Host modulation therapy as an adjunct in peri-implantitis treatment

Terapi modulasi inang sebagai terapi tambahan dalam penanganan peri-implanitis

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ABSTRACT
Peri-implantitis is an inflammatory condition surrounding dental implants that often persists following mechanical debridement. Host modulation therapy (HMT) targets the destructive host response and has been proposed as an adjunctive therapy; however, its role remains unclear. In accordance with PRISMA 2020, a search was conducted in PubMed, ScienceDirect, the Cochrane Library and Google Scholar for human studies (2015–2025) evaluating HMT as an adjunct to peri-implantitis therapy. Methodological quality was assessed using the Joanna Briggs Institute checklist. The protocol was registered with PROSPERO (CRD420261322132). Seven studies (four RCTs, one retrospective cohort, one retrospective comparative study, one case series; 579 participants) were included. Three HMT approaches were tested: topical tetracyclines (doxycycline gel, minocycline microspheres/ointment, tetracycline fibres), systemic sub-antimicrobial dose doxycycline (SDD), and the probiotic *Lactobacillus reuteri*. Topical tetracyclines demonstrated the most consistent short-term improvements in probing depth, bleeding on probing, plaque, suppuration, and pro-inflammatory biomarkers. SDD was associated with long-term peri-implant stability in one case series, whilst probiotics only reduced the plaque index. It was concluded that adjunctive HMT, particularly topical doxycycline and minocycline, provides short-term clinical benefits in peri-implantitis.
Keywords: peri-implantitis, host modulation therapy, doxycycline, tetracycline, probiotics

ABSTRAK
Peri-implanitis adalah kondisi inflamasi di sekitar implan gigi yang sering menetap setelah debridemen mekanis. *Host modulation therapy* (HMT) menargetkan respon inang yang destruktif dan diusulkan sebagai terapi tambahan, namun perannya belum jelas. Sesuai PRISMA 2020, penelusuran dilakukan pada PubMed, ScienceDirect, Cochrane Library, dan Google Scholar untuk studi pada manusia (2015-2025) yang mengevaluasi HMT sebagai pelengkap pada terapi peri-implanitis. Kualitas metodologi dinilai menggunakan *checklist* Joanna Briggs Institute. Protokol terdaftar pada PROSPERO (CRD420261322132). Tujuh studi (empat RCT, satu kohort retrospektif, satu studi komparatif retrospektif, satu serial kasus; 579 partisipan) disertakan. Tiga pendekatan HMT diuji: tetrasiklin lokal (gel doksisiklin, mikrosfer/salep minosiklin, serat tetrasiklin), doksisiklin dosis sub-antimikroba sistemik (SAS), dan probiotik *Lactobacillus reuteri*. Tetrasiklin lokal menunjukkan perbaikan jangka pendek paling konsisten pada *probing depth*, *bleeding on probing*, plak, supurasi, dan biomarker pro-inflamasi. SAS dikaitkan dengan stabilitas peri-implan jangka panjang pada satu serial kasus, sedangkan probiotik hanya menurunkan indeks plak. Disimpulkan bahwa HMT tambahan, terutama doksisiklin dan minosiklin lokal, memberikan manfaat klinis jangka pendek pada peri-implanitis.
Kata kunci: peri-implanitis, *host modulation therapy*, doksisiklin, tetrasiklin, probiotik
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INTRODUCTION

Peri-implantitis (PIP) is an inflammatory disease of the soft and hard tissues around an osseointegrated dental implant, and it leads to progressive loss of supporting bone.[1,2] It begins when bacterial biofilm accumulates on the implant surface, triggering inflammation that, if unchecked, destroys crestal bone and can cause implant failure.[1-3] Several local and systemic factors worsen the disease, including diabetes, smoking, a history of periodontitis, and absent or thin keratinized mucosa around the implant.[3,4] Cytokine gene polymorphisms and titanium particles released from implant surfaces may also affect the host response and disease progression.[4,5]

Standard treatment relies on mechanical debridement, with or without surgical access, and sometimes adds antiseptics or antibiotics.[6] These approaches do not always resolve the disease, and recurrence is common. That gap has pushed clinicians to look at the host-microbiome imbalance that keeps inflammation going.[6,7] Host modulation therapy (HMT) means using drugs alongside standard treatment to dampen the destructive part of the host response while leaving protective immunity intact.[7,8] HMT agents include sub-antimicrobial dose doxycycline (SDD), locally delivered minocycline and doxycycline, NSAIDs, bisphosphonates, statins, probiotics, and newer compounds such as chemically modified tetracyclines and pro-resolving lipid mediators.[9-10] Of these, only SDD has FDA approval as an adjunct to scaling and root planing in periodontitis.[11]

Evidence for HMT in periodontitis is reasonably strong, but the picture for peri-implantitis is less clear. The implant surface, the local microbiome, and the host response interact differently around an implant than around a tooth, which changes how a drug behaves at that site.[10,12] Variation between patients and the lack of agreed protocols also make it harder to translate findings to the clinic.[13,14] Do, this review summarizes human clinical studies of adjunctive HMT for peri-implantitis published 2015-2025, looking at clinical, microbiological, and biomarker outcomes.

METHODS

This systematic review uses the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) 2020 guidelines. The eligibility criteria for this systematic review were defined according to the PICOS framework, which is summarized in Table 1.

Table 1 PICOS criteria

PICOS Variable	Definition
Population (P)	Human patients diagnosed with peri-implantitis (≥18-y-o)
Intervention (I)	HMT which includes: • systemic or local sub-antimicrobial dose doxycycline • NSAIDs • Bisphosphonates • monoclonal antibodies, statins, probiotics • other pharmacological/immunomodulatory approaches
Comparator (C)	Conventional approach for peri-implantitis without HMT
Outcomes (O)	Clinical parameters (PD, CAL, BoP & implant survival), RBL, biomarker expression
Study Design (S)	RCT, clinical trial, observational study, cohort study, case report/series

Study registration

This systematic review was conducted and reported in accordance with the PRISMA 2020 checklist. The protocol for the systematic review was registered to PROSPERO under ID CRD420261322132.

Eligibility criteria placed inclusion criteria namely adult human subjects (≥18 years) diagnosed with peri-implantitis affecting osseointegrated dental implants. Eligible studies had to evaluate HMT administered as an adjunct to conventional peri-implantitis treatment, including but not limited to systemic sub-antimicrobial dose doxycycline, locally delivered doxycycline or minocycline formulations, or combination antimicrobial regimens with host-modulatory effects. Studies were required to include either a comparison group receiving convention-

al mechanical debridement or to report pre- and post-treatment clinical outcomes within the same cohort.

Only studies reporting quantitative clinical or biological outcomes were included, such as probing depth (PD), bleeding on probing (BoP), plaque index (PI), gingival or sulcus bleeding index (GI/SBI), radiographic bone level changes, or inflammatory biomarkers. Both randomized controlled trials, controlled clinical trials, cohort studies, case-control studies, observational studies, experimental clinical studies, and case reports or case series (with ≥5 participants) were considered eligible. Only peer-reviewed original research articles published 2015-2025 were included, and all studies had to focus exclusively on human populations. Furthermore, only studies published in English.

Studies were excluded if they involved animal models, in vitro experiments, or purely laboratory-based investigations without human clinical data. Studies focusing exclusively on peri-implant mucositis without confirmed peri-implantitis were excluded unless separate peri-implantitis data were clearly reported. Case reports or case series involving fewer than five participants were excluded unless they provided exceptional long-term host modulation data. Studies that did not evaluate host modulation therapy as an adjunctive intervention, or that focused solely on surgical regenerative techniques, implant surface modifications, laser therapy, or antimicrobial photodynamic therapy without a host-modulatory component, were excluded.

Additionally, studies that did not report measurable clinical or inflammatory outcomes relevant to peri-implantitis resolution were excluded. Reviews, systematic reviews, meta-analyses, conference abstracts without full-text availability, letters to the editor, and secondary analyses without new clinical data were not considered for inclusion. Publications before 2015, non-English language articles, and duplicate reports were also excluded from the review.

Information sources

We conducted a comprehensive search across multiple electronic databases, including PubMed/MEDLINE, ScienceDirect, Google Scholar, and Cochrane Library. The time frame for the published research articles is restricted to the last 10 years (2015–2025) to reflect the latest information. The first search was carried out in January 2025 and updated in September 2025. We manually searched the reference lists from relevant articles and key journals related to radiographic assessment of alveolar bone in edentulous patients with diabetes mellitus were undertaken to identify additional eligible studies. No restrictions were applied based on geographic location. Only studies published in the English language were considered.

Search strategy

The strategy was organized using a combination of *medical subject headings* (MeSH) terms and free-text keywords related to edentulism, alveolar bone characteristics, DM and radiographic imaging techniques. A summary of the search strategies and the total number of studies retrieved is provided in Table 2.

Data selection and the collection process

Data extraction was performed independently by two reviewers (NA and MH) using a predefined data extraction form. The extracted data were subsequently cross-checked for accuracy and completeness, and any discrepancies were resolved through discussion. A third reviewer (HSH) verified the extracted data to ensure consistency and accuracy across the included studies. When required, clarification was sought through discussion among the reviewers based on information available in the published reports. No attempts were made to contact study authors for additional or missing data. No automation tools or software-assisted data extraction methods were used during the data collection process.

Data items

The primary outcomes of interest focused on the clinical and biological response to host modulation therapy when used as an adjunct in the management of peri-implantitis. These outcomes included quantitative clinical parameters such as PD, BoP, PI, GI/SBI, and radiographic bone level changes around affected implants. In addition, where available, inflammatory biomarkers, including interleukin-6 (IL-6), IL-1β, tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinase-8 (MMP-8), were recorded to assess the biological impact of host modulation therapy. For each included study, key descriptive data were extracted, including the first author's name, year of publication, country of origin, study design, total sample size, and number of participants allocated to intervention and control groups. Details regarding the type of host modulation therapy administered, treatment duration, and adjunctive conventional therapy were also collected.

A structured summary of the included studies, detailing intervention characteristics, clinical outcomes, and biomarker findings, is presented in Table 3. A separate synthesis table (Table 4) summarizes the reported biomarkers/mechanisms and the short- and long-term clinical outcomes of adjunctive host modulation approaches.

Risk of bias assessment

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists, according to each study design. As the review incorporated randomized controlled trials, cohort studies, observational studies, and case series the appropriate JBI tool was applied for each design. Two independent reviewers (NA and MH) evaluated all studies, and any discrepancies were resolved through discussion. When consensus could not be reached, a third reviewer (HSH) was consulted. The overall risk of bias was categorized based on the JBI scoring guidance.

Effect measures and data synthesis

The primary outcomes evaluated in this review were clinical and biological indicators of peri-implantitis improvement following adjunctive HMT. These included PD, BoP, PI, suppuration, radiographic bone level (RBL), implant survival, and when available, biomarker expression such as a MMP-8 or microbiological changes.

Table 2 Databases search query

Database	Search Query
Pubmed	("peri-implantitis"[MeSH] OR "peri-implantitis" OR "periimplantitis" OR "peri-implant disease") AND ("host modulation therapy" OR "host-modulating agents" OR "subantimicrobial dose doxycycline" OR "low-dose doxycycline" OR "NSAID" OR "statin" OR "bisphosphonate" OR "probiotic" OR "monoclonal antibody" OR "immunomodulatory therapy" OR "cytokine modulation")
Science Direct	("peri-implantitis" OR "periimplantitis") AND ("host modulation therapy" OR "doxycycline" OR "NSAID" OR "statin" OR "bisphosphonate" OR "probiotic" OR "immunomodulatory")
Google Scholar	"peri-implantitis" AND doxycycline "peri-implantitis" AND statin "peri-implantitis" AND probiotic

Clinical results were reported descriptively using the original units provided in each study. For comparative studies, treatment effects were described based on reported mean differences, percentage reductions, or statistical significance between intervention and control groups. No statistical transformation, pooling, or imputation of missing data was performed. Given the heterogenity in study design (RCT, cohort, case series), intervention type (systemic SDD, local doxycycline gel, minocycline microspheres, probiotics), follow-up duration, and outcome reporting, a quantitative meta-analysis was not undertaken. Instead, findings were synthesized qualitatively using structured tables summarizing intervention type, short-term and long-term outcomes, and biomarker effects.

RESULT

Study selection

The electronic search across PubMed, ScienceDirect, Cochrane Library, and Google Scholar identified a total of 332 records, comprising PubMed (n=132), ScienceDirect (n=45), Cochrane Library (n=5), and Google Scholar (n = 150). After removing 10 duplicate records, 322 articles remained for title screening. Following title and abstract screening, 120 were excluded due to irrelevance. Subsequently, 20 full-text articles were assessed for eligibility. Of these, 13 articles were excluded, including 5 systematic review articles and 8 studies that did not meet the inclusion criteria. Finally, seven studies fulfilled all eligibility criteria and were included in the qualitative synthesis. The study selection process is illustrated in the PRISMA flow diagram (Fig.1).

Study characteristics

The seven included studies were published 2020-2025, with sample sizes ranging 5-209 participants. The study designs comprised four RCTs, one retrospective cohort study, one retrospective comparative study, and one clinical observational case series. All studies involved adult patients diagnosed with peri-implantitis affecting osseointegrated dental implants. The HMT evaluated included local minocycline delivery (microspheres or hydrochloride), 14% topical doxycycline gel, systemic SDD, combination metronidazole-minocycline therapy, and probiotic supplementation (*Lactobacillus reuteri*). The primary outcomes assessed across studies were clinical parameters such as PD, BoP, PI, modified plaque and sulcus bleeding indices (mPLI/mSBI), suppuration, and RBL. Several studies additionally evaluated inflammatory biomarkers, including IL-6, IL-1β, TNF-α, MMP-8, and aMMP-8, to assess the biological impact of HMT.

We rated the methodological quality of the seven included studies with the JBI critical appraisal checklists. Scores for the four RCTs is ranged 84.6-100% (mean 90.4%) and were classified as low risk of bias.[15,19-21] The retrospective cohort scored 81.8% (low risk)[18] and the retrospective comparative study scored 72.7% (mode-rate risk), mainly because confounders were not well controlled.[16] The case series scored 90% (low risk).[17] Overall the quality was acceptable, but the small number of cohort and case-series studies and the lack of large multicenter trials introduced some heterogeneity. Table 5 shows the per-study risk of bias assessment.

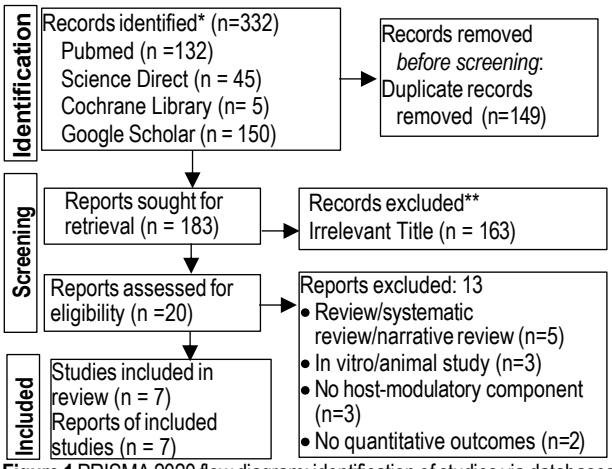

Figure 1 PRISMA 2020 flow diagram: identification of studies via databases and registers

The seven included studies tested three main HMT approaches: local tetracyclines (minocycline microspheres or hydrochloride ointment, slow-release doxycycline gel, tetracycline fibers, and 14% doxycycline gel), systemic SDD, and *L.reuteri* probiotic. Local tetracyclines gave the most consistent short-term clinical improvements, with reductions in PD, bleeding indices, plaque, and suppuration, and lower IL-6, TNF-α, IL-1β, and MMP-8 levels where measured.[15-18] The probiotic only reduced plaque index, with no useful effect on PD or BoP at the implant level.[20] One RCT also showed that a single dose of minocycline microspheres added nothing to NSMD alone,[21] suggesting that delivery frequency and form matter for clinical effect.

Clinical outcome analysis

Five of seven studies reported significant clinical improvement after HMT.[15-19] Wei et al.[15] found that minocycline hydrochloride ointment added to mechanical debridement reduced PPD, mPLI, and mSBI, with a higher total effective rate (93.0% vs 72.1%) and fewer adverse events (4.6% vs 23.3%) than iodine glycerin. Zhang et al.[16] reported that combined metronidazole and minocycline hydrochloride produced significantly greater reductions in PD, PLI, and SBI than metronidazole alone, and IL-1β and TNF-α emerged as independent predictors of treatment success on logistic regression. D'Orto and Polizzi[18] reported significant reductions in PPD, BoP, PI, and suppuration in patients given 14% topical doxycycline gel as an adjunct to non-surgical therapy, while the control group did not improve significantly. Khare et al.[19] compared five local drug delivery options and found that minocycline microspheres and 0.2% chlorhexidine gel gave the largest short-term PD and BoP reductions, although by 12 months all groups had similar improvements. Alhumaidan et al.[21] reported a different result: a single dose of subgingival minocycline hydrochloride microspheres added no clinical benefit over NSMD alone at 6 months, and CBL did not change. Long-term data are sparse. Sorsa et al[17] described five patients on sub-antimicrobial dose doxycycline (Periostat®) added to mechanical therapy who stayed clinically stable for 3 to 17 years. The sample is small, there was no randomized comparator, and case series carry inherent bias, so this finding should be read as hypothesis-generating, not as proof.

Biomarker analysis

Three studies reported biomarker outcomes.[15-17] Wei et al.[15] showed that adjunctive minocycline reduced IL-6 and TNF-α in gingival crevicular fluid, in line with an anti-inflammatory effect. Zhang et al[16] found that combined metronidazole and minocycline lowered serum IL-6, IL-1β, TNF-α, and MMP-8 more than metronidazole only, and on logistic regression IL-1β and TNF-α were independent predictors of treatment success. Sorsa et al[17] validated the aMMP-8 chairside point-of-care test for peri-implantitis, with perfect diagnostic discrimination (AUC 1.000) compared with BoP (AUC 0.675); they also reported that long-term SDD reduced collagenolytic activity and was associated with stable peri-implant conditions. These findings give HMT a plausible biological basis through suppression of host-derived destructive enzymes and pro-inflammatory cytokines.

Table 4 Study characteristics across included studies.

Author, Year	Country	Study Design	Diagnosis	Sample	Intervention	Comparator	Outcomes	Key Findings
Wei Na et al., 2020[15]	China	RCT	Peri-implantitis	86	Mechanical debridement + minocycline hydrochloride	Mechanical debridement + iodine glycerin	PPD, mPLI, mSBI, IL-6, TNF-α in GCF, total effective rate, adverse reactions	Adjunctive minocycline significantly reduced PPD, mSBI, IL-6, & TNF-α ($p<0.05$), with higher treatment success (93.0% vs 72.1%) & fewer adverse events (4.6% vs 23.3%), indicating a significant anti-inflammatory host-modulation effect.
Zhang Y et al., 2024[16]	China	Retrospective comparative study	Peri-implantitis	107	Metronidazole + Minocycline hydrochloride ointment	Metronidazole	Clinical: PLI, SBI, PD. Inflammatory markers: IL-6, IL-1β, TNF-α, MMP-8. ROC & logistic regression	Combination therapy showed significantly better clinical efficacy (P=0.010), greater reduction in PD, PLI, SBI, and lower IL-1β, TNF-α, MMP-8 levels. IL-1β and TNF-α were independent predictors of treatment success.
Sorsa T et al., 2020[17]	Finland & Sweden	Clinical observational case series	Peri-implantitis	5	Subantimicrobial-dose doxycycline (SDD/Periostat®) adjunctive to mechanical debridement	Standard mechanical therapy	Clinical status, radiographic evaluation, aMMP-8 levels, ROC analysis (AUC), inflammatory biomarkers	Long-term SDD prevented peri-implantitis. aMMP-8 PoC showed superior diagnostic accuracy (AUC=1.000 vs 0.675), supporting adjunctive HMT with biomarker monitoring.
D'Orto & Polizzi, 2025[18]	Italy	Retrospective cohort	Peri-implantitis	209	Non-surgical mechanical debridement + 14% topical doxycycline gel (Ligosan®)	Non-surgical mechanical debridement	PPD, BoP, PI, suppuration	significant reductions in PPD, BoP, PI, suppuration ($p<0.05$), while controls showed no significant improvement. Adjunctive doxycycline significantly enhanced clinical outcomes.
Khare et al., 2023[19]	India	RCT	Peri-implantitis	105	Mechanical debridement + one of: 0.2% chlorhexidine gel, 0.2% chlorhexidine chip, minocycline microspheres, slow-release doxycycline gel, tetracycline fibers	Chlorhexidine gel/chip adjuncts	Plaque score (%), Probing Depth (mm), Bleeding on Probing (%), microbiological counts	Minocycline microspheres and 0.2% CHX gel produced greater short-term PD and BoP reduction. All groups improved at 12 months, with no significant microbiological differences.
Laleman et al., 2020[20]	Belgium	RCT	Peri-implantitis	19	Mechanical debridement + local application of *Lactobacillus reuteri* (DSM 17938 & ATCC PTA 5289. drops + lozenges, 10^8 CFU/strain) for 12 weeks	Mechanical debridement + placebo drops & lozenges	BoP, PPD, plaque index, microbiology	No added effect on PPD/BoP. only plaque index improved.

RCT = randomised controlled trial, PD = probing depth, mPLI = modified plaque index, mSBI = modified sulcus bleeding index, IL = interleukin, TNF-α = tumour necrosis factor-alpha, GCF = gingival crevicular fluid, PI = plaque index, SBI = sulcus bleeding index, MMP-8 = matrix metalloproteinase-8, SDD = sub-antimicrobial dose doxycycline, aMMP-8 = active MMP-8, ROC = receiver operating characteristic, PoC = point-of-care, AUC = area under the curve, BoP = bleeding on probing, CHX = chlorhexidine, CFU = colony-forming units, mGI = modified gingival index, CBL = crestal bone level.

Table 2 Biomarker/mechanistic outcomes and clinical effects (short- and long-term) of host modulation therapy as an adjunct to peri-implantitis management across included studies

Author (Year)	Biomarker/Mechanism Reported	Effect	Short-Term Outcomes	Long-Term Outcomes
Wei Na et al., 2020[15]	IL-6, TNF-α (GCF)	Anti-inflammatory + clinical improvement	↓ PPD, ↓ mSBI, ↓ IL-6 & TNF-α, higher total effective rate, fewer adverse events	Not Reported
Zhang Y et al., 2024[16]	IL-6, IL-1β, TNF-α, MMP-8	Combination therapy more effective than comparator	Greater reductions in PD, PLI, SBI, lower IL-6/IL-1β/TNF-α/MMP-8 in combination group	Not Reported
Sorsa T et al., 2020[17]	aMMP-8 PoC test (ROC/AUC); SDD (Periostat®) as host modulation via MMP inhibition	Supports HMT + biomarker-based monitoring	aMMP-8 PoC showed superior diagnostic accuracy vs BoP (higher AUC)	Long-term SDD associated with stable peri-implant conditions without clinical/radiographic peri-implantitis (3–17 years)
D'Orto & Polizzi, 2025[18]	Not reported	Adjunct doxycycline improved non-surgical therapy outcomes	Significant reductions in PPD, BoP, PI, and suppuration in test group; controls not significant	Not Reported
Khare et al., 2023[19]	Microbiology (TVC, P. gingivalis, enteric rods)	Adjunct local delivery improved short-term clinical outcomes	Minocycline microspheres and 0.2% CHX gel showed greater PD/BoP reduction (10 days–6 months)	Overall PD reduction at 12 months in all groups, no significant microbiological differences between antimicrobials
Laleman et al., 2020[20]	Microbiology (qPCR peri-implant pathogens); probiotics (L. reuteri)	No meaningful adjunctive benefit for main outcomes	Clinical parameters improved after debridement in both groups, greater reduction in plaque index with probiotics	No additional effect on PPD/BoP, follow-up up to 24 weeks

IL = interleukin, TNF-α = tumour necrosis factor-alpha, GCF = gingival crevicular fluid, MMP = matrix metalloproteinase, aMMP-8 = active MMP-8, PoC = point-of-care, ROC = receiver operating characteristic, AUC = area under the curve, SDD = sub-antimicrobial dose doxycycline, PPD/PD = probing (pocket) depth, mSBI = modified sulcus bleeding index, SBI = sulcus bleeding index, PLI/PI = plaque index, BoP = bleeding on probing, CHX = chlorhexidine, TVC = total viable count, mPI = modified plaque index, mGI = modified gingival index, CBL = crestal bone level, NSMD = non-surgical mechanical debridement, HMT = host modulation therapy.

Risk of bias in studies

Tabel 4 The synthesis table

JBI assessment tools	Author & Year of article	Criteria Based on Questions in Checklist Form												Result (%)
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	
RCT	Wei et al., 2020[15]	√	√	√	√	?	?	√	√	√	√	√	√	√	84.6 (Low risk)
	Khare et al.,2023	√	√	√	√	?	?	√	√	√	√	√	√	√	84.6 (Low risk)
	Laleman et al., 2020[20]	√	√	√	√	√	√	√	√	√	√	√	√	√	100 (Low risk)
	Alhumaidan et al.,2022[21]	√	√	√	√	?	√	√	√	√	√	√	√	√	92.3 (low risk)
Average score															90.4 (low risk)
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11			
Cohort study	D'Orto & Polizzi, 2025[18]	√	√	√	√	?	?	√	√	√	√	√			81.8 (low risk)
	Zhang Y et al., 2024[16]	√	√	√	√	?	?	√	√	√	?	√			72.7 (moderate risk)
Average score															77.3 (moderate risk)
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10				
Case series study	Sorsa et al., 2020[17]	√	?	√	√	√	√	√	√	√	√				90 (low risk)
Average score															90 (low risk)

Microbiological analysis

Two studies reported microbiological outcomes.[19,20] Khare et al[19] measured total viable counts, *Porphyromonas gingivalis*, and enteric rod counts after five different local drug delivery regimens. All groups showed reductions in indicator bacteria, with no significant intergroup differences at 12 months. Laleman et al[20] used quantitative PCR to track peri-implant pathogens after *L.reuteri* probiotic application. They detected no significant intergroup or intragroup differences at any time point up to 24 weeks, even though PI improved more in the probiotic group. Local tetracycline-based adjuncts therefore appear to shift microbial counts in the short term, while a single-strain probiotic does not seem to reshape the peri-implant microbial composition in a meaningful way.

DISCUSSION

This review examined human clinical evidence on host modulation therapy as an adjunct in peri-implantitis. The seven included studies, run in seven different countries between 2020 and 2025, suggest that adjunctive HMT, most clearly local tetracycline delivery, gives clinically useful short-term improvements when added to standard non-surgical therapy. Whether those benefits last and what role non-tetracycline agents have are still open questions. Local tetracycline delivery as 14% doxycycline gel, minocycline hydrochloride ointment, minocycline microspheres, slow-release doxycycline gel, or tetracycline fibers reduced PPD, BoP, PI, and suppuration across several study designs.[15,16,18,19,21] These findings fit the known pharmacology of tetracyclines, which inhibit MMP-8 and MMP-9 in particular, modulate cytokine secretion, and have antioxidant effects independent of their antibacterial action.[8,12,17] The combined antibacterial and host-modulatory effect is the most likely reason these agents outperformed comparators such as iodine glycerin[15] or chlorhexidine alone[19] in the short-term. Long-term efficacy is harder to pin down. In Khare et al, between group differences in PD reduction faded by 12 months, even though all groups continued to improve on average.[19] Alhumaidan et al reported no extra benefit from a single dose of minocycline microspheres at six months.[21] Both findings suggest that the size and duration of the effect depend on how often the agent is given and on the delivery vehicle. Sorsa et al proposed continuous low-dose SDD as a way to keep peri-implant tissues stable over many years.[17] The mechanistic case is reasonable and is supported by RCTs in periodontitis,[8,12] but the primary clinical evidence in peri-implantitis is still limited to a small case series.

L.reuteri probiotic only reduced plaque index, with no useful effect on PPD or BoP at the implant level.[20] Earlier reviews and clinical work have reported similarly inconsistent or limited probiotic benefits in peri-implant disease, especially when probiotics are compared with established mechanical or pharmacological adjuncts.[5,6] Differences in strain, dose, route of delivery, and follow-up likely explain part of the va-riation between trials. Biomarker data, especially aMMP-8, IL-1β, TNF-α, and MMP-8, support a biological basis for HMT in peri-implantitis.[15-17] Sorsa et al's validation of the aMMP-8 chair-side test offers a practical way to monitor HMT response at the chair, since residual collagenolytic activity is not always visible on conventional clinical examination.[17] Zhang et al went further and showed that IL-1β and TNF-α were independent predictors of treatment success after HMT, which opens the door to biomarker-guided therapy in future trials.[16]

A few wider points are worth noting. Peri-implantitis is increasingly seen as local and systemic inflammatory condition, with elevated MMP -8 and pro-inflammatory cytokines in oral fluids and circulation.[8,10,17] HMT may therefore offer benefits beyond the implant site by lowering systemic low-grade inflammation. Patient-level risk factors such as smoking, diabetes, and a history of periodontitis matter too, because they shift the response to any adjunctive treatment.[3,4,8] The prosthodontic side of management (prosthesis design, occlusion, and supportive maintenance) also has to be considered alongside HMT.[22,23]

There are several limitations to this review and to the underlying evidence. Only seven studies met the eligibility criteria after searching four databases, which itself shows how thin the primary clinical evidence on adjunctive HMT in peri-implantitis still is. The included studies were also heterogeneous in design (RCT, retrospective cohort, retrospective comparative, case series), intervention type, dosing schedule, and follow-up duration, which is why we did not pool the data. Three of the seven studies were retrospective or non-randomized and carry a risk of selection and confounding bias.[16-18] Follow-up was generally short, from 12 weeks[20] to 12 months,[19] apart from one case series that reported very long observation.[17]

Biomarker reporting was inconsistent, and only three studies reported quantitative biomarker outcomes.[15-17] Future research should focus on adequately powered, multicenter RCTs with standardized protocols (dose, frequency, and form of delivery), comparable inclusion criteria, and at least 12 to 24 months of follow-up. Head-to-head trials would be especially useful: systemic versus local HMT, tetracycline versus non-tetracycline agents (statins, NSAIDs, pro-resolving lipid mediators), and probiotic versus antibiotic adjuncts. Standardized biomarker reporting using validated point-of-care platforms such as the aMMP-8 test would let researchers compare biological response across studies. Patient-reported outcomes and cost-effectiveness analyses would add the practical context that clinicians and patients ac-

tually need.

It is concluded that adjunctive HMT, most clearly local doxycycline and minocycline delivery, gives short-term clinical improvements in peri-implantitis, with reductions in PD, bleeding, plaque, and suppuration, and lower pro-inflammatory biomarkers where measured. Systemic SDD looks promising for long-term peri-implant stability, but the supporting evidence is limited to a small case series. *L.reuteri* probiotic did not show consistent clinical benefit in established peri-implantitis. The methodological quality of the available evidence is acceptable, but heterogeneity, short follow-up, and small samples limit how far the findings can be generalized. Larger RCTs with longer follow-up, biomarker-guided monitoring, and integration with prosthodontic maintenance are needed before HMT can be recommended as routine practice in peri-implantitis.

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Conflict of interest

No conflict of interest was declared by the author.

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