CCA = k - r / r (c - r)$ where k is the number of reports in reviews (sum of ticked boxes), r is the number of rows (index publications), and c is the number of columns (SRs included). Criteria for interpreting the overlap index are: slight (0-5%), moderate (6-10%), high (11-15%) or very high (>15%) overlap. The CCA was calculated both across all reports included and for specific outcomes.

Summary of the evidence and appraisal of the quality of evidence

For the quantitative synthesis, we report the effect size [odds ratio (OR), risk ratio (RR), risk difference (RD), or standardized mean difference (SMD) with the 95% confidence intervals (CIs)] as reported in individual reviews, and their main conclusions.

The quality of evidence was appraised following the GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation)[25]. Whenever available, the grading of the quality of evidence reported in each SR was considered to define the quality of evidence. When the authors of the study did not report grading of evidence, the GRADE approach was applied based on the information available from the individual review. Studies can be downgraded for concerns over risk of bias, indirectness (applicability of the results to the question), inconsistency (heterogeneity between study results), imprecision (low number of studies and/or participants), and publication bias. The GRADE approach has four levels of certainty; very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the

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estimated effect), moderate (the true effect is probably close to the estimated effect), and high (the true effect is similar to the estimated effect).

RESULTS

The electronic and manual search retrieved 328 references The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is reported in **Figure 1**. At the first stage of screening titles and abstracts, 42 references were selected for eligibility, and the full text examined. After the full texts were examined with regards to inclusion and exclusion criteria, 29 records were excluded (traditional reviews, SRs on other clinical conditions, SRs on PRP for plastic surgery, SRs on facial fat grafting). Finally, 13 SRs were included in the umbrella review[28-40].

Description of the studies

The 13 SRs included 114 overlapping reports based on 28 individual primary studies. All the studies in the SRs included in this overview used autologous PRP, often in combination with fractional laser therapy or fat grafting; primary studies always report the type of preparation and where available the anticoagulant used for activation but the final number of platelets obtained is never reported. The primary studies included 8 RCTs (3 parallel groups, 5 split-face), 3 non-randomized split-face studies, 1 controlled cohort study, and 18 uncontrolled studies (case-report or case-series). Eight primary studies (5 RCTs, 1 cohort study, and 2 case reports) evaluated PRP in combination, and with other treatments (laser therapy, fat grafting, hyaluronic acid, basic fibroblast growth factor), while 20 (3 RCTs, 1 non-randomized split-face study, and 16 case report/series) PRP monotherapy. Therefore, 16/20 (80%) of the PRP monotherapy studies were uncontrolled, compared to 2/8 (25%) of the studies with PRP in combination. The main characteristics of the SRs included are summarized in **Table I**. Two SRs included only controlled or uncontrolled studies with PRP monotherapy[34,40], while the remaining SRs included both studies with PRP monotherapy or in combination with other treatment. All primary studies reported PRP used by injection and only one study evaluated topical PRP (with the addition of fractional laser technology).

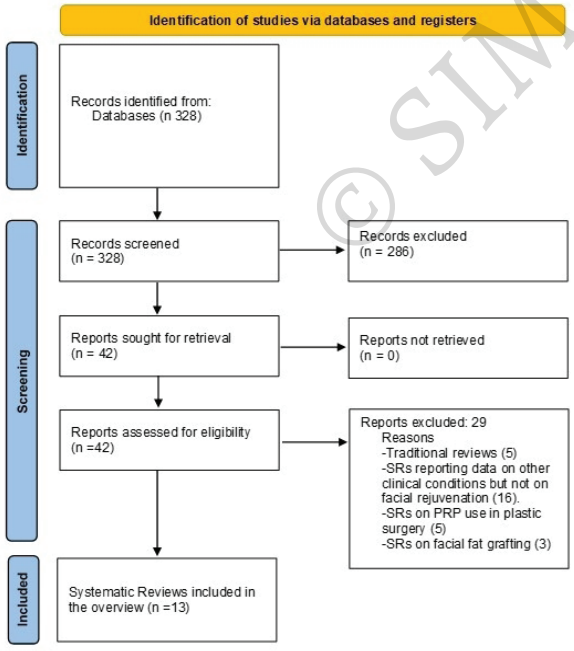

Figure 1 - PRISMA Flow chart of study selection process
PRP: platelet-rich plasma; SR: systematic review.

Methodological quality of SRs (Table II)

Of the included SRs, one had only two methodological requirements partially met[38], 5 had several methodological requirements partly met[31,33,35,37,40], and 7 had several requirements unmet/partially met[28-30,32,34,36,39]. All the reviews did not report details of the funding source that had supported the work, and did not assess publication of bias. Only 2 SRs reported a list of excluded studies and reasons for exclusion[37,38]; meta-analysis was performed with appropriate statistical methods in 2 SRs[33,38], but only one did it for outcomes related to facial rejuvenation[38]. Other commonly unmet or partially met requirements included evaluation of ROB and heterogeneity assessment. Overall, almost all of the included SRs demonstrated poor compliance with the AMSTAR 2 items; as a consequence, confidence in the results was graded as low in 6 SRs[31-33,35,37,40], critically-low in 6[28-30,34,36,39], and moderate in one[38].

Concerning the overlap across all reports included in the overview, the CCA index shows a very high rate of overlapping across the SRs.

Summary of the effect of PRP on the main outcomes

The most commonly reported outcomes were patient's satisfaction and clinical assessment by dermatologists. Various clinical evaluator tools (e.g., Skin Homogeneity and Texture Scale; Wrinkle Severity Rating Scale, Global

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Table I - *Main characteristics of SRs included in the overview update*

First author, year [ref]	Clinical setting	Studies included in quantitative analysis for facial rejuvenation			Interventions		Main outcomes	Main results as reported in the SR
		Overall (patients)	RCT	Other	Experimental	Control		
Leo, 2015 [28]	PRP in various dermatologic indications including hair restoration, scar revision, striae distensae, skin rejuvenation and dermal augmentation	4 (75)	2 (1 split face)	2 case series	PRP (1-3 injections); PRP plus Fractional Laser therapy (3 topical applications)	Saline; platelet poor plasma; Fractional laser therapy only	Patient's satisfaction, clinical assessment by dermatologists	Future studies should utilize control treatments, preferably split-side treatments, so that the efficacy of PRP treatments can be better defined
Lynch, 2015 [29]	PRP for a range of dermatological indications including wound healing, fat grafting, alopecia, scar revision, striae distensae e and dermal volume augmentation	2 (45)ve	1	1 case serie	PRP (3 injections); PRP plus Fractional Laser therapy (3 topical applications)	Fractional laser therapy only	Patient's satisfaction, clinical assessment by dermatologists	Current evidence is not sufficiently robust to recommend routine use of PRP for any dermatologic indication Further study may be justified in the context of well-designed trials
Sclafani, 2015 [30]	PRP in facial rejuvenation and wound healing	7 (197)	3 (2 split face)	3 case series, 1 cohort study (retrospective)	PRP (1- 3 injections); PRP plus Fractional Laser therapy (3 topical applications); PRP plus carbon dioxide laser	Fractional laser therapy only; saline	Patient's satisfaction, clinical assessment by dermatologists	PRP represent an as-of-yet untapped adjunct in facial rejuvenation, but the level of evidence from the available published data is low
Frautschi, 2017 [31]	PRP for esthaetic aesthetic surgery (aging skin, scalp alopecia, lipofilling, fractional laser and facial surgery)	5 (147)	1	3 case series, 1 cohort study	PRP (1- 3 injections); PRP plus Fractional Laser therapy (3 topical applications); PRP + fat grafting; PRP + MACS-lift-fat grafting (1 injection)	Fractional laser therapy only; fat grafting only; MACS-lift-fat grafting only	Patient's satisfaction, clinical assessment by dermatologists	The evidence for PRP clinical effectiveness in aesthetic practice remains largely speculative
Lei, 2019 [32]	PRP in animal models, and for facial rejuvenation, and alopecia	8 (282)	2	5 case series, 1 cohort study	PRP (1- 3 injections); PRP plus Fractional Laser therapy (3 topical applications); PRP + Fat grafting; PRP + MACS-lift-fat grafting (1 injection); PRP plus HA	Fractional laser therapy only; Fat grafting only; MACS-lift-fat grafting only	Patient's satisfaction, clinical assessment by dermatologists	PRP may play a role in promoting tissue regeneration, oxidative stress and revascularization, which form the theoretical basis for the use of PRP in the clinical treatment of facial rejuvenation
Gupta, 2019 [33]	PRP in various dermatologic indications including hair restoration, scar revision, aging skin	9 (168)	2 (1 split face)	6 case series, 1 cohort study	PRP (1- 6 injections); PRP plus Fractional Laser therapy (3 topical applications)	Saline; growth factors; Fractional laser therapy only	Patient's satisfaction, clinical assessment by dermatologists	Only upon completion of well-designed clinical trials can standardized protocols for PRP to treat dermatologic conditions be defined
Kaushik, 2019 [34]	PRP in various dermatologic indications including androgenetic alopecia and facial/ skin rejuvenation	4 (50)	1 (split face)	3 case series	PRP (1-3 injections)	Saline	Patient's satisfaction, clinical assessment by dermatologist	PRP is a potentially interesting modality in facial rejuvenation, but further well-designed evidence is needed before it can be considered an established therapy in this setting

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Table I - *Main characteristics of SRs included in the overview update (continues from previous page)*

First author, year [ref]	Clinical setting	Studies included in quantitative analysis for facial rejuvenation			Interventions		Main outcomes	Main results as reported in the SR
		Overall (patients)	RCT	Other	Experimental	Control		
Maisel-Campbell, 2020[35]	PRP for treatment of the visible signs of skin aging	18 (374)	7 (5 split face)	10 case series, 1 cohort study	PRP (1- 3 injections), PRP plus Fractional Laser therapy (3 topical applications); PRP + Fat grafting; PRP + MACS-lift-fat grafting (1 injection); PRP plus carbon dioxide laser	Saline; platelet poor plasma; growth factors; Fractional Laser therapy only; fat grafting only; MACS-lift-fat grafting only	Patient's satisfaction, clinical assessment by dermatologist, adverse events	PRP injections are safe and may be modestly beneficial for aging skin
Nanda, 2021[36]	PRP for skin rejuvenation and acne scars.	7 (574)	4 (2 split face)	2 case series, 1 cohort study	PRP (1-3 injections), PRP plus Fractional Laser therapy (3 topical applications); PRP + Fat grafting; PRP + MACS-lift-fat grafting (1 injection)	Saline; platelet poor plasma; Fractional Laser therapy only; fat grafting only; MACS-lift-fat grafting only	Patient's satisfaction, clinical assessment by dermatologist, adverse effects	Further well-designed trials are required
Xiao, 2021[37]	PRP for facial rejuvenation	13 (376)	4 (2 split face)	8 case series , 1 cohort study	PRP (1-3 injections); PRP plus Fractional Laser therapy (3 topical applications); PRP + Fat grafting; PRP + MACS-lift-fat grafting (1 injection); PRP + HA	Saline; platelet poor plasma; Fractional Laser therapy only; fat grafting only; MACS-lift-fat grafting only	Patient's satisfaction, clinical assessment by dermatologist	There is very limited clinical evidence to establish the effectiveness of PRP in facial rejuvenation
Evans, 2021[38]	PRP for facial rejuvenation	14 (365)	4 (2 split face)	10 case series	PRP (1-6 injections); PRP plus Fractional Laser therapy (3 topical applications); PRP + HA	Saline; platelet poor plasma; Topical TCA + LA; growth factors; Fractional Laser therapy only	Patient's satisfaction, clinical assessment by dermatologist, adverse effects	Meta-analysis of 3 RCTs shows increased satisfaction of PRP treated pts. over controls of saline, platelet-poor plasma, mesotherapy, and as an adjunct to laser therapy Further studies are required to address limitations of the current literature
Buzalaf, 2022[39]	PRP for facial rejuvenation	17 (443)	4 (3 split face)	13 case series	PRP (1-6 injections), PRP plus CO2 laser, PRP + HA	Saline; platelet poor plasma; growth factors; plasma gel	Patient's satisfaction, clinical assessment by dermatologist	The quality of the available evidence is low, and further studies are needed
Gentile, 2023[40]	PRP for facial rejuvenation	8 (125)	3 (3 split face)	5 case series	PRP (1-6 injections)	Saline; platelet poor plasma; growth factors;	Patient's satisfaction, clinical assessment by dermatologist, Adverse effects	Further well-designed studies are needed to confirm the efficacy of PRP for facial rejuvenation and to define standard protocols

HA: hyaluronic acid; LA: lactic acid; MACS: Minimal Access Cranial Suspension; PRP: platelet rich plasma; RCT: randomized controlled trial; TCA: trichloroacetic acid.

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Table II - *Assessment of methodological quality with AMSTAR 2 tool for each comparison of the efficacy and safety outcomes*

Author, year [reference]	AMSTAR-2 DOMAIN																Overall confidence in the results*
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Leo, 2015[28]																	Critically low
Lynch, 2015[29]																	Critically low
Sclafani, 2015[30]																	Critically low
Frautschi, 2017[31]																	Low
Lei, 2019[32]																	Low
Gupta, 2019[33]																	Low
Kaushik, 2019[34]																	Critically low
Maisel-Campbell, 2020[35]																	Low
Nanda, 2021[36]																	Critically low
Xiao, 2021[37]																	Low
Evans, 2021[38]																	High
Buzalaf, 2022[39]																	Critically low
Gentile, 2023[40]																	Low

Methodological requirement met	Methodological requirement partly met, or not specified	Methodological requirement unmet

Amstar-2 domains. Although AMSTAR 2 consists of 16 items, critical domains include items 2, 4, 7, 9, 11, 13, and 15

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

*We rated overall confidence in the results of the review according to Shea *et al.*[24], as follows:
- high, no or one non-critical weakness;
- moderate, more than one non-critical weakness but no critical flaws. Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence;
- low, one critical flaw with or without non-critical weaknesses;
- critically low, more than one critical flaw with or without non-critical weaknesses.

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Aesthetic Improvement Scale), collagen mean optical density, and skin measures of homogeneity were also reported. Due to the fact that most of the included primary studies were uncontrolled, meta-analysis (the quantitative synthesis) for outcome related to facial rejuvenation was conducted in only 1 of the 13 SRs, and relates to patient satisfaction score following treatment with PRP as an adjunct treatment over controls (including saline, mesotherapy, platelet-poor plasma and laser alone) from 3 RCTs (Mean Difference, 0.63; 95% CIs,

0.25/1; p=0-001; low certainty of evidence due to ROB and inconsistency)[38]. No other quantitative synthesis is available from the SRs, although 4 of the SRs concluded in a descriptive way that PRP combined with laser therapy increased subject satisfaction and skin elasticity, and decreased the erythema index[29-31,36].

The occurrence of adverse events was reported in detail in only 2 of the 13 SRs (15%)[35,38]. Five SRs did not mention the occurrence of adverse events at all[28,30-33], while other 4 SRs reported only general statements on PRP safety[29,34,37,39]. Two SRs stated that PRP is safe, the most commonly reported side effects being pain at the injection site, erythema, and edema[36,40]. The SR by Maisel-Campell *et al.*[35] reported only mild and transient adverse events with PRP monotherapy in 320 subjects from 16 studies; there were no reports of infection, scarring or post-inflammatory hyperpigmentation, while transient post-injection pain or burning was observed in approximately two-thirds of subjects, lasting minutes to an hour. Erythema resolving within days was also commonly reported, while edema and tenderness lasting less than 1 week were less commonly reported. No serious adverse events were reported. Likewise, the SR by Evans *et al.* shows that PRP injections provide a minimal risk to the patient, without risk of infection, allergy, or post-inflammatory hyperpigmentation[38]. Mild side effects attributable to any dermal injection are to be expected, and include erythema, pain, a burning sensation, ecchymosis, swelling, a feeling of pressure, and tenderness. The addition of calcium chloride without use of topical anesthetics may produce significant pain, but is preventable with the addition of topical anesthetic to PRP[38].

The results of the analyses for the main outcomes and the GRADE assessment are summarized in **Table III**.

DISCUSSION

Overviews of reviews (umbrella reviews) assemble several SRs on the same condition and permit to consider for inclusion the highest level of evidence available, such as SRs and meta-analyses[22,23,41]. Indeed, in this umbrella review we have reappraised the results of 13 SRs, published between 2015 and 2023, on the clinical use of PRP, as monotherapy or in combination with other treatments, as a non-surgical therapy for facial rejuvenation. The SRs included in this overview present data from 114 overlapping reports, based on 28 individual primary studies, mostly non randomized. The studies evaluated more commonly PRP monotherapy, but also PRP in combination with other treatments (laser therapy, fat grafting, hyaluronic acid, basic fibroblast growth factor). Since most of the studies (71%) included in the SRs were uncontrolled, on average the certainty of evidence from primary studies with GRADE assessment ranged from very-low to low, and this represents the main limit of the analysis, both in the SRs evaluated and in the current overview. The quality of the evidence for the outcomes analysed in primary studies was downgraded due to risk of bias, imprecision, unsystematic clinical observations, inconsistency between studies, and imprecision[25].

Further limits of the overview are related to the high rate of overlap of primary studies, as indicated by the CCA index (22%). Overlap in overviews of reviews comes from the use of multiple identical primary studies in similar reviews, usually when the reviews are updated frequently, as the authors will often add new studies in addition to the original studies, or with reviews that cover similar topics but may have a different focus[42].

Beside the limits of primary studies, we have also to consider the confidence we can have on the results of the SRs included in the umbrella reviews basing on the AMSTAR-2 evaluation[24]. The majority of evaluated SRs had many critical requirement (for example absence of a registered protocol, ROB, publication bias and heterogeneity assessment) unmet or only partially met, and meta-analysis was performed with appropriate statistical methods only in one SR. For these reasons, 12 of the 13 SRs were graded critically low or at best low for the methodological quality.

The quantitative synthesis for outcomes related to facial rejuvenation was conducted in only one SR and involved "patient satisfaction score" following treatment with PRP as an adjunct treatment over controls not receiving PRP[38]. Data from 3 RCTs in this SR show a significant increase in patients' satisfaction in PRP recipients compared to control, but the quality of the evidence was rated as low due to ROB and inconsistency. Patient satisfaction is an important and necessary consideration for cosmetic treatments, such as facial rejuvenation. However, this outcome as well as

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Table III - *Main conclusions of SRs with PRP for facial rejuvenation*

Review, year[ref]	Main outcome/s	Meta-analysis results	GRADE assessment of primary studies: certainty of evidence (reason/s for downgrading)	Comment
Leo, 2015[28]	Effect of PRP on wrinkles; augmentation in dermal collagen in pts receiving PRP in conjuction with laser therapy	Quantitative synthesis not feasible	Very low (imprecision, unsystematic clinical observations, ROB)	No firm conclusions can be drawn
Lynch, 2015[29]	Patient satisfaction and blind assessment of dermatologist	Quantitative synthesis not feasible	Very-low (serious imprecision, ROB)	PRP combined with fractional laser increased subject satisfaction and skin elasticity and decreased the erythema index
Sclafani, 2015[30]	Patients satisfaction, assessment of dermatologist	Quantitative synthesis for facial rejuvenation not feasible	Very-low (serious imprecision, ROB)	PRP combined with fractional laser increased subject satisfaction and skin elasticity and decreased the erythema index
Frautschi, 2017[31]	Patients satisfaction, assessment of dermatologists	Quantitative synthesis for facial rejuvenation not feasible	Very-low (serious imprecision, ROB)	PRP combined with fractional laser increased subject satisfaction and skin elasticity and decreased the erythema index
Lei, 2019[32]	Patient's satisfaction, clinic assessment by dermatologists	Quantitative synthesis for facial rejuvenation not feasible	Very low (imprecision, unsystematic clinical observations, ROB)	The available evidence about PRP in promoting facial rejuvenation is inadequate
Gupta, 2019[33]	Patient's satisfaction, clinic assessment by dermatologists,	Quantitative synthesis for facial rejuvenation not yet feasible	Very low (imprecision, unsystematic clinical observations, ROB)	Inconsistent outcomes
Kaushik, 2019[34]	Patient's satisfaction, clinic assessment by dermatologists	Quantitative synthesis for facial rejuvenation not yet feasible	Very low (imprecision, unsystematic clinical observations, ROB)	No firm conclusions can be drawn
MaiselCampbell, 2020[35]	Patient's satisfaction, clinic assessment by dermatologists, Adverse events	Quantitative synthesis for facial rejuvenation not feasible	Very low (imprecision, unsystematic clinical observations, ROB)	PRP injections are safe and may be modestly beneficial for aging skin
Nanda, 2021[36]	Patient's satisfaction, clinic assessment by dermatologists	Quantitative synthesis not available	Very low (imprecision, unsystematic clinical observations, ROB)	PRP combined with fractional laser increased subject satisfaction and skin elasticity and decreased the erythema index
Xiao, 2021[37]	Patient's satisfaction, clinic assessment by dermatologists	Quantitative synthesis not available	Very low (imprecision, unsystematic clinical observations, ROB)	No firm conclusions can be drawn
Evans, 2021[38]	Patient's satisfaction, clinic assessment by dermatologists; adverse events	Mean Difference in pts. satisfaction score: 0.63 (from 0.25 to 1; p=0-001)	Low (ROB, inconsistency due to heterogeneity)	PRP produces increased pts. satisfaction scores over controls. Mild side effects related to PRP injections are to be expected
Buzalaf, 2022[39]	Patient's satisfaction, clinic assessment by dermatologists.	Quantitative synthesis not available	Very low (imprecision, unsystematic clinical observations, ROB)	No firm conclusions can be drawn
Gentile, 2023[40]	Patient's satisfaction, clinic assessment by dermatologists, Adverse events	The principal summary measures were reported as p-value, percentage and ratio	Very low (imprecision, unsystematic clinical observations, ROB	No firm conclusions can be drawn

PRP: platelet-rich plasma; ROB: risk of bias.

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other subjective outcomes (e.g., clinicians satisfaction scores) in the absence of a control group or blindness in RCTs, are susceptible to bias, particularly performance and detection biases.

Due to the fact that most of the included primary studies were uncontrolled, no other quantitative synthesis is available from the SRs, although 4 of the SRs concluded in a descriptive way that PRP combined with laser therapy increased subject satisfaction and skin elasticity, and decreased the erythema index (very-low certainty of evidence due to imprecision, unsystematic clinical observations, and ROB).

The large majority of the SRs did not mention the occurrence of adverse events at all, or reported only general statements on PRP safety. Only 2 SRs included the occurrence of adverse events among the predefined outcomes. Only mild and transient adverse events with PRP injection were reported.

Another important limit for interpreting PRP research, in this field as well as for other clinical conditions, is lack of standardization of PRP preparation protocols, administration schedules, and follow-up duration. There was a large variability in the number of PRP administration (from 1 to 6); moreover, PRP was applied as a topical administration in one study and as an injection in all other primary studies.

In conclusion, this overview of reviews summarizes the existing evidence about the efficacy and safety of PRP, either alone or in combination with other treatment modalities, for facial rejuvenation. The results suggest very limited clinical evidence of PRP in this setting, mostly for uncontrolled studies. Further well-designed randomized controlled trials need to be performed to evaluate the efficacy of PRP in facial rejuvenation, ideally with a blind design in order to prevent the risk of bias related to subjective outcomes in open-label trials.

AUTHORS' CONTRIBUTIONS

Conceptualization: MC. Methodology: MC. Data extraction: FM, IP, MC. Writing-preparation original draft: MC. Writing-review and editing: FM, IP, SP, VDA. All Authors have read and agreed to the published version of the manuscript.

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