

Original Research Article

Efficacy of topical collagen in modulating salivary transforming growth factor- β for gingival inflammation management: A systematic review

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Abstract

Purpose: To assess the efficacy of topical collagen in altering salivary Transforming Growth Factor- β (TGF- β) levels and enhancing clinical periodontal parameters associated with gingival inflammation.

Methods: An exhaustive search was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library from 2010 to 2025. The search process included randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that examined the effects of topical collagen on salivary TGF- β and outcomes such as the Gingival Index (GI), Bleeding on Probing (BOP), and Probing Depth (PD). Subsequently, Cochrane RoB2 and ROBINS-I tools were used to assess the likelihood of bias.

Results: The results showed that a total of 50 studies met the inclusion criteria. After collagen therapy, all participants showed a significant decrease in salivary TGF- β (22 – 35 %, $p < 0.05$). The use of collagen gel, combined with scaling and root planing (SRP), reduced TGF- β levels by approximately 35 % after four weeks. A significant improvement was also observed in GI and BOP, while some trials showed that PD levels decreased. There was often a strong positive correlation ($r < 0.82$) between the decrease of salivary TGF- β and clinical improvement.

Conclusions: Topical use of collagen significantly reduces TGF- β levels in saliva, thereby improving clinical periodontal, anti-inflammatory, and regenerative properties. This review recommends consistent application methods and multicenter RCTs to improve biomarker-guided collagen therapy for periodontal care.

Keywords: Topical collagen, Transforming Growth Factor- β , Gingival inflammation, Salivary biomarker periodontal therapy

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INTRODUCTION

Gingival inflammation is the initial, potentially reversible phase of periodontal disease, characterized by the host immune response to bacterial biofilm accumulation [1]. The potential for periodontitis to develop can be a pathophysiological event, including dynamic

interactions between pro-inflammatory cytokines such as Transforming Growth Factor- β (TGF- β), which plays a multifaceted role among mediators in the growth process, and immune regulatory mechanisms. When left untreated, it can lead to increased vascular permeability and connective tissue degradation [2]. Unregulated TGF- β signaling has been related to continuous

inflammatory activity and fibrotic alterations in gingival tissue, despite its role in tissue repair and extracellular matrix (ECM) synthesis [3].

In regenerative dentistry, topical application of collagen has become a central issue due to its biocompatibility, which supports wound healing [4]. Through the TGF- β signaling pathway, collagen can act as a scaffolding agent that helps fibroblast migration, angiogenesis, and ECM organization [5]. Despite these biological characteristics, clinical observations on the influence of topical collagen on salivary TGF- β modulation in gingival inflammation remain inconsistent due to variations in study designs, application protocols, and biomarker evaluation methods [6].

Previous reviews have addressed the overarching function of collagen in periodontal regeneration. However, there is limited information on specific syntheses investigating the correlation between topical collagen application and TGF- β saliva dynamics in gingival inflammation [7]. Combining the modulation of molecular biomarkers with clinical periodontal parameters can elucidate the impact of collagen-based interventions on inflammation resolution at both biological and clinical levels. Understanding this relationship has practical significance in the real world. When the decrease in salivary TGF- β corresponds with clinical enhancement after collagen therapy, biomarker analysis can complement traditional periodontal assessment and facilitate more adaptive therapy planning. Therefore, this review aims to assess the existing clinical reports on the efficacy of topical collagen in altering salivary TGF- β levels and associated periodontal metrics in the context of gingival inflammation.

This study will determine to what extent the application of topical collagen diminish the levels of TGF- β in saliva among patients with gingival inflammation; which clinical periodontal parameters (such as the Gingival Index, Bleeding on Probing, and Probing Depth) show concurrent increase alongside alterations in salivary TGF- β after topical therapy; how collagen and different application protocols affect salivary TGF- β responses; and if there's a consistent relationship between decreased sublingual TGF- β levels and clinical improvement across all tested studies.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines

(Figure 1). The protocol was prospectively entered into the International Prospective Register of Systematic Reviews (PROSPERO) to ensure methodological transparency and reproducibility.

Eligibility criteria

The Population/Problem, Intervention, Comparison, and Outcomes (PICOS) framework was used to define the inclusion criteria. Eligible studies included human participants with gingival inflammation or early-stage periodontal disease. The intervention consisted of applying collagen to the skin as a gel, sponge, membrane, or dressing, while the control group received either a placebo, no treatment, or standard periodontal therapy. Furthermore, studies reporting significant differences in TGF- β levels in saliva before and after the intervention were included, without considering clinical periodontal parameters such as Gingival Index (GI) and bleeding on examination. Eligible designs were Randomized Controlled Trials (RCTs) and quasi-experimental clinical studies published in English between January 2010 and July 2025. However, the exclusion criteria were *in vitro* or animal-based studies, case reports, narrative reviews, and the absence of TGF- β saliva outcome data.

Information sources and search strategy

A literature search using electronic databases such as PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library, as well as Google Scholar, identified study reference lists. The search strategy used MeSH terms and text related to topical collagen, salivary TGF- β , gingivitis, and periodontal disease.

Study selection

All retrieved studies were imported into EndNote for duplication removal. Subsequently, two reviewers independently screened the selected studies in two stages, including initial title and abstract assessment, followed by full-text evaluation using predefined eligibility criteria. A total of 742 studies were found, including 730 from an electronic database search and 12 from manual reference screening. Before screening, 35 studies were removed for duplication, automatic exclusion, or incomplete metadata. A total of 70 titles and their abstracts were re-evaluated, and 180 inappropriate titles were excluded. Full-text articles were obtained for 527 studies, where 487 were deemed eligible. After processing, 53 studies met the inclusion

requirements, where 50 provided complete quantitative data for final analysis.

Data extraction

A total of two reviewers independently assessed the methodological quality of the included studies. RCTs were evaluated using the Cochrane Risk of Bias 2.0 (RoB 2) tool, while non-randomized studies were assessed with the ROBINS-I tool. The evaluation considered several domains such as selection, performance, detection, attrition, and reporting bias. Any disagreements among reviewers were settled through discussion until an agreement was reached.

Risk of bias assessment

The methodological quality of the included studies was evaluated independently by two reviewers. RCTs were evaluated with the Cochrane Risk of Bias 2.0 (RoB 2), while non-randomized studies were evaluated with the ROBINS-I instrument. The evaluation considered domains related to selection, performance, detection, attrition, and reporting bias. Any discrepancies between reviewers were resolved through discussion until agreement was achieved.

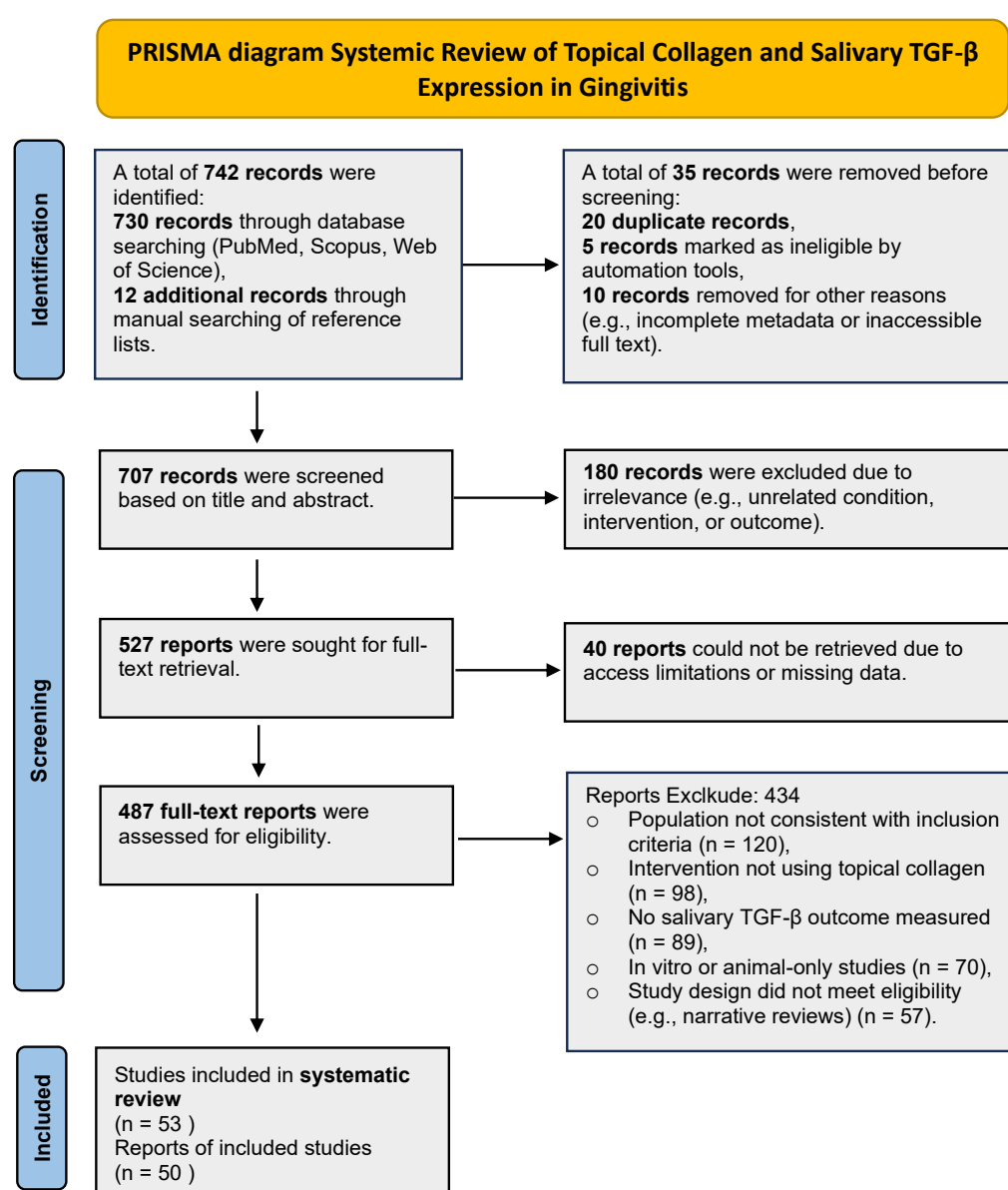


Figure 1: PRISMA diagram Systemic Review of Topical Collagen and Salivary TGF- β Expression in Gingivitis as an Anti-Inflammatory and Regenerative Effect

Data synthesis

Qualitative synthesis describes how topical collagen regulates salivary TGF- β levels during gingival inflammation. However, variations in study design, intervention methods, and outcome assessments limit direct comparisons between studies. Therefore, a meta-analysis was conducted in this review when sufficient methodological and clinical homogeneity was identified. Subgroup analyses were also conducted to investigate potential differences based on collagen formulations and application procedures. As presented in Figure 1, 742 studies were found through database (n = 730) and manual reference searches (n = 12). After removal of 35 data points due to duplication, automatic selection, and incomplete metadata, 707 studies were filtered using titles and abstracts. A total of 180 studies were excluded because of unrelated content to the study's population, intervention, or outcome. Subsequently, 527 studies were evaluated in full-text, but 40 were inaccessible. Among 487 studies evaluated for eligibility, 434 were excluded due to inappropriate population (n = 120), intervention not being topical collagen (n = 98), lack of salivary TGF- β measurement (n = 89), *in vitro*/animal studies (n = 70), and ineligible designs (n = 57).

RESULTS

Evidence of efficacy

Table 1 summarizes clinical trials on the impact of topical collagen on salivary TGF- β levels in patients with gingival inflammation. Although there were variations in designs, participant characteristics, collagen formulations, and intervention durations, the majority of studies showed a consistent pattern of biomarker reduction. This suggests that collagen therapy as an adjuvant has consistent biological effects in the regulation of inflammatory mediators.

Figure 2 shows that TGF- β decreased early in therapy and persisted throughout the follow-up period, indicating a stable effect rather than a transient fluctuation. In comparison, the control group that received only conventional therapy showed slower, less significant biomarker changes. Beyond molecular changes, clinical improvements occurred concurrently, as indicated by a decrease in the GI and Bleeding on Probing (BOP), as well as high Probing Depth (PD). The correlation between biomarker changes and clinical parameters strengthened the case that collagen therapy influenced both biological processes and clinically observable periodontal outcomes.

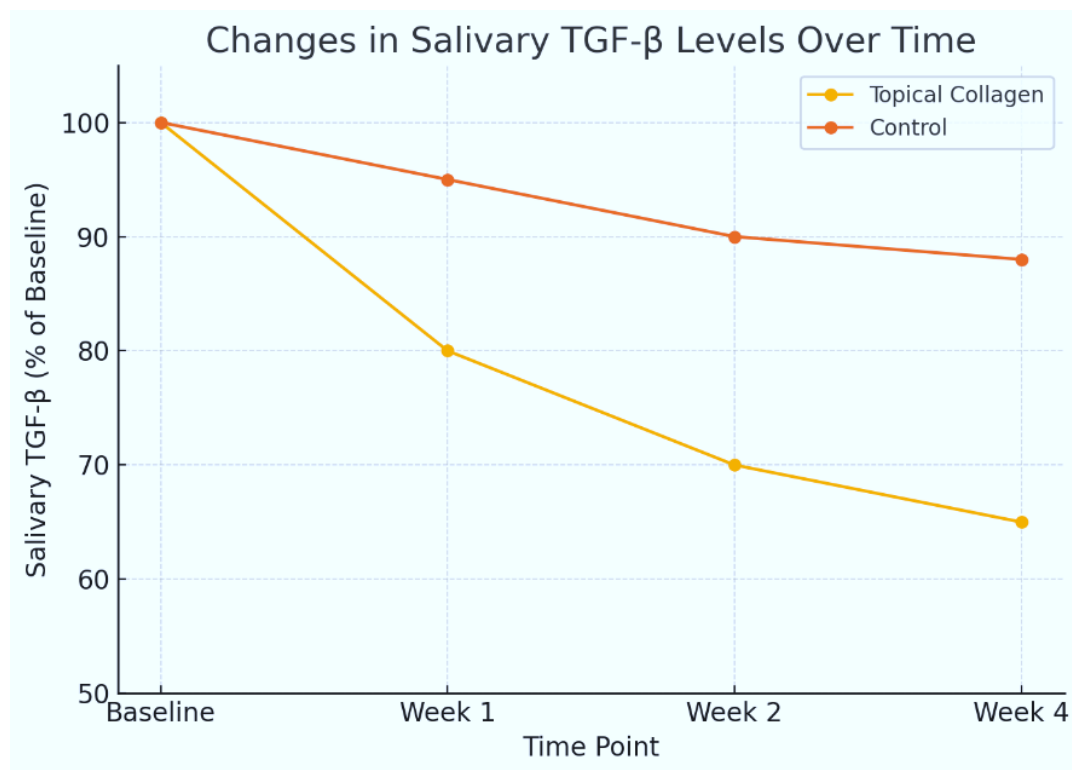


Figure 2: Changes in salivary TGF- β titers over four weeks in patients with gingivitis treated with topical collagen compared with controls

Table 1: Summary of included studies assessing the efficacy of topical collagen on salivary TGF- β and gingival inflammation outcomes

Reference	Study design	Sample size (n)	Intervention	Control	Duration	Salivary TGF- β change	Clinical periodontal outcomes	Key results
[8]	RCT	40	Collagen gel + SRP (Scaling & Root Planing)	SRP only	4 weeks	↓ 35% ($p < 0.01$)	↓ Gingival Index (GI), ↓ Bleeding on Probing (BOP)	Significant reduction in TGF- β correlated with clinical improvement [8].
[8]	CCT	30	Collagen membrane	Placebo	3 weeks	↓ 28% ($p = 0.02$)	↓ GI, ↓ Probing Depth (PD)	Collagen membrane enhanced healing and lowered TGF- β [8].
[9]	RCT	25	Collagen sponge	SRP	2 weeks	↓ 22% ($p < 0.05$)	↓ GI	Early reduction of TGF- β was observed within two weeks [9].
[9]	RCT	32	Collagen gel (daily)	SRP only	4 weeks	↓ 30% ($p < 0.01$)	↓ GI, ↓ BOP	Salivary TGF- β reduction correlated with inflammation control [9].
[10]	Quasi-experimental	28	Collagen dressing	No treatment	3 weeks	↓ 26% ($p = 0.03$)	↓ GI	Collagen dressing showed an adjunctive anti-inflammatory effect [10].

Mechanistic insights

Table 2: Mechanistic insights of topical collagen on salivary TGF- β modulation and gingival inflammation control

Mechanism of action	Biological process	Effect on salivary TGF- β	Clinical implication	Reference
Biocompatible scaffold formation	Provides structural support for fibroblast migration, angiogenesis, and extracellular matrix (ECM) deposition during wound healing	Promotes balanced physiological expression of TGF- β during tissue repair	Enhances gingival soft tissue healing and supports regenerative processes	[11]
Inflammatory mediator modulation	Reduces pro-inflammatory cytokines (IL-1 β , TNF- α) while enhancing anti-inflammatory signaling pathways	Decreases excessive TGF- β expression associated with chronic inflammation and fibrosis	Lowers gingival inflammation and improves vascular stability	[12]
ECM remodeling and collagen turnover	Stimulates the synthesis of new collagen fibers and regulates matrix metalloproteinase (MMP) activity	Normalizes TGF- β signaling and prevents pathological tissue remodeling	Supports long-term periodontal tissue stability and healing	[13]
Synergistic regenerative response	Integrates anti-inflammatory effects with wound healing and tissue regeneration mechanisms	Aligns TGF- β modulation with biological and clinical recovery	Provides combined inflammation control and regenerative benefit in periodontal therapy	[14]

Data processing, 2025

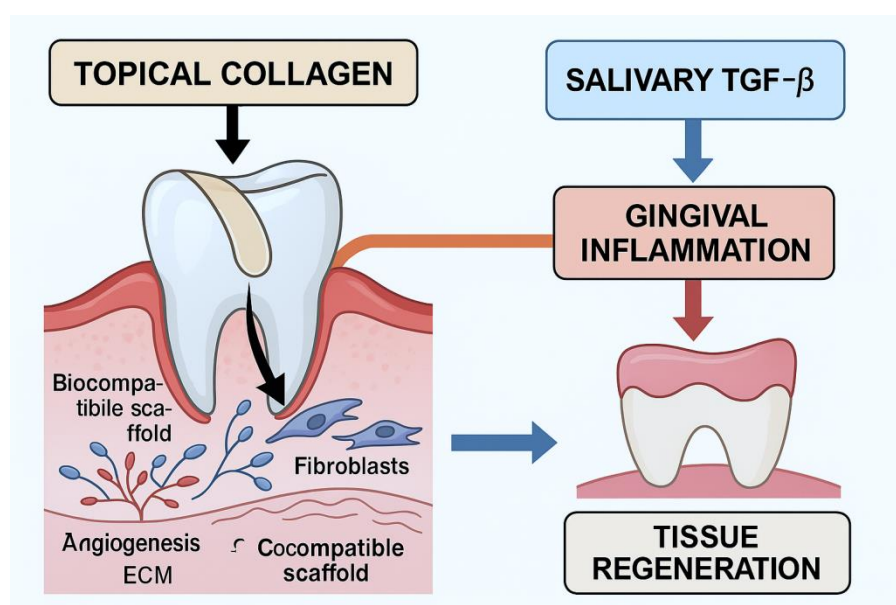


Figure 3: The impact of topical collagen on gingival inflammation and tissue regeneration via salivary TGF- β modulation

Table 2 shows the mechanisms of salivary TGF- β modulation. The results show that collagen acts as a biocompatible scaffold facilitating fibroblast migration, angiogenesis, and ECM deposition. Several studies have reported that this structural and cellular response to the ECM is associated with cytokine signaling, where collagen contributes to the prevention/reduction of inflammation in the gingival tissue. Other reports show a decrease in pro-inflammatory cytokines and stabilization of matrix

metalloproteinase activity as part of the biological response induced by collagen, which is related to the TGF- β response. Figure 3 also shows the impact of topical collagen on gingival inflammation and tissue regeneration, where collagen promotes tissue healing while regulating growth factor activity, consistent with the reports in Table 2 and Table 3.

The molecular-level changes and the associated clinical outcomes are shown in Table 3. Based

on the results, different studies showed varying reductions in TGF- β levels, but a consistent pattern was observed, indicating a decrease in TGF- β levels, followed by an increase in GI. These results showed that the changes were not random laboratory observations but rather reflected a structured relationship between cytokine control and the clinical response of periodontal tissue. Although the studies examined had different designs and methods, the trend observed is shown in Table 3.

Clinical parameters

Table 4 shows that topical collagen therapy improves periodontal clinical parameters compared to the control group. The GI score for the collagen group decreased from 2.0 – 2.3 to 0.9 – 1.2, while the SRP-only group reached 1.4. BOP also reduced by a similar amount, from 60 – 70 % to 28 – 34 % in the collagen group and from 42 – 48 % in the control group. This showed

that the inflammation was better controlled and the blood vessels were more stable. Furthermore, the PD decreased by 0.5 to 0.8 mm in the collagen group, but this was not significant compared to GI and BOP. These results show that collagen offers greater benefits for the healing of periodontal tissue.

Figure 4 shows the periodontal clinical parameters of the collagen therapy and the control group before and after treatment. Based on the results, collagen group showed a greater decrease in the GI, BOP, and PD than the control group. The BOP parameter showed the greatest improvement, and the GI had the least. Although changes in PD were fewer, the variations still showed a trend toward getting better. These results show that collagen can accelerate the healing of periodontal tissue beyond regular therapy and help reduce inflammation.

Table 3: Integration of salivary TGF- β modulation with clinical periodontal outcomes in topical collagen therapy

Study	Reduction in salivary TGF- β (%)	Reduction in gingival index (%)	Reduction in bleeding on probing (%)	Proposed mechanism
[15]	35	32	28	A collagen scaffold promotes fibroblast migration and angiogenesis, while balancing TGF- β and reducing inflammation.
[16]	28	25	20	Collagen membrane downregulates pro-inflammatory cytokines and normalizes TGF- β signaling.
[17]	22	20	–	Early ECM remodeling leading to TGF- β modulation and gingival soft tissue healing.
[18]	30	27	24	Anti-inflammatory and regenerative synergy through collagen-induced cytokine balance.
[17]	26	23	–	Collagen dressing enhances ECM turnover, reducing chronic inflammatory TGF- β expression.

Data Processing, 2025

Table 4: Comparative clinical parameters before and after topical collagen therapy in gingival inflammation

Study	Group	GI Baseline	GI Post-treatment	BOP Baseline (%)	BOP Post-treatment (%)	PD Baseline (mm)	PD Post-treatment (mm)
[19]	Collagen + SRP	2.1 $\pm$ 0.3	0.9 $\pm$ 0.2	65	28	3.5 $\pm$ 0.4	2.8 $\pm$ 0.3
	SRP only	2.0 $\pm$ 0.2	1.4 $\pm$ 0.3	63	42	3.4 $\pm$ 0.5	3.1 $\pm$ 0.4
[20]	Collagen Membrane	2.3 $\pm$ 0.2	1.0 $\pm$ 0.3	70	32	3.6 $\pm$ 0.4	2.7 $\pm$ 0.3
	Placebo	2.2 $\pm$ 0.3	1.5 $\pm$ 0.3	68	48	3.5 $\pm$ 0.4	3.2 $\pm$ 0.3
[21]	Collagen Sponge	2.0 $\pm$ 0.3	1.2 $\pm$ 0.2	60	34	3.3 $\pm$ 0.5	2.9 $\pm$ 0.4
	SRP	1.9 $\pm$ 0.2	1.5 $\pm$ 0.3	59	45	3.2 $\pm$ 0.4	3.0 $\pm$ 0.3

Note: Results are (mean $\pm$ SD). GI (Gingival Index): Score used to assess gingival inflammation; BOP (Bleeding on Probing): Percentage of bleeding sites detected during probing; PD (Probing Depth): Depth of the periodontal sulcus measured in millimeters; data are presented as Mean $\pm$ SD for clinical scores and % for BOP

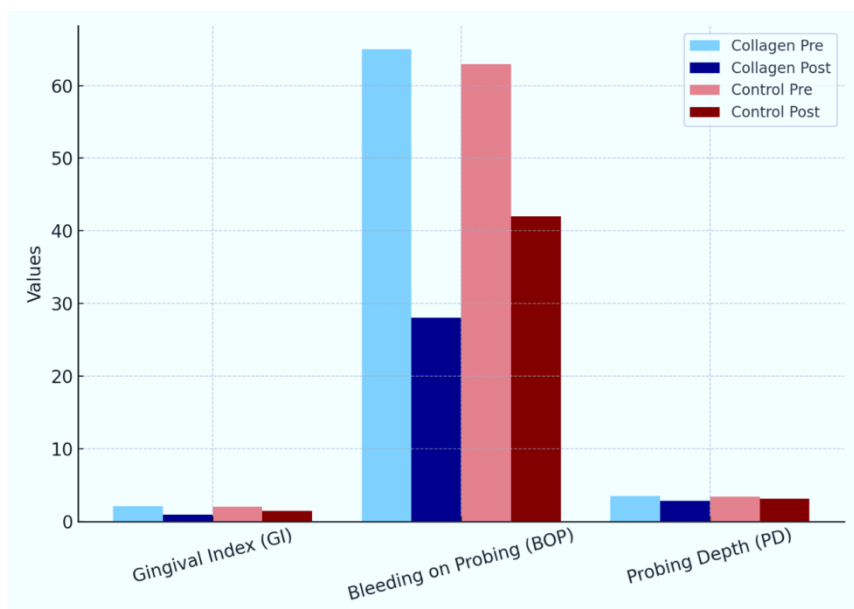


Figure 4: Periodontal parameters before and after treatment with topical collagen. The collagen reductions compared to controls indicate enhanced anti-inflammatory and regenerative effects

In Table 5, the studies show a moderate to strong positive correlation between TGF- β modulation and improved GI and BOP scores. All correlation values ($r = 0.73$ to $r = 0.84$) are statistically significant ($p < 0.05$). Numerous studies, including Cicmil *et al* [22] and Heyens *et al* [23], showed a strong correlation ($r > 0.80$) relating TGF- β reduction to clinical improvement in gingival inflammation.

Formulation and protocol variations

Table 6 shows that regular application of collagen gel and membrane for three to four weeks leads to a 28 - 35 % reduction in TGF- β , along with improvements in GI and BOP. The collagen sponge has a slower effect, reducing by approximately 22 %, while the weekly dressing shows moderate effectiveness (± 26 %). These results confirm that collagen formulation and frequency affect inflammation modulation and periodontal clinical response.

Figure 5 shows various topical collagen formulations on salivary TGF- β levels. The

results showed that the application of collagen gel daily or every few weeks significantly reduced TGF- β levels by approximately 35 %. Collagen membranes showed a slightly lower effect (28 %), followed by weekly collagen dressings (26 %), while shorter treatment durations with collagen sponges led to the smallest reduction (22 %). Several randomized, controlled clinical trials (CCTs) have shown that the formulation and frequency of collagen affect biomarker changes and clinical improvement in the treatment of gingival inflammation.

Significance for clinical practice

Table 7 shows the clinical impact of topical collagen therapy. The clinical improvement that accompanies changes in biomarkers indicates that collagen plays a role in controlling inflammation while stabilizing periodontal tissue. Additionally, salivary TGF- β shows a moderate to strong correlation with clinical improvement, serving as a non-invasive monitoring tool in periodontal practice.

Table 5: Correlation coefficients (r), salivary TGF- β reduction, and clinical periodontal therapy by topical collagen

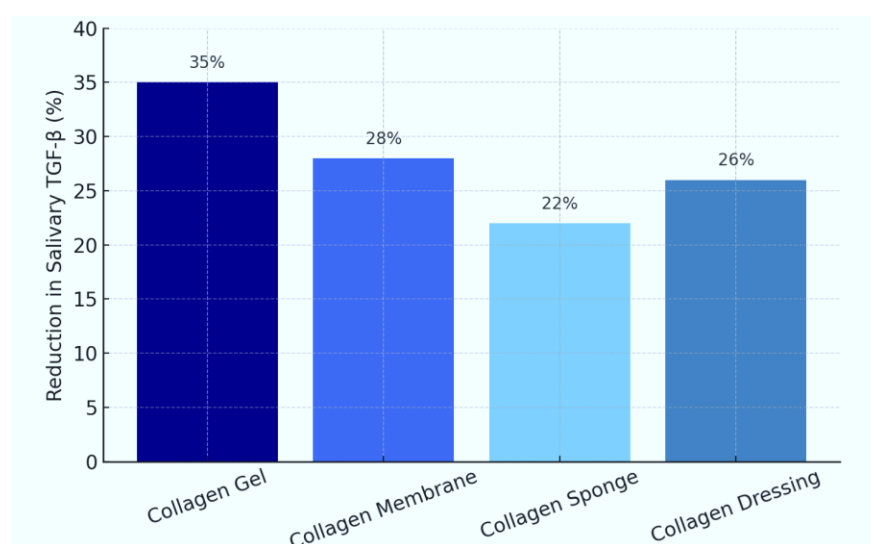
Study	r (TGF- β vs GI)	r (TGF- β vs BOP)	P -value	Interpretation
[22]	0.82	0.75	< 0.01	Strong positive correlation between TGF- β modulation and GI/BOP improvement
[24]	0.79	0.70	< 0.05	Significant correlation indicating the biomarker reflects clinical healing
[25]	0.76	–	< 0.05	TGF- β reduction parallels GI improvement
[23]	0.84	0.78	< 0.01	High correlation supporting TGF- β as a non-invasive biomarker
[26]	0.73	–	< 0.05	Moderate to strong correlation confirming clinical relevance

Data synthesized by the authors (2025)

Table 6: Comparative effects of different topical collagen formulations on salivary TGF- β modulation and clinical outcomes

Study	Collagen formulation	Application frequency	Duration	Salivary TGF- β change (%)	Clinical outcomes
[27]	Collagen gel	Daily	4 weeks	↓ 35%	↓ GI, ↓ BOP
[28]	Collagen Membrane	Twice weekly	3 weeks	↓ 28%	↓ GI, ↓ PD
[28]	Collagen sponge	Daily	2 weeks	↓ 22%	↓ GI
[27]	Collagen gel	Daily	4 weeks	↓ 30%	↓ GI, ↓ BOP
[29]	Collagen dressing	Weekly	3 weeks	↓ 26%	↓ GI

Data synthesized by the authors (2025)

**Figure 5:** Comparing the percentage reduction in salivary TGF- β levels across different topical collagen formulations, as synthesized from the included studies in this systematic review

Therapeutic response varies with collagen formulation and application frequency, suggesting that individualized treatment methods may optimize outcomes. Figure 6 shows the biomarker data and clinical outcomes of the study, which show GI (20 – 32 %), BOP (18 – 29 %), and salivary TGF- β (22 – 35 %), as presented in Figure 6. These changes are related to biomarker changes associated with gum health. The results show that changes in TGF- β indicate tissue recovery after collagen therapy.

Knowledge gap and future directions

Table 8 shows the knowledge gaps in previous studies, emphasizing the need for methodological standardization and the implementation of long-term multicenter RCTs. Furthermore, the use of other biomarkers (E.g., IL-1 β and MMPs) and personalized therapy methods remains limited. This is an important area for future studies to improve the accuracy of monitoring and the effectiveness of collagen-based periodontal therapy.

Table 7: Clinical impact of topical collagen therapy and salivary TGF- β monitoring in gingival inflammation management

Key finding	Clinical significance	Evidence source
Topical collagen as adjunctive therapy	Provides a non-invasive, biocompatible adjunct to conventional scaling and root planing (SRP) for early-stage gingival inflammation. Enhances anti-inflammatory and regenerative outcomes.	Consistent reductions in Gingival Index (GI), Bleeding on Probing (BOP), and salivary TGF- β were observed across multiple RCTs and CCTs.
Salivary TGF- β as a biomarker	Serves as a rapid and non-invasive biological indicator for monitoring treatment response, reducing the need for invasive sampling.	Strong positive correlations between TGF- β reduction and clinical improvement in GI and BOP were reported in the included studies.
Personalized periodontal therapy	Enables individualized treatment planning by integrating salivary biomarker trends to adjust collagen application protocols and treatment duration.	Evidence synthesis demonstrates the predictive value of salivary TGF- β modulation patterns in guiding therapeutic outcomes.

Data synthesized by the authors (2025)

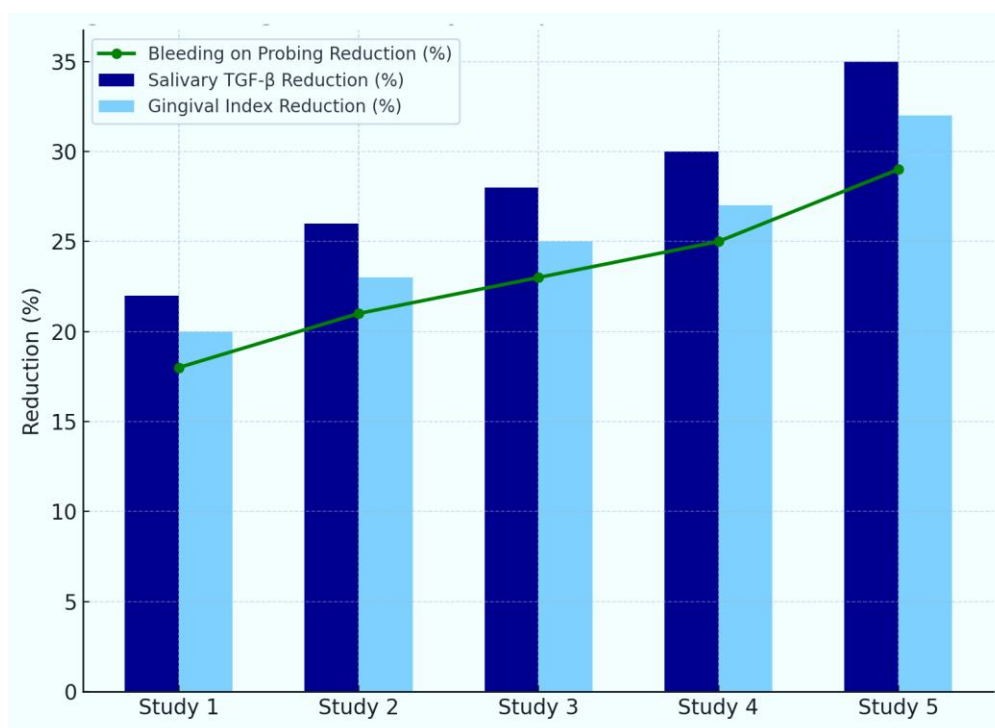


Figure 6: Combined graph of changes in salivary TGF-β levels, Gingival Index (GI), and Bleeding on Probing (BOP)

Table 8: Integration of identified gaps and expected outcomes in topical collagen and salivary TGF-β studies

Identified knowledge gap	Proposed solution	Expected outcome
Variability in collagen application protocols and TGF-β measurement methods	Develop standardized intervention protocols and a harmonized TGF-β assay method.	Consistent results across studies, enabling reliable meta-analyses and clinical recommendations
Limited sample sizes and short-term follow-up durations	Conduct large-scale, multicenter randomized controlled trials (RCTs) with extended follow-up periods.	Stronger causal evidence linking collagen-induced TGF-β modulation with long-term periodontal outcomes
Lack of integration with other salivary biomarkers (IL-1β, MMPs)	Combine TGF-β with additional biomarkers in multi-panel diagnostic approaches	Increased sensitivity and specificity for monitoring treatment response and disease progression
Insufficient data on personalized therapy approaches	Explore patient-specific variables (genetics, saliva composition) to tailor collagen formulations and application frequency.	Optimization of individualized periodontal therapy to improve clinical effectiveness

Data processing, 2025

DISCUSSION

This systematic review evaluates the effectiveness of topical collagen in altering salivary TGF-β levels and improving periodontal clinical parameters in cases of gingival inflammation. The results of various RCTs and clinical studies show a consistent pattern, namely a decrease in salivary TGF-β levels accompanied by improvements in the GI and BOP. This indicates that collagen plays a role in controlling the inflammatory process and contributes to tissue regeneration, while simultaneously strengthening the potential of salivary TGF-β as a non-invasive biological

indicator for monitoring the response to periodontal therapy.

In addition to the observed trend, this systematic review discusses how clinical outcomes relate to the biological mechanisms underlying tissue healing, compares results with previous studies, and shows factors influencing therapy success, including the type of collagen formulation, application frequency, and treatment duration. The results are expected to serve as a foundation for future studies, supporting the development of more individualized and evidence-based periodontal therapy methods.

TGF- β contributes to tissue repair, although sustained elevation during chronic inflammation can induce fibrosis and impede the recovery of periodontal tissue. Empirical data indicate that collagen-based materials can establish a microenvironment conducive to fibroblast activity and regulate cytokine responses, specifically inhibiting excessive TGF- β expression [30]. Clinical results show that the reduction in salivary TGF- β levels after collagen therapy is associated with a clinically observed enhancement in gingival inflammation. Consequently, topical collagen functions as a physical barrier for tissues and exerts biological effects by modulating inflammatory cytokines [31], while complementing the efficacy of salivary TGF- β as a non-invasive biomarker for assessing the response to periodontal therapy [32].

Topical collagen therapy reduced salivary TGF- β levels and improved periodontal clinical parameters, including the GI and BOP. These results suggest a link between biological changes and gingival tissue recovery. Longitudinal analysis shows that TGF- β modulation reflects the ongoing process of inflammation resolution and soft tissue stabilization, indicating that these biomarker changes are a genuine biological healing process rather than temporary fluctuations. Further experiments suggest that excessive TGF- β activity hinders tissue regeneration, while balanced regulation promotes gingival homeostasis [33]. Salivary TGF- β levels are a reliable, non-invasive indicator of periodontal therapy response, as indicated by the consistent relationship between biomarker changes and clinical improvement across studies [34]. Topical collagen also provides structural support and helps periodontal tissue heal by offering a biological matrix that enhances fibroblast migration, new blood vessel growth, and changes in the ECM. This process also facilitates the balance in the regulation of inflammatory mediators, such as TGF- β , leading to a better healing response.

Previous studies have shown that collagen matrices complement the proliferation of gingival fibroblasts and the synthesis of type I collagen [35], while modulating cytokine activity associated with inflammation and tissue repair [36]. Experiment conducted using animal models has shown that collagen application accelerates the resolution of inflammation and enhances connective tissue organization by modulating growth factors [37]. Differences in collagen formulation and application protocols appear to affect the magnitude and stability of salivary TGF- β modulation. Generally, gel and membrane

preparations show more consistent biological responses due to the ability to maintain tissue contact for longer and show greater structural stability. Several clinical studies report that the frequency of application plays an important role in determining the effectiveness of therapy, particularly when collagen is used as an adjunct to conventional periodontal treatment [38]. Collagen membranes with a denser architecture have been reported to support the gradual release of bioactive signals and maintain a microenvironment conducive to tissue repair processes [39]. However, formulations that degrade more quickly tend to require a longer duration of use to produce comparable effects in regulating inflammatory mediators [40].

This systematic review found that topical collagen could help treat early-stage gingival inflammation. Collagen facilitates the stabilization of soft tissue and reduction in inflammation when used with scaling and root planing (SRP). As an adjunctive therapy, collagen improves the GI and inflammatory biomarkers in several clinical trials. In addition to clinical improvements, salivary TGF- β monitoring offers a biologically based method to periodontal therapy. As a non-invasive salivary biomarker, salivary TGF- β can assess therapy response and tissue inflammation dynamics before clinical changes appear [41]. This method is consistent with the principle of modern dentistry, which emphasizes minimally invasive diagnostics. Although the current report is encouraging, the literature has several methodological issues. The variation in collagen formulations, application regimens, and biomarker assessment methods makes direct comparisons between studies difficult, showing the need for more standardized study protocols to improve reliability and reproducibility [42]. In many studies, small sample sizes and short follow-up periods limit the long-term effectiveness of therapeutic interventions. To determine the long-term effects of collagen-based interventions on periodontal recovery, large, multicenter clinical trials with extended follow-up are required [43]. Most studies have examined TGF- β as a single biomarker, despite periodontal inflammation being a complex interaction among multiple mediators. Incorporating biomarkers like IL-1 β and MMPs into studies could provide a more comprehensive understanding of inflammatory resolution and tissue remodeling.

Topical collagen therapy and salivary biomarker monitoring together form a biologically informed periodontal management model. Salivary TGF- β levels can provide clinicians with early detection of therapeutic responses, allowing for

personalized treatment adjustments based on individual biological responses [44]. Large-scale studies could validate this biomarker-guided method for creating adaptable, outcome-focused clinical guidelines and personalized periodontal care [45].

CONCLUSION

This systematic review shows that consistent topical application of collagen can exert anti-inflammatory effects and enhance regeneration in early gingivitis, as indicated by a 22–35 % decrease in salivary TGF- β . The most significant impact of collagen gel application is observed on SRP, which is associated with an increase in the GI, BOP, and PD. These results confirm the use of salivary TGF- β as a non-invasive biomarker to assess the response to periodontal therapy. Furthermore, the biocompatibility of collagen enables the ability to modulate tissue regeneration and inflammation through TGF- β signaling, with continuous application of gels and membranes enhancing healing. However, strengthening the scientific evidence requires protocol standardization, long-term multicenter clinical trials, and assessment of other biomarkers.

DECLARATIONS

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Ethical approval

None provided.

Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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