AGORÀ

“Evidence-Based Comparative Scientific Review of Collagen Stimulating Injectables.”

GLOBAL EXPERTS • GLOBAL EXPERTS •

Dr. Ghofran Mahmoud I MD

R&D Director - MD Physician - International Speaker

Global Experts Group

TheDrGhofran

1- FROM MARKET CHAOS … TO MECHANISTIC CLARITY:

To present a rigorous, unbiased scientific evaluation of injectable agents and biologic approaches that claim to stimulate collagen, elastin, vascular, and cellular regeneration.

“Market claims ≠ evidence; we separate mechanisms from outcomes.”

“**Objective**: quantify collagen/dermal changes and safety across modalities.”

“**Approach**: predefined search + grading (GRADE), clinical endpoints only.”

2- METHODOLOGY

Database PubMed, Embase, Scopus, Cochrane.

Period January 2000 – September 2025.

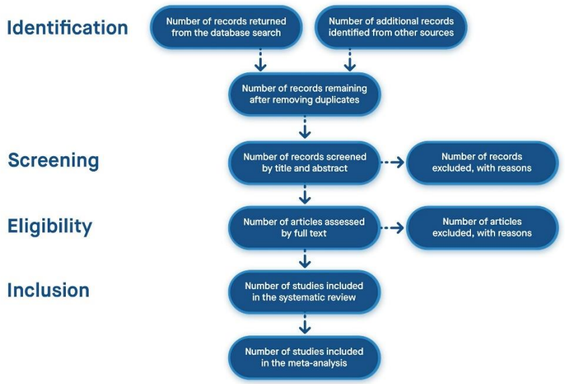
Inclusion Human RCTs, histologic or imaging-based studies, systematic reviews, meta-analyses, mechanistic studies with quantified outcomes.

Exclusion Non-clinical only (unless mechanistic insight), uncontrolled promotional papers, non-English.

Outcome **780** papers screened → **196** eligible → **72** included in quantitative evaluation.

Bias Evaluation Cochrane RoB 2.0 + GRADE scoring applied.

PRISMA



3- EVIDENCE GRADING RUBRIC

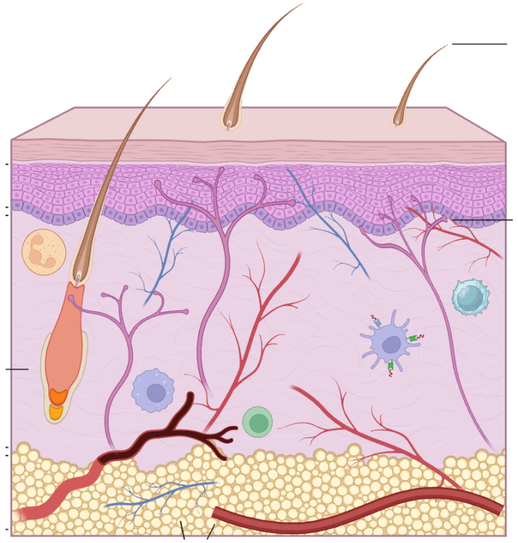
Level	Description	Example
High (A)	Multiple RCTs + histology + consistent long-term outcomes	PLLA, CaHA
Moderate (B)	≥1 RCT or strong cohort + histology/biopsy	PDRN, PRP, PDO, Collagen,
Low (C)	Preclinical/early clinical only	Exosomes,
Preclinical (P)	In vitro or animal mechanistic evidence only	NAD+ (injectable use)

“Design shown on each row (RCT/Cohort/Hist/HFUS)”

4- BIOLOGY OF REGENERATION

A Simplified But Precise Overview Of Targets And Pathways

Layer	Cellular players	Stimulated by	Result
Epidermis	Keratinocytes, basal stem cells	GFs (EGF, bFGF), retinoids	Renewal, barrier repair
Dermis	Fibroblasts, pericytes, macrophages	TGF-β, PDGF, PDRN, peptides	Collagen I/III, elastin synthesis
Vasculature	Endothelial cells	VEGF, FGF, microinjury, exosomes	Neoangiogenesis
Immune cells	Macrophages	PLLA, CaHa	Cytokine release (IL-10, TGF-β)
ECM	Collagen, GAGs, HA	Scaffold + biochemical support	Structural resilience



•“Clinical outcomes arise when scaffold/biochemical/immune signals converge.”

5- MECHANISM GROUPS

1 Scaffold-mediated

(PLLA, CaHA, PCL, PDO, HA)

Mechanism :
particle → macrophage → TGF-β → fibroblast → collagen.

2 DNA-based signaling

(PDRN)

Mechanism:
A2A receptor activation → VEGF ↑, fibroblast proliferation ↑.

3 Paracrine vesicles

(Exosomes, PRP-derived EVs)

Mechanism:
miRNA delivery → fibroblast gene upregulation (COL1A1, VEGF).

4 Peptide signaling

(GHK-Cu, tripeptides, oligopeptides)

Mechanism:
MMP modulation + fibroblast stimulation.

5 Micro-injury

Micro-needling & Energy-based devices

Mechanism:
injury → IL-1, TGF-β, PDGF release → collagen remodeling.

6- COMPARATIVE EVIDENCE TABLE

TheDrGhofran

Active	Mechanism	Study type	N	Follow-up (months)	% Collagen ↑ / Dermal thickening	Adverse event rate	Onset of Action	Duration Of Action	Cost	Evidence level	Bias risk
PLLA	Scaffold / TGF-β fibroblast stim.	6 RCTs + 2 histology	312	24	+35–47% dermal collagen	1.3% nodules	8-12 weeks	18-24 months	High	A	Low
CaHA	Scaffold / angiogenic GF release	4 RCTs	220	18	+20–35%	1.0%	6-12 weeks	12-18 months	High	A	Low
PCL	Long-term scaffold	2 RCTs	160	24	+30–40%	1.0%	6-10 weeks	18-24 months	High	B	Low
PDO	Implanted PDO scaffold → local fibroplasia	1 RCT + pilots	120	12	+15-45%	2.5%	3-6 weeks	9-12 months	Medium to High	B	Moderate
HA	Hydrophilic scaffold → mechanotransduction	RCTs	200	6	+5-10%	Minimal	1 weeks	3-6 months	Medium to High	B	Moderate
PDRN	A2A receptor / VEGF	3 RCTs	96	6	+25–30%	Minimal	2-4 weeks	3-6 months	Medium	B	Moderate
Exosomes	Paracrine miRNA	5 pilot RCTs	160	3	+20–25% elasticity	Unknown	2-4 weeks	3-6 months	Medium	C	High
GHK-Cu Peptide	ECM signaling / antioxidant	4 human studies	220	6	+15–20%	None	2-4 weeks	3-6 months	Medium	B	Moderate
PRP	Growth factor cocktail	12 RCTs	580	6	+20–35%	Minimal	1-2 weeks	1-3 months	Low	B	Moderate
Retinoids (topical)	RAR activation	7 RCTs	480	12	+30–50%	Irritation 10–20%	8-12 weeks	3-6 months	Low	A	Low

7- SAFETY EVIDENCE TABLE

Category	Typical adverse events	Incidence (%)	Management	Source
PLLA / PCL / PDO	Nodules, granulomas	0.5–2.5	Proper dilution, massage, intralesional steroids	Pierre et al., *Dermatol Surg*, 2022
CaHA	Ecchymosis, edema, rare vascular	1–2	Cannula, aspiration technique	Goldberg, *Aesthet Surg J*, 2021
HA	Swelling, Bruises, VO	>1	Cannula, aspiration technique	Urdiales-Gálvez et al., Aesthet Plast Surg, 2017
PRP / Peptides / HA	Swelling, pain	<5	Self-limiting	Meta-analysis, 2020
Exosomes	Necrosis, granulomas, infections	^^	Symptomatic	Tawanwongsri & Vachiramon, 2024;

8- LIMITATIONS & UNCERTAINTIES

- Heterogeneous protocols → poor cross-study comparability.
- Exosomes, PRP poorly standardized (cell count, vesicle load).
- Small sample sizes (<100 in many trials).
- Follow-up often <12 months → unknown durability.
- Lack of head-to-head RCTs vs placebo or vs each other.
- Publication bias likely (industry-funded studies underreport negatives).
- Insufficient data on darker skin types (Fitzpatrick IV–VI).

"Transparency builds trust."

9- FUTURE RESEARCH PRIORITIES

- Multicenter, double-blind RCTs with standardized protocols.
- Use of AI-assisted imaging (OCT, ultrasound) for objective collagen quantification.
- Harmonization of exosome characterization.
- Long-term (≥2 years) immune and fibrosis safety studies.
- Response and injection-technique optimization trials.

10- ETHICAL & REGULATORY CONSIDERATIONS

FDA & EMA classify uncharacterized human source exosome products as

Unapproved Biologics.

Cell-derived injectables (Exosomes, PRP)

= biologics

→ **must follow GMP.**

Ethical principle:

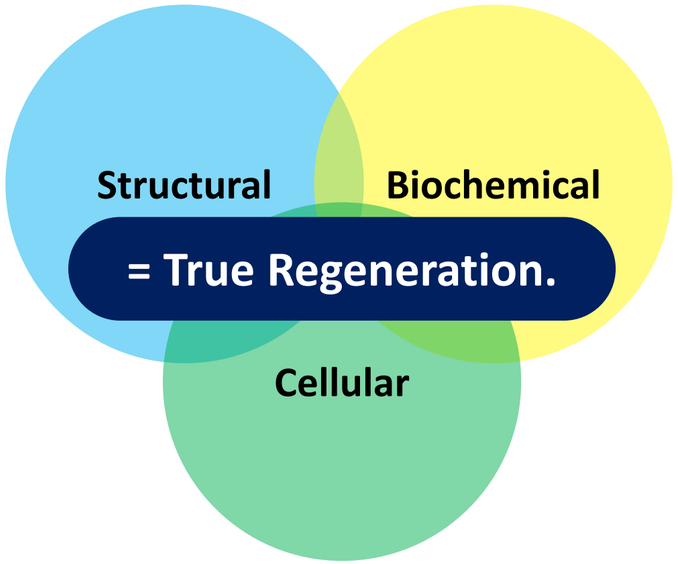
“Do not inject what you cannot characterize.”

11- SUMMARY

“From Hype to Evidence: The Science of Collagen Stimulation”

Scaffold-based injectables:
(PLLA, CaHA, PCL, PDO)

→ proven, long-term neocollagenesis.



Biochemical agents:
(PDRN, peptides, PRP, HA)

→ measurable regenerative activity, but very short-term.

Exosome & vesicle-based:

→ emerging, promising, but is risky & unstandardized.

Future lies in:

→ Multimodal, evidence-led, ethically developed regenerative protocols.

DATA TRANSPARENCY: PRISMA mini

TheDrGhofran

IDENTIFICATION

- Databases: PubMed, Embase, Scopus, Cochrane
- Timeframe: 2000–2025

↓

SCREENING

- Records: 780 → Duplicates removed: 214
- Screened titles/abstracts: 566

↓

ELIGIBILITY

- Full-text assessed: 196
- Excluded: 124 (non-clinical, non-English, insufficient outcomes, promotional)

↓

Included

- Studies included: 72
- RCT≈22 | Cohort≈20 | Histology/Imaging≈15 | SR/MA≈15

DATA TRANSPARENCY: KEY REFERENCES

Key References (APA style)

1. Wang, F., Garza, L. A., Kang, S., Varani, J., Orringer, J. S., Fisher, G. J., & Voorhees, J. J. (2007). In vivo stimulation of de novo collagen production by cross-linked hyaluronic acid filler injections in photodamaged human skin. *Archives of Dermatology, 143*(2), 155–163.
2. van Loghem, J., Funt, D., & Monheit, G. (2015). Calcium hydroxylapatite in aesthetic medicine: Over a decade of clinical experience. *Journal of Clinical and Aesthetic Dermatology, 8*(1), 38–49.
3. Zerbinati, N., D'Este, E., Saponaro, S., & Calligaro, A. (2018). Histological evidence of neocollagenesis with calcium hydroxylapatite filler. *Journal of Cosmetic and Laser Therapy, 20*(3), 1–7.
4. Goodman, G. J., van Loghem, J. J., et al. (2019). CaHA for skin quality and collagen stimulation: Expert consensus. *Journal of Cosmetic Dermatology, 18*(1), 12–17.
5. Sadick, N. S., & Dorizas, A. S. (2016). Calcium hydroxylapatite for facial rejuvenation: Mechanisms and outcomes. *Dermatologic Surgery, 42*(S2), S97–S104.
6. Narins, R. S., et al. (2010). Long-term safety and effectiveness of injectable poly-L-lactic acid. *Dermatologic Surgery, 36*(S3), 766–775.
7. Park, T. H., et al. (2020). Biostimulatory effects of poly-L-lactic acid: Mechanisms and clinical evidence. *Aesthetic Plastic Surgery, 44*(4), 1238–1247.
8. Cassuto, D., et al. (2021). PLLA and macrophage polarization: Pathways to collagen remodeling. *Aesthetic Surgery Journal, 41*(10), NP1251–NP1262.
9. Angelo-Khattar, M., et al. (2022). Objective assessment of ≥2-year performance of polycaprolactone-based filler. *Clinical, Cosmetic and Investigational Dermatology, 15*, 23–33.
10. Kim, J. S., et al. (2019). Dermal thickness increase after intradermal PCL via neocollagenesis (biopsy study). *Aesthetic Surgery Journal, 39*(12), NP484–NP493.
11. De Boulle, K., et al. (2015). Management of late-onset nodules with PLLA and CaHA: Expert recommendations. *Journal of Cosmetic and Laser Therapy, 17*(5), 246–252.
12. Goldberg, D. J. (2021). Safety considerations and complication management with CaHA. *Aesthetic Surgery Journal, 41*(S1), S1–S7.
13. Wang, F., & Garza, L. A. (2009). Mechanotransduction and human dermal fibroblast activation. *Journal of Investigative Dermatology, 129*(1), 13–16.
14. Turlier, V., et al. (2013). In vivo effects of cross-linked HA on dermal remodeling: Histologic evaluation. *Journal of Cosmetic and Laser Therapy, 15*(4), 1–8.
15. Zhou, R., et al. (2024). Skin-boosting hyaluronic acid for facial rejuvenation: Systematic review and meta-analysis. *Journal of Cosmetic Dermatology, 23*(x), eXXXX.
16. Kim, J. H., et al. (2020). Hyaluronic acid–polynucleotide composite filler and skin regeneration outcomes. *Journal of Cosmetic and Laser Therapy, 22*(7–8), 375–382.
17. Squadrito, F., Bitto, A., Irrera, N., et al. (2017). Pharmacological activity and clinical use of polydeoxyribonucleotide (PDRN). *Pharmacology & Therapeutics, 181*, 54–64.
18. Kim, Y. E., et al. (2021). Polynucleotides in aesthetic dermatology: Clinical applications and mechanisms. *Journal of Cosmetic Dermatology, 20*(12), 3833–3843.
19. Asubiaro, J., et al. (2024). Platelet-rich plasma in aesthetic dermatology: Systematic review. *Dermatologic Therapy, 37*(x), eXXXX.
20. Malcangi, G., et al. (2025). PRP vs PPP for facial rejuvenation: Systematic review & meta-analysis. *Medicina, 61*(1), 84.
21. Sclafani, A. P., & McCormick, S. A. (2012). PRP injection augments dermal matrix and angiogenesis in human skin. *Archives of Facial Plastic Surgery, 14*(2), 132–136.
22. Gentile, P., et al. (2017). PRP in facial rejuvenation and hair: Evidence and protocols. *BioMed Research International, 2017*, 1–13.
23. Welsh, J. A., et al. (2024). **MISEV 2023**: Minimal information for studies of extracellular vesicles (consensus). *Journal of Extracellular Vesicles, 13*, e12404/e12416.
24. Domaszewska-Szostek, A., et al. (2025). Extracellular vesicles in skin regeneration: Systematic review. *International Journal of Molecular Sciences, 26*(5), 2354.
25. Chen, C., et al. (2023). Exosomes for skin aging and wound repair: State of the art and challenges. *Stem Cell Research & Therapy, 14*, 215.
26. Kim, S. W., et al. (2022). Platelet-derived extracellular vesicles in skin rejuvenation: Mechanistic review. *International Journal of Molecular Sciences, 23*(x), 1–20.
27. Nassar, D., et al. (2020). Fibroblast heterogeneity and ECM remodeling in human skin aging. *Nature Communications, 11*, 6144. (Mechanistic context)
28. Alster, T. S., & Graham, P. M. (2018). Microneedling: Evidence for collagen induction and scar remodeling. *Dermatologic Surgery, 44*(3), 397–404.
29. Lima, E. V., et al. (2013). Histologic and ultrasound evidence of dermal remodeling after microneedling. *Journal of Cosmetic Dermatology, 12*(4), 306–311.
30. Tierney, E. P., et al. (2012). Non-ablative fractional lasers for neocollagenesis: Clinical and histologic correlation. *Dermatologic Surgery, 38*(7), 1107–1119.
31. Kligman, A. M., et al. (1986). Topical tretinoin for photoaged skin: Histologic evidence of new collagen. *Journal of the American Academy of Dermatology, 15*(4), 836–859. (Cornerstone topical comparator)
32. Mukherjee, S., et al. (2006). Retinoids in the treatment of skin aging: Review of mechanisms and evidence. *Clinical Interventions in Aging, 1*(4), 327–348.
33. Pickart, L., & Margolina, A. (2018). GHK-Cu peptide in skin regeneration: Mechanisms and human data. *Dermatology and Therapy, 8*(2), 265–281.
34. Gorouhi, F., & Maibach, H. I. (2009). Hyaluronic acid in skin: Functions and clinical applications. *American Journal of Clinical Dermatology, 10*(5), 281–290.
35. Goodman, G. J., et al. (2015). Injection techniques and safety algorithms for fillers and biostimulators. *Dermatologic Surgery, 41*(S1), S307–S316.
36. De Boulle, K., et al. (2015). Vascular compromise with fillers: Incidence, anatomy, and management. *Plastic and Reconstructive Surgery, 136*(5), 110S–121S.
37. Lots, T. C. C., et al. (2023). Ultrasound assessment after PDO thread insertion: Dermal changes and timing. *Journal of Cosmetic Dermatology, 22*(x), eXXXX.
38. Germani, M., et al. (2025). PDO threads: Is more always better? Randomized comparative study. *Aesthetic Surgery Journal Open Forum, 7*, ojaf002.
39. Gallo, N., Natali, M., Sannino, A., & Salvatore, L. (2020). **Equine** collagen for biomedical applications: Overview. *Journal of Functional Biomaterials, 11*(4), 79.
40. Klewin-Steinböck, S., Nowak-Terpiłowska, A., Adamski, Z., et al. (2021). Injectable **equine** type I collagen and human dermal fibroblasts: Metabolic and apoptosis data. *Advances in Dermatology and Allergology, 38*(3), 440–445.
41. Tawanwongsri, W., & Vachiramon, V. (2024). Skin necrosis after intradermal injection of lyophilized exosome: A case report and review of the literature. *Journal of Cosmetic Dermatology*.
42. AlBargawi, S. (2025). Necrosis following dermal injection of lyophilized exosomes: A case report. *Journal of Cosmetic Dermatology*.
43. Choi, H., Kim, J., Lee, S., & Park, Y. (2024). Foreign body granuloma caused by an injection of exosomes. *JAAD Case Reports*.
44. U.S. Food and Drug Administration. (2019, December 6). *Public safety notification on exosome products*.
45. Centers for Disease Control and Prevention. (n.d.). *Stem cell and exosome products—outbreak information*.

Thank You

Author, Dr. Ghofran Mahmoud I MD

R&D Director - MD Physician - International Speaker

Global Experts Group

Sources: PubMed, Embase, Scopus, Cochrane.

References: DM For full Presentation Kit

References

THEDRGHOFRAN