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Efficacy of Minocycline Hydrochloride Combined with Tinidazole in the Treatment of Chronic Periodontitis and Its Impact on Inflammatory Cytokine Levels

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ABSTRACT

The aim of this study was to evaluate the clinical and inflammatory outcomes of minocycline hydrochloride combined with tinidazole in patients with chronic periodontitis.

PubMed, Cochrane Library, Embase, CNKI, WanFang Data, and VIP were searched through December 2025 for randomized and nonrandomized controlled studies. Randomized trials were assessed using the Cochrane Risk of Bias tool, while the cohort study was assessed using ROBINS-I. Meta-analysis was conducted using RevMan 5.3. Random-effects models were applied when substantial heterogeneity was present, and sensitivity analyses were performed by excluding the cohort study.

Fourteen studies were included. Compared with the control treatment, combination therapy was associated with greater improvements in gingival index (MD=−0.71; 95% CI, −0.77 to −0.65), probing pocket depth (MD=−0.87; 95% CI, −1.07 to −0.66), clinical attachment level (MD=−0.77; 95% CI, −1.06 to −0.49), plaque index (MD=−0.38; 95% CI, −0.45 to −0.32), and sulcus bleeding index (MD=−0.68; 95% CI, −0.96 to −0.40). Changes were also observed in several inflammatory and immune-related indicators, whereas CRP did not differ significantly between the groups. Substantial heterogeneity was present for most outcomes.

Overall, minocycline hydrochloride combined with tinidazole may provide additional short-term benefits for patients with chronic periodontitis. Nevertheless, these findings should be interpreted cautiously because of methodological limitations, substantial heterogeneity, incomplete safety reporting, and short follow-up periods.

Keywords: Combination; Cytokines; Drug therapy, Minocycline; Tinidazole; Tinidazole chronic periodontitis

INTRODUCTION

Oral health functions as a pivotal defensive barrier safeguarding overall physical well-being, as its maintenance status exerts a direct and profound influence on an individual's long-term health trajectory and daily quality of life. Chronic periodontitis (CP), a globally prevalent chronic infectious disorder affecting the oral cavity, imposes a substantial burden on the adult population across various regions and demographic groups.[1] Triggered by the formation and accumulation

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of dental plaque biofilm—a complex microbial community adhering to tooth surfaces—CP initiates a sustained inflammatory cascade within the periodontal supporting tissues (encompassing gingiva, periodontal ligament, cementum, and alveolar bone).[2] Over time, this persistent inflammation progresses to induce pathological changes such as periodontal pocket formation, progressive alveolar bone resorption, gingival recession, and, in advanced stages, irreversible tooth loss.[3] Notably, CP stands as the leading etiological factor contributing to tooth loss among adults worldwide, underscoring its clinical and public health significance.

Epidemiological investigations consistently reveal that the global prevalence of CP remains at a persistently high level, with a distinct age-dependent distribution pattern.[4] In the Chinese population, for instance, among individuals aged 35–44 years, the detection rate of deep periodontal pockets (defined as ≥6 mm in depth) is approximately 6.9%, while the prevalence of clinical attachment loss (≥4 mm) reaches 33.2%. As age advances, these prevalence rates escalate markedly: in the 55–64 age group, the detection rate of deep periodontal pockets climbs to 15.1%, and clinical attachment loss affects nearly 70% (69.9%) of individuals. Among those aged 65–74 years, the rate of clinical attachment loss further rises to 74.2%.[5] Beyond its localized oral manifestations, CP is increasingly recognized as a systemic health concern: as a chronic inflammatory focus, it can propagate systemic inflammation via the circulatory system. This propagates a heightened risk of multiple systemic comorbidities, including type 2 diabetes mellitus (by impairing insulin sensitivity), cardiovascular diseases (such as atherosclerosis and coronary artery disease), respiratory infections (e.g., pneumonia), and adverse pregnancy outcomes (including preterm birth and low birth weight).[6–10] This dual impact—on both oral health and systemic well-being—also imposes considerable socioeconomic costs, including direct medical expenditures and indirect losses due to reduced work productivity. Consequently, the development of safe, effective, and cost-efficient treatment strategies for CP is not only a central research priority in the field of dentistry but also an urgent objective in public health management.

The pathogenesis of CP involves a complex interplay between microbial colonization and the host's immunoinflammatory reactions. Dental plaque biofilms contain a broad spectrum of pathogenic microbes, including major periodontal pathogens: *Porphyromonas gingivalis* (a keystone organism driving CP progression), *Prevotella intermedia*, *Prevotella melaninogenica*, *Fusobacterium nucleatum* (a bridging microbe connecting early and late biofilm colonizers), and *Aggregatibacter actinomycetemcomitans*.[11] Metabolic end products of these pathogens—such as lipopolysaccharides (LPS), proteolytic enzymes, and cytotoxic toxins—stimulate the host's innate immune defenses, initiating a localized inflammatory response.

Within this cascade, the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome exerts a pivotal regulatory function: upon activation by periodontal pathogens (or their components), it promotes the secretion of proinflammatory cytokines (e.g., interleukin-1β [IL-1β] and interleukin-18 [IL-18]) and damage-associated molecular patterns, which further enhance inflammatory cell infiltration and accelerate periodontal tissue breakdown.[12]

Concurrently, both systemic and local inflammatory mediators—including C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and matrix metalloproteinase-9 (MMP-9)—directly contribute to the degradation of periodontal connective tissue and osteoclastic resorption of alveolar bone. Reduced secretory immunoglobulin A (sIgA) levels in gingival crevicular fluid (GCF) also reflect impaired mucosal immune function in the periodontium, weakening the host's capacity to control microbial overgrowth.[13]

These dynamic alterations in clinical and biochemical markers not only act as core biomarkers for tracking CP progression but also represent key therapeutic targets for assessing treatment efficacy. Thus, an optimal CP management strategy should ideally address 3 interconnected objectives: eliminating or inhibiting pathogenic periodontal microbes, modulating the host's excessive inflammatory response (to prevent tissue injury), and reducing proinflammatory cytokine levels—thereby supporting the repair and functional remodeling of damaged periodontal tissues.

At present, mechanical debridement constitutes the foundational treatment approach for CP, primarily encompassing supragingival scaling (removal of plaque and calculus above the gingival margin), subgingival scaling (elimination of subgingival plaque and calculus), and root planing (smoothing of root surfaces to remove bacterial toxins and calculus remnants).[14] The core

objective of these procedures is to eliminate dental plaque and calculus—the primary etiological agents of CP. However, mechanical debridement has inherent limitations: it is challenging to fully eradicate pathogens that are hidden in deep periodontal pockets (especially those >6 mm in depth), furcation areas (the space between multi-rooted teeth), and within the irregularities of cementum surfaces. For patients with moderate to severe CP, mechanical treatment alone often fails to adequately control the progression of inflammation, as residual pathogens can recolonize the periodontal environment and reinitiate the inflammatory cascade.[15] Clinical studies have confirmed that mechanical debridement alone can only reduce periodontal pocket depth (PPD) to a limited extent, and approximately 32% of patients with moderate CP require adjunctive pharmacotherapy to achieve optimal clinical outcomes (e.g., sustained reduction in PPD and improvement in clinical attachment level).[16] Therefore, antimicrobial agents play a vital auxiliary role in CP management: the rational selection of antibiotics can compensate for the shortcomings of mechanical therapy, further eliminate residual pathogens, suppress inflammatory activity, and alleviate clinical symptoms (such as gingival bleeding and pain).

Minocycline hydrochloride—a second-generation tetracycline with broad antimicrobial coverage—exerts strong bactericidal and bacteriostatic effects against diverse microorganisms. It targets multiple aerobic bacteria (e.g., *Staphylococcus*, *Streptococcus*, *Neisseria gonorrhoeae*, *Escherichia coli*) as well as key periodontal pathogens like *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. Beyond its antibacterial action, this agent also has anti-inflammatory properties: it curbs the production and release of proinflammatory cytokines (e.g., TNF-α, IL-1β), contributing to its extensive use in CP treatment.[17] When applied locally as an ointment directly into periodontal pockets, it quickly forms a high-concentration drug depot at the lesion site: peak drug levels are reached within 2 hours, and its effects last up to 168 hours (7 days), enabling sustained antibacterial and anti-inflammatory action.

Tinidazole—a nitroimidazole derivative—targets anaerobic bacteria (the dominant pathogens in periodontal pockets) selectively, making it a common choice for treating anaerobic infections. In periodontitis care, it precisely eliminates anaerobic pathogens in periodontal pockets, complementing minocycline hydrochloride's antimicrobial spectrum (which covers both aerobic and anaerobic organisms).[18] Due to their complementary antimicrobial coverage and potential synergistic anti-inflammatory effects, the minocycline hydrochloride–tinidazole combination is increasingly used in clinical practice to expand the antimicrobial range, enhancing therapeutic efficacy, and more effectively regulating the local and systemic inflammatory response in CP patients.

Some research findings indicate that the combined therapy group achieves a significantly higher total clinical effectiveness rate (defined as the proportion of patients with marked improvement in periodontal parameters) compared to monotherapy groups (e.g., minocycline hydrochloride alone or tinidazole alone). Additionally, the combined treatment group demonstrates superior improvements in periodontal clinical parameters (including plaque index, gingival bleeding index, PPD, and clinical attachment level) and greater reductions in proinflammatory factors (such as CRP, TNF-α, and IL-1β), without a significant increase in adverse reactions (e.g., gastrointestinal discomfort or local irritation).[19,20] However, other studies have reported conflicting conclusions—attributed to differences in study design factors such as sample size (small vs. large cohorts), patient inclusion criteria (e.g., severity of CP), treatment duration (short-term vs. long-term), and methods for detecting inflammatory cytokines (serum vs. GCF measurements). These inconsistencies have resulted in a lack of consistent, reliable evidence regarding the overall efficacy and safety of this combination regimen. Furthermore, most existing studies are small-sample, single-center clinical observations, which limits their generalizability (representativeness) and methodological reliability. As a result, it remains challenging to comprehensively and accurately assess the application effects of this combination therapy across diverse patient populations (e.g., different age groups or comorbidity statuses) and disease severities, as well as its specific impact on the dynamic changes of inflammatory cytokine levels.

As a core method of systematic review, meta-analysis enables the quantitative synthesis of data from multiple relevant studies through comprehensive literature retrieval, strict study screening, and standardized data extraction. This approach helps to minimize the bias associated with individual studies (e.g., selection bias or small-sample variability) and enhances the reliability and persuasiveness of the overall conclusions. Given the limitations (e.g., small sample

sizes) and inconsistencies in current clinical research on minocycline hydrochloride combined with tinidazole for CP, a systematic meta-analysis is urgently needed to integrate and evaluate the existing evidence base. The present study aims to conduct a comprehensive search of both domestic and international clinical controlled trials (including randomized controlled trials and nonrandomized controlled trials) investigating the combination therapy for CP. Accordingly, this systematic review and meta-analysis evaluated the effects of minocycline hydrochloride combined with tinidazole on periodontal clinical outcomes, including GI, PPD, CAL, PLI, and SBI, as well as inflammatory and immune-related indicators, including CRP, MCP-1, IL-6, TNF-α, TGF-β, IL-10, Th17 cells, and Treg cells. The stability of the pooled estimates was further examined through sensitivity analyses.

MATERIALS AND METHODS

Search Strategy

This systematic review was conducted in accordance with the PRISMA 2020 statement. Six electronic databases were searched, including PubMed, Cochrane Library, Embase, CNKI, WanFang Data, and VIP Database. The initial search was performed in December 2025, and the final search update was completed in December 2025. No restriction was imposed on publication year. Chinese and English publications were eligible.

The search strategy combined subject headings and free-text terms related to minocycline hydrochloride, tinidazole, chronic periodontitis, and controlled clinical study design. The English search terms included "minocycline hydrochloride," "minocycline," "tinidazole," "chronic periodontitis," "periodontitis," "randomized controlled trial," "controlled clinical trial," and "clinical study." Equivalent Chinese terminology was applied to Chinese databases. Boolean operators, including AND and OR, were used to combine the search terms. The reference lists of the included studies and relevant reviews were also manually screened to identify additional eligible studies.

Eligibility Criteria

Inclusion criteria were as follows: (1) Study design: randomized controlled trials or controlled clinical studies with comparable baseline characteristics; (2) Population: adult patients diagnosed with chronic periodontitis; (3) Intervention: minocycline hydrochloride combined with tinidazole; (4) Control: tinidazole alone, conventional periodontal treatment, or placebo control according to the original study design; (5) Outcomes: at least one periodontal clinical indicator, such as gingival index (GI), probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PLI), or sulcus bleeding index (SBI), or one inflammatory or immune-related indicator, such as CRP, monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), TNF-α, transforming growth factor-β (TGF-β), interleukin-10 (IL-10), T_H17, or regulatory T cells (Treg), with extractable quantitative data.

Exclusion criteria were as follows: (1) Reviews, case reports, animal studies, cell experiments, or conference abstracts without full data; (2) Studies involving patients with systemic diseases that could substantially affect inflammatory cytokine levels; (3) Studies in which either group received additional periodontal surgery or other confounding interventions; (4) Duplicate publications or studies with incomplete outcome data; (5) Studies published in languages other than Chinese or English.

Study Selection and Data Extraction

Two trained researchers independently conducted literature screening and data extraction, then cross-validated their results. Initial screening relied on titles/abstracts to rule out ineligible studies; promising candidates underwent full-text evaluation for final inclusion.

Extracted data covered 5 categories: (1) Study fundamentals (first author, year, region); (2) Participant baselines (sample size, age, gender, CP severity); (3) Intervention specifics (administration route, dosage, duration for both groups); (4) Outcome metrics (time points, values, SD, sample size); (5) Risk-of-bias indicators.

Discrepancies were resolved via discussion; unresolved cases were referred to a senior evidence-based medicine investigator. We documented the number of studies at each screening stage and exclusion reasons, then constructed a literature selection flow diagram.

Quality Assessment

The methodological quality of included RCTs was evaluated using the Cochrane Collaboration's Risk of

Bias tool (Handbook v5.1.0)[21] and RevMan 5.3 software. This assessment addressed 7 core domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and study staff; (4) blinding of outcome assessors; (5) outcome data completeness; (6) selective reporting; and (7) other potential biases (e.g., baseline characteristic imbalance, conflicts of interest).

Each domain was independently categorized into 3 risk levels: "low," "high," or "unclear." Studies were also assigned an overall quality grade: Grade A (full adherence to criteria, minimal bias), Grade B (partial adherence, moderate bias), and Grade C (failure to meet key criteria, substantial bias).

Statistical Analysis

Meta-analysis was performed using RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs), and continuous outcomes were expressed as mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs. Heterogeneity was assessed using the χ^2 test and I^2 statistic. When $p \geq 0.10$ and $I^2 \leq 50\%$, heterogeneity was considered low, and a fixed-effects model was used. When $I^2 > 50\%$, substantial heterogeneity was considered present, and a random-effects model was used.

Sensitivity analyses were performed by sequentially excluding individual studies to examine the stability of the pooled results. Considering that one included study was reported as using a cohort method, an additional sensitivity analysis was conducted by excluding this study. Publication bias was assessed using funnel plots when at least 10 studies were available for an outcome.

RESULTS

Literature Search Results

PRISMA-compliant literature screening (workflow: Figure 1) yielded 467 initial records from 6 databases (PubMed, Cochrane Library, Embase, CNKI, WanFang Data, VIP Database) via keywords on minocycline hydrochloride, tinidazole, chronic periodontitis, and inflammatory factors. Post-duplicate removal (EndNote X9), 318 studies underwent title/abstract screening; 268 were excluded (non-RCTs [n=112], irrelevant conditions [n=76], non-combination therapy [n=80]).

Fifty studies proceeded to full-text review; 36 were excluded (systemic diseases [n=9], confounding treatments [n = 12], incomplete outcomes [n=10], non-Chinese/English publications [n=5]). Ultimately, 14 controlled clinical studies were included in the qualitative and quantitative analyses (Table 1). Most studies reported random allocation, while one study was reported as using a cohort method. Therefore, this study was further examined in a sensitivity analysis.

Risk-of-bias assessment showed that the methodological quality of the included studies was variable (Figure 2 and Figure 3). Although most studies reported baseline comparability and several used a random number table method, allocation concealment, blinding, outcome assessment, and trial registration were insufficiently described in many studies. Therefore, several domains were judged as having unclear risk rather than low risk. Because most included studies were single-center studies with relatively small sample sizes, the possibility of selection bias, performance bias, and reporting bias could not be excluded.

Meta-analysis Results

Because substantial heterogeneity was observed for most pooled outcomes, random-effects models were used when I^2 was greater than 50%. Sensitivity analyses based on sequential exclusion of individual studies showed that the direction of the pooled estimates was generally unchanged. However, given the high heterogeneity and limited methodological quality of the included studies, the pooled results should be interpreted cautiously.

Improvement in Gingival Index (GI)

Eight trials documented post-treatment GI changes. Due to high heterogeneity (I^2=79%, p<0.001), a random-effects model was applied. Meta-analysis revealed a significant intergroup difference (MD=−0.71; 95% CI, −0.77 to −0.65; p<0.01), demonstrating that minocycline hydrochloride combined with tinidazole enhanced GI more effectively than tinidazole monotherapy in chronic periodontitis patients (Figure 4).

Table 1. Basic characteristics of the included studies.

Author	Year	Region	Grouping method	Gender (male/female), control	Gender (male/female), treatment	Age, y, control	Age, y, treatment	Treatment duration, control	Treatment duration, treatment	Treatment method, control	Treatment method, treatment
Chen et al[22]	2025	China	RNTM	37/26	35/28	NR	NR	5 days	5 days	TNZ	TNZ+MH
Liu et al[23]	2023	China	RNTM	23/21	25/19	46.34±9.50		4 weeks	4 weeks	TNZ	TNZ+MH
He et al[24]	2022	China	RNTM	32/28	33/27	42.35±5.17	43.02±5.49	4 weeks	4 weeks	TNZ	TNZ+MH
Yan et al[19]	2024	China	RNTM	26/24	27/23	52.34±4.65	52.29±4.62	4 days	4 days	TNZ	TNZ+MH
Wang et al[20]	2023	China	RNTM	31/19	29/21	47.3±9.8	46.4±9.1	4 weeks	4 weeks	TNZ	TNZ+MH
Liu et al[25]	2023	China	RNTM	24/11	23/12	54.12±8.26	53.25±8.46	4 weeks	4 weeks	TNZ	TNZ+MH
Xia et al[26]	2023	China	RNTM	25/22	26/22	44.26±2.56	44.54±2.34	4 weeks	4 weeks	TNZ	TNZ+MH
Xu et al[27]	2022	China	RNTM	32/29	36/25	26.40±2.37	27.40±2.60	4 weeks	4 weeks	TNZ	TNZ+MH
Ou et al[28]	2022	China	LM	25/21	26/20	39.8±4.1	39.6±4.4	1 month	1 month	TNZ	TNZ+MH
Yan et al[29]	2021	China	RNTM	31/29	32/28	55.42±2.20	55.45±2.24	2 months	2 months	TNZ	TNZ+MH
Liu et al[30]	2019	China	RNTM	28/15	25/18	52.73±10.12	53.12±8.35	4 weeks	4 weeks	TNZ	TNZ+MH
Jiang et al[31]	2020	China	RNTM	28/22	30/20	32.74±4.11	37.65±5.07	4 weeks	4 weeks	TNZ	TNZ+MH
Zhang et al[32]	2018	China	RNTM	25/22	21/26	60.48±3.40	59.76±3.42	4 weeks	4 weeks	TNZ	TNZ+MH
Guo et al[33]	2017	China	RNTM	64/66	62/68	44.2±6.5	44.7±6.2	4 weeks	4 weeks	TNZ	TNZ+MH

The baseline age data for Chen et al were not available in the original report.

For Chen et al and Yan et al, the durations of 5 days and 4 days refer to the reported treatment or observation course rather than independent long-term post-treatment follow-up.

CM: cohort method; LM: lottery method; MH: minocycline hydrochloride; NR: not reported; RNTM: random number table method; TNZ: tinidazole.

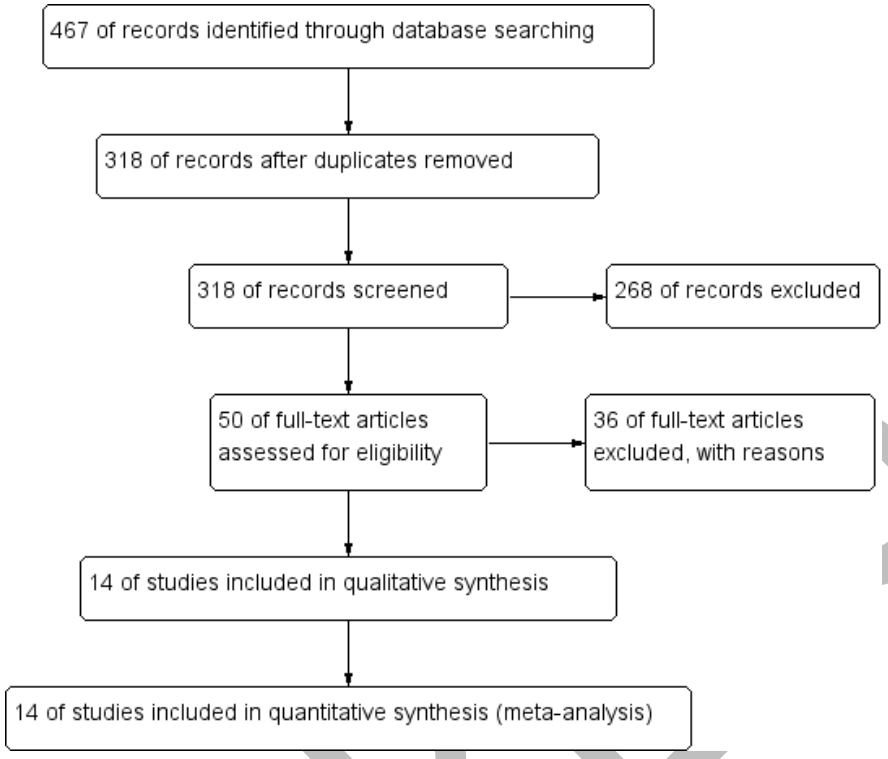

Figure 1. PRISMA flow diagram of study selection

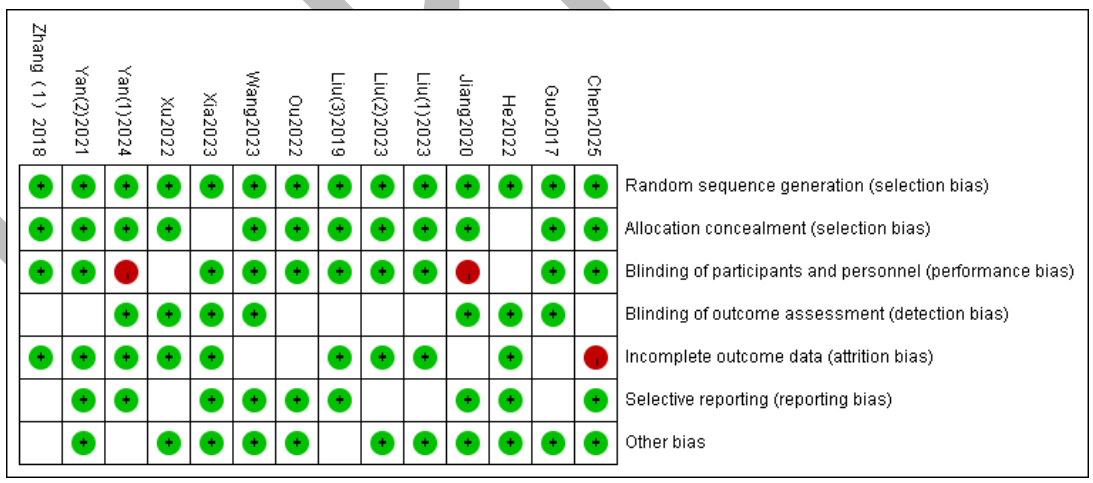

Figure 2. Risk-of-bias graph

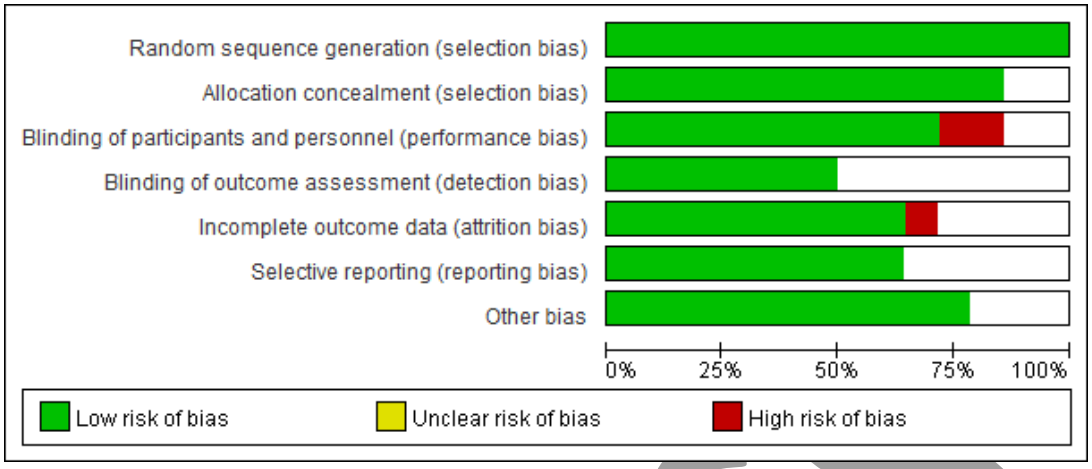

Figure 3. Risk-of-bias summary

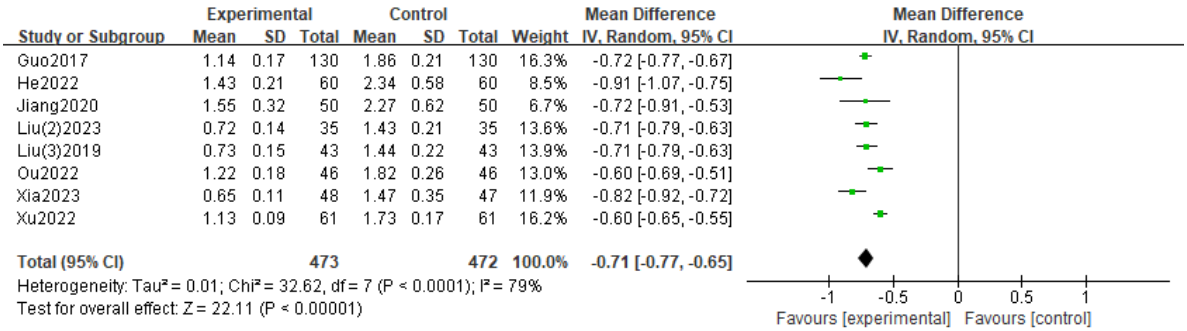

Figure 4. Forest plot for gingival index

Improvement in Probing Pocket Depth (PPD)

Nine trials reported PPD. Given the extremely high heterogeneity (I^2=93%, p<0.00001), a random-effects model was used. Meta-analysis showed a significant intergroup difference (MD=−0.87; 95% CI, −1.07 to −0.66; p<0.00001), suggesting that minocycline hydrochloride combined with tinidazole was associated with greater PPD reduction than the control treatment in patients with chronic periodontitis (Figure 5).

Improvement in Clinical Attachment Level (CAL)

Five trials reported CAL data. High heterogeneity (I^2=91%, p<0.0001) led to the use of a random-effects model. Meta-analysis revealed a significant intergroup difference (MD=−0.77; 95% CI, −1.06 to −0.49; p<0.0001), indicating that the combined regimen was associated with greater improvement in CAL than the control treatment (Figure 6).

Improvement in Plaque Index (PLI)

PLI outcomes were reported in 11 trials. High heterogeneity was noted across these studies (I^2=89%, p<0.00001), so a random-effects model was applied for data pooling. Meta-analysis revealed a significant intergroup difference (MD=−0.38; 95% CI, −0.45 to −0.32; p<0.00001), indicating that minocycline hydrochloride combined with tinidazole was more effective than tinidazole monotherapy in reducing PLI in chronic periodontitis patients (Figure 7).

Improvement in Sulcus Bleeding Index (SBI)

Six trials documented post-treatment SBI changes. Extremely high heterogeneity (I^2=98%, p<0.00001) led to the use of a random-effects model for data pooling. Meta-analysis identified a significant intergroup difference (MD=−0.60; 95% CI, −0.89 to −0.31; p<0.0001), confirming that minocycline hydrochloride combined with tinidazole was more effective than tinidazole monotherapy in improving SBI in chronic periodontitis patients (Figure 8).

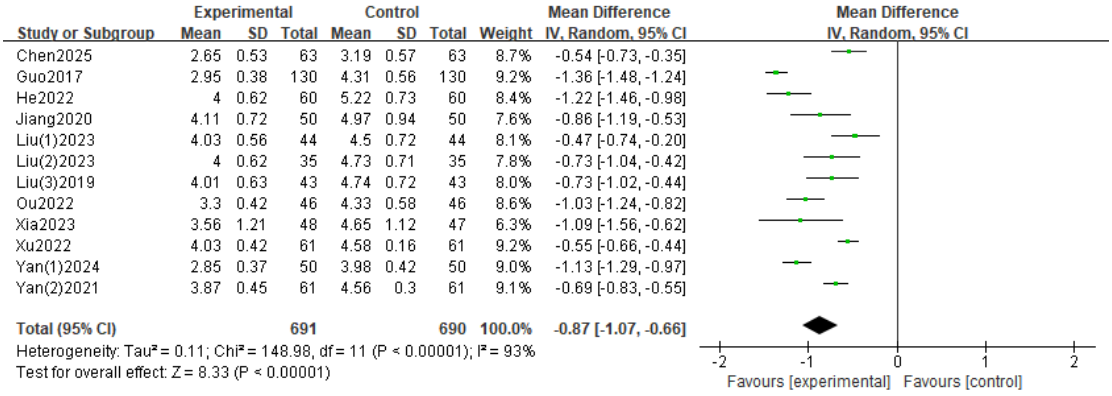

Figure 5. Forest plot for probing pocket depth

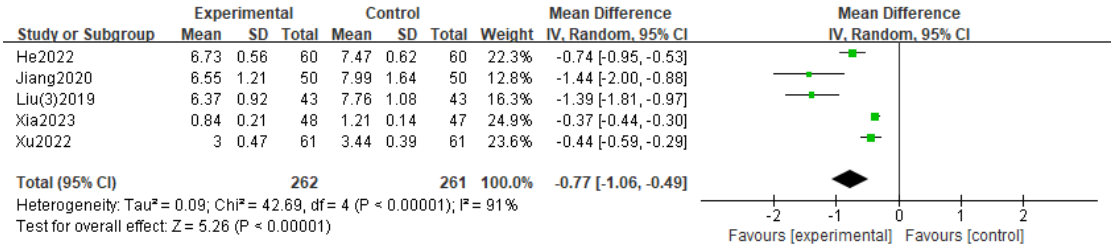

Figure 6. Forest plot for clinical attachment level

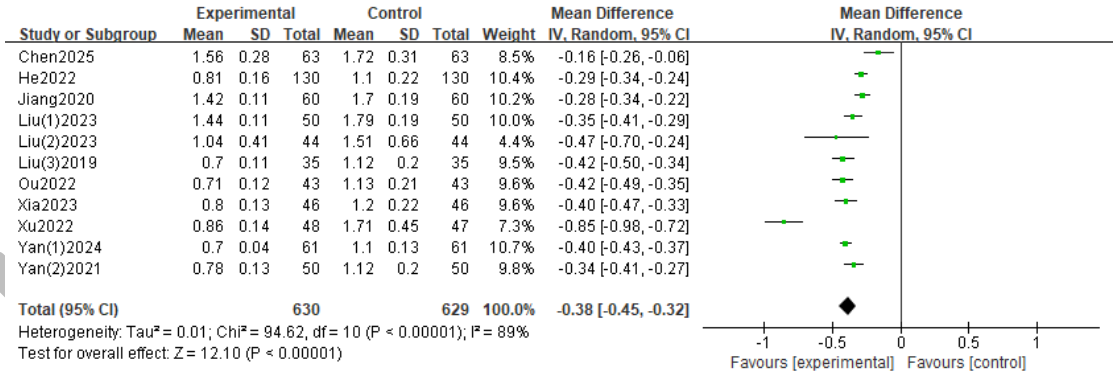

Figure 7. Forest plot for plaque index

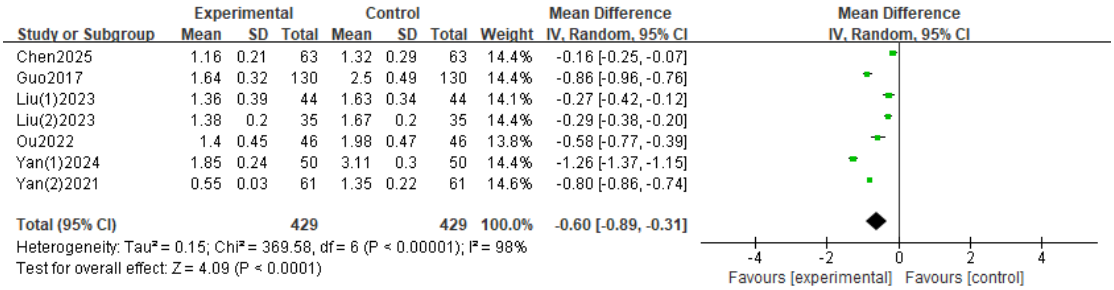

Figure 8. Forest plot for sulcus bleeding index

Changes in C-Reactive Protein (CRP) Levels

Three trials recorded post-treatment CRP level changes. Extremely high heterogeneity (I^2=99%, p<0.00001) was observed across the studies, so a random-effects model was used for data pooling. Meta-analysis found no significant intergroup difference (MD=−0.37; 95% CI, −3.91 to 3.16; p=0.84), indicating that minocycline hydrochloride combined with tinidazole had a similar effect on CRP levels compared to tinidazole monotherapy (or conventional treatment plus placebo) in chronic periodontitis patients (Figure 9).

Changes in Monocyte Chemoattractant Protein-1 (MCP-1) Levels

Five trials documented post-treatment MCP-1 level changes. Extremely high heterogeneity (I^2=96%, p<0.00001) was identified across the studies, so a random-effects model was applied for data pooling. Meta-analysis showed a significant intergroup difference (MD=−19.73; 95% CI, −26.89 to −12.56; p<0.00001), indicating that minocycline hydrochloride combined with tinidazole was more effective than tinidazole monotherapy in reducing MCP-1 levels in chronic periodontitis patients (Figure 10).

Changes in Interleukin-6 (IL-6) Levels

Six trials provided post-treatment IL-6 data. High heterogeneity (I^2=90%, p<0.00001) was observed across the studies, so a random-effects model was applied for data pooling. Meta-analysis revealed a significant intergroup difference (MD=−2.89; 95% CI, −4.17 to −1.62; p<0.00001), showing that minocycline hydrochloride combined with tinidazole was more effective than tinidazole monotherapy in reducing IL-6 levels in chronic periodontitis patients (Figure 11).

Changes in Transforming Growth Factor-β (TGF-β) Levels

Six trials documented post-treatment TGF-β changes. Extremely high heterogeneity (I^2=99%, p<0.00001) was noted across the studies, so a random-effects model was used for data pooling. Meta-analysis identified a significant intergroup difference (MD=11.54; 95% CI, 1.90 to 21.17; p=0.02). As TGF-β is a key anti-inflammatory cytokine, elevated levels reflect enhanced anti-inflammatory activity. These results suggest that minocycline hydrochloride combined with tinidazole was more effective than tinidazole monotherapy in increasing TGF-β levels, thus boosting local anti-inflammatory capacity in chronic periodontitis patients (Figure 12).

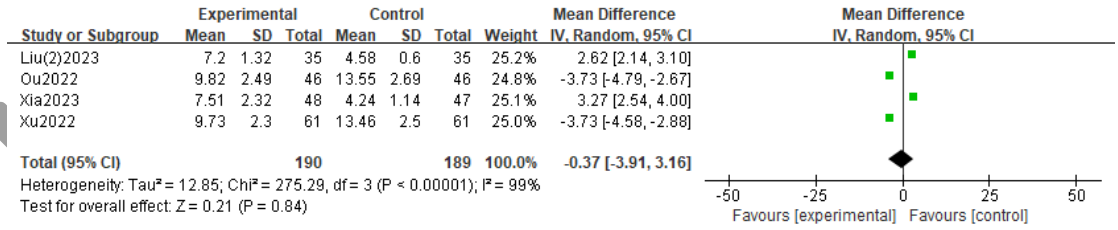

Figure 9. Forest plot for C-reactive protein

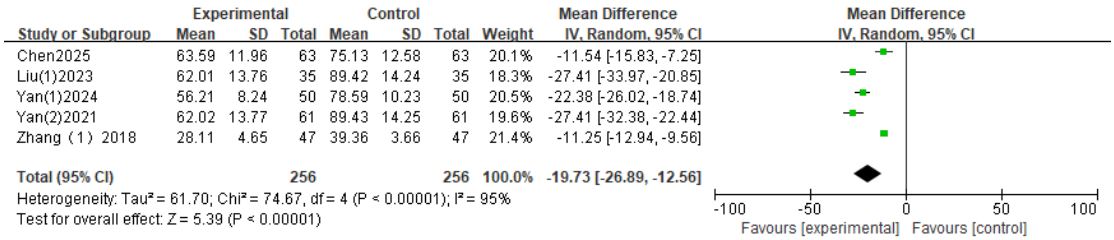

Figure 10. Forest plot for monocyte chemoattractant protein-1

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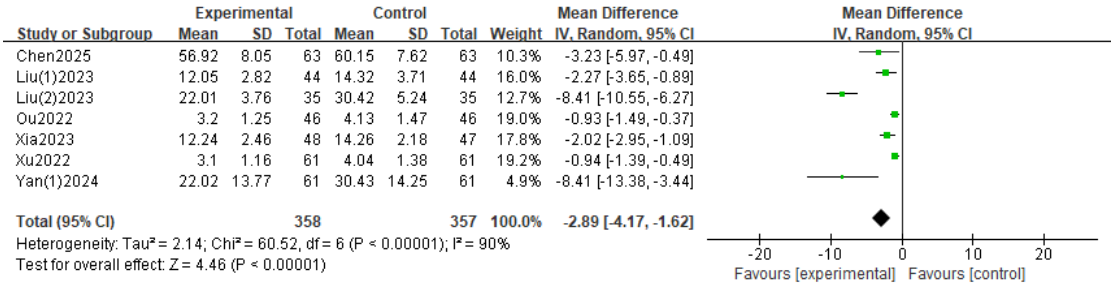

Figure 11. Forest plot for interleukin-6

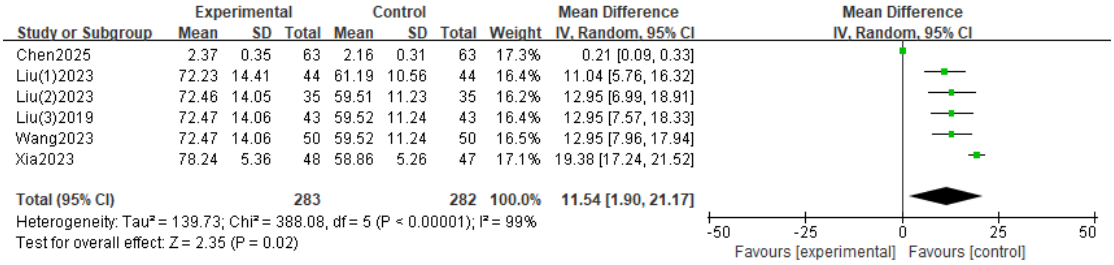

Figure 12. Forest plot for transforming growth factor-β

Changes in Interleukin-10 (IL-10) Levels

Three trials reported post-treatment IL-10 changes. No significant heterogeneity was observed across the studies (I^2=0%, p=1.00), so a fixed-effects model was applied for data pooling. Meta-analysis revealed a significant intergroup difference (MD=3.87; 95% CI, 3.08 to 4.65; p<0.00001), indicating that minocycline hydrochloride combined with tinidazole was more effective than tinidazole monotherapy in increasing IL-10 levels in chronic periodontitis patients (Figure 13).

Changes in T_H17 Levels

Four trials documented post-treatment T_H17 levels. No significant heterogeneity was detected across the studies (I^2=0%, p=0.99), so a fixed-effects model was used for data pooling. Meta-analysis identified a significant intergroup difference (MD=−0.35; 95% CI, −0.41 to −0.28; p<0.00001), suggesting that the combined regimen was associated with lower T_H17 levels than the control treatment (Figure 14).

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Changes in Treg Levels

Four trials reported post-treatment Treg level changes. No significant heterogeneity was observed across the studies (I^2=0%, p=1.00), so a fixed-effects model was applied for data pooling. Meta-analysis revealed a significant intergroup difference (MD=−0.63; 95% CI, −0.79 to −0.47; p<0.00001), indicating that the minocycline hydrochloride–tinidazole combination was more effective than tinidazole monotherapy in reducing Treg levels in chronic periodontitis patients (Figure 15).

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Changes in Tumor Necrosis Factor-α (TNF-α) Levels

Three trials documented post-treatment TNF-α levels. Moderate to high heterogeneity was identified across the studies (I^2=74%, p=0.02), so a random-effects model was applied for data pooling. Meta-analysis revealed a significant intergroup difference (MD=−0.64; 95% CI, −0.71 to −0.57; p<0.00001), suggesting that the combined regimen was associated with lower TNF-α levels than the control treatment (Figure 16).

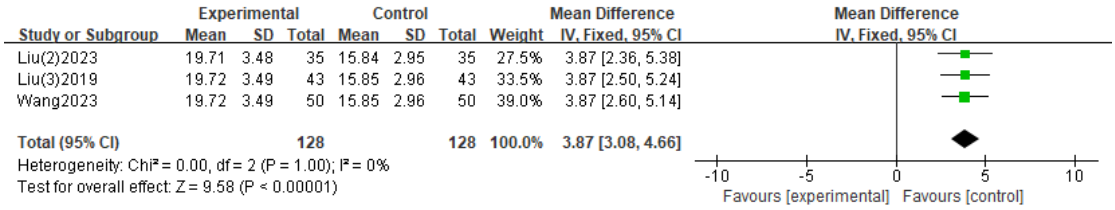

Figure 13. Forest plot for interleukin-10

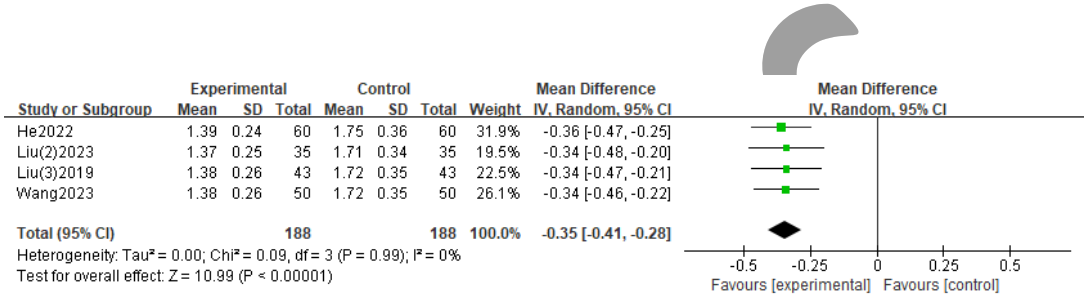

Figure 14. Forest plot for T helper 17 cells

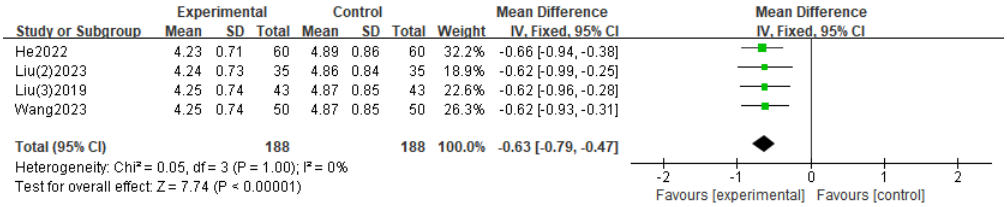

Figure 15. Forest plot for regulatory T cells

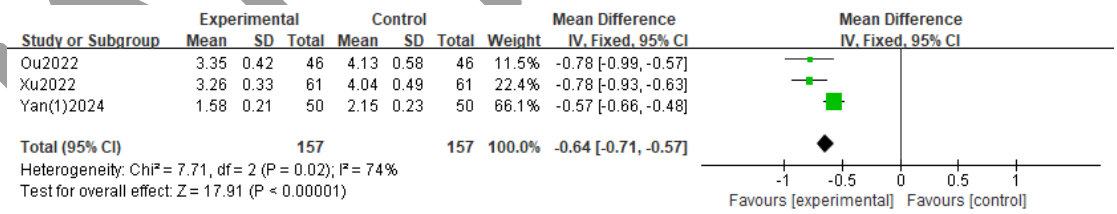

Figure 16. Forest plot for tumor necrosis factor-α

DISCUSSION

Chronic periodontitis is a widespread chronic oral infectious disease worldwide, defined by the gradual destruction of periodontal supporting tissues; it poses a notable risk to adults' oral health and general well-being. The traditional therapeutic framework for CP has long centered on 3 interconnected goals: eliminating pathogenic microbial communities, suppressing excessive immunoinflammatory responses, and promoting the repair and regeneration of damaged periodontal tissues. Developing safe, effective, and clinically practical treatment strategies is not only a long-standing research focus in dentistry[12] but also a pressing need for public health management, considering the disease's high prevalence and socioeconomic impact.

This meta-analysis included 14 controlled clinical studies to assess the clinical efficacy of minocycline hydrochloride combined with tinidazole for chronic periodontitis and its association with inflammatory and immune-related indicators. The pooled results suggested that the combined regimen was associated with greater improvement in GI, PPD, CAL, PLI, and SBI than the control treatment. Several inflammatory markers, including MCP-1, IL-6, TNF-α, and T_H17, were lower after combined therapy, whereas IL-10 and TGF-β were higher. However, these findings should be interpreted as clinical and biomarker associations rather than direct evidence of a confirmed immunological mechanism. No significant difference was observed in CRP, which may reflect the limited sensitivity of systemic inflammatory markers to short-term local periodontal treatment.

The enhanced clinical performance of minocycline hydrochloride–tinidazole combination therapy arises from the precise complementary overlap of their antimicrobial spectra and synergistic boost to anti-inflammatory activities—aligning with CP's core pathogenesis: the "microbial infection–immune-inflammatory cascade." In terms of antimicrobial action, CP's pathogenic microbial community is highly diverse: anaerobic bacteria (e.g., *Porphyromonas gingivalis*, a keystone pathogen driving CP progression; *Fusobacterium nucleatum*, a biofilm-bridging organism; *Prevotella intermedia*) are primary etiological agents, while aerobic bacteria like *Aggregatibacter actinomycetemcomitans* contribute to inflammation onset and progression. Dental plaque biofilm formation further strengthens bacterial resistance to host immunity and antimicrobials, worsening tissue damage. Minocycline hydrochloride—a broad-spectrum second-generation tetracycline—exerts strong bacteriostatic effects on aerobic bacteria (e.g., *Staphylococcus*, *Streptococcus*) by binding to the 30S subunit of bacterial ribosomes, inhibiting protein synthesis. It also shows moderate activity against key anaerobic pathogens such as *Porphyromonas gingivalis*.[16] Importantly, when administered locally as a 2% ointment via periodontal pocket injection, it forms a high-concentration drug reservoir at the lesion site, achieving sustained bacterial elimination within the pocket without significant systemic exposure. Tinidazole, a nitroimidazole derivative, displays highly selective cytotoxicity against anaerobic bacteria: it is reduced to reactive nitro radicals within bacterial cells, which disrupt DNA synthesis and induce bacterial apoptosis. With a minimum inhibitory concentration of only 0.125 to 0.5 μg/mL against *Porphyromonas gingivalis* and *Prevotella intermedia*, tinidazole precisely targets the dominant anaerobic pathogens in periodontal pockets.[18] The combination of these 2 agents achieves "full-spectrum antimicrobial coverage" of both aerobic and anaerobic pathogens in the periodontal microenvironment, which directly explains the significant reduction in PLI observed in this study (MD=−0.38; 95% CI, −0.45 to −0.32; p<0.00001). Effective clearance of plaque biofilm reduces the stimulation of periodontal tissues by bacterial metabolites (e.g., lipopolysaccharides, proteolytic enzymes, toxins, and metabolic waste), thereby alleviating local inflammatory manifestations such as gingival hyperemia, bleeding, and periodontal pocket deepening—consistent with the observed improvements in GI and SBI.

From an anti-inflammatory standpoint, minocycline hydrochloride's "nonantibacterial anti-inflammatory activities" set it apart from traditional antibiotics and support the combination therapy's synergistic effects. Specifically, this agent inhibits the synthesis and activation of matrix metalloproteinases (notably MMP-9), lessening collagen breakdown in periodontal connective tissues. It also interferes with the nuclear factor-κB signaling pathway—a key regulator of inflammatory responses—thus curbing the transcription and secretion of proinflammatory cytokines.[12] Tinidazole eliminates anaerobic pathogens, thereby reducing NLRP3 inflammasome activation triggered by bacterial LPS. This in turn limits the release of proinflammatory cytokines (e.g., IL-1β and TNF-α). The cytokine analysis results of this study clearly reflect these combined anti-inflammatory effects.

In terms of proinflammatory factor regulation, the pooled analysis revealed significant reductions in MCP-1 (MD=−19.73; 95% CI, −26.89 to −12.56; p<0.00001), IL-6 (MD=−2.89; 95% CI, −4.17 to −1.62; p<0.00001), TNF-α (MD=−0.64; 95% CI, −0.71 to −0.57; p<0.00001), and T_H17 cell levels (MD=−0.35; 95% CI, −0.41 to −0.28; p<0.00001). These findings indicate that the combination therapy effectively inhibits the activation and chemotaxis of proinflammatory immune cells: MCP-1 reduction blocks the recruitment of monocytes and macrophages to periodontal tissues, while T_H17 cell suppression disrupts the cascade of inflammatory mediator release. Collectively, these effects reduce inflammatory cell infiltration, mitigate connective tissue degradation, and inhibit alveolar bone

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resorption. Regarding anti-inflammatory factor regulation, significant increases were observed in TGF-β (MD=11.54; 95% CI, 9.20 to 21.17; p=0.02) and IL-10 (MD=3.87; 95% CI, 3.08 to 4.65; p<0.00001). TGF-β not only exerts anti-inflammatory effects but also promotes the proliferation of periodontal ligament cells and induces osteoblastic differentiation, facilitating the repair of alveolar bone and periodontal ligament tissues. IL-10 further attenuates inflammatory damage by inhibiting the antigen-presenting function of macrophages and dendritic cells, thereby suppressing excessive proinflammatory cytokine secretion. This regulatory pattern—"downregulating proinflammatory factors and upregulating anti-inflammatory factors"—reflects the remodeling of the local immune-inflammatory network by the combination therapy, which not only halts inflammatory progression but also creates a favorable microenvironment for periodontal tissue repair. Ultimately, this translates to significant reductions in PPD (MD=−0.88; 95% CI, −0.94 to −0.83; p<0.00001) and improvements in CAL (MD=−0.77; 95% CI, −1.06 to −0.49; p<0.0001), fully validating the clinical effectiveness of the combination regimen.

Most outcome indicators in this meta-analysis exhibited high heterogeneity (e.g., PPD: I^2=93%, GI: I^2=79%, TGF-β: I^2=99%, MCP-1: I^2=96%), a common phenomenon in meta-analyses of clinical intervention studies. This heterogeneity primarily stems from 3 key dimensions: variations in intervention protocols, differences in baseline characteristics of study participants, and inconsistencies in outcome measurement methods. In-depth analysis of these sources is critical for interpreting results and guiding future study design.

Regarding intervention protocols, variations in the route of administration, dosage, and treatment duration of minocycline hydrochloride and tinidazole across included studies were major contributors to heterogeneity. Minocycline hydrochloride was administered via either local or oral routes: most studies used 2% minocycline hydrochloride ointment injected locally into periodontal pockets once weekly for 4 to 8 weeks, a regimen that achieves local drug concentrations 100 to 1000 times higher than serum levels, acts directly on the lesion, and minimizes systemic adverse effects.[25] In contrast, a small number of studies used oral formulations (100 mg twice daily), which result in lower local drug concentrations and may cause systemic side effects such as gastrointestinal discomfort. These differences in administration routes directly led to variations in the magnitude of clinical indicator improvement. Similarly, tinidazole regimens varied: oral doses ranged from 400 mg to 500 mg twice daily, with treatment durations of 4 to 8 weeks, leading to differences in drug exposure and antimicrobial efficacy. Additionally, some studies in the combination therapy group concurrently performed basic mechanical treatments (supragingival scaling, subgingival scaling, and root planing), while others lacked clear documentation of such interventions. The presence, absence, and standardization of basic mechanical therapy may have further interfered with clinical outcomes and increased heterogeneity.

In terms of participant baseline characteristics, included studies enrolled patients with a wide range of CP severity: some focused on moderate CP (PPD = 4–6 mm), while others included severe cases (PPD ≥ 6 mm). Patients with severe CP typically exhibit deeper baseline PPD, more intense inflammatory responses, and greater tissue destruction, leading to larger absolute improvements in PPD post-treatment—contributing to heterogeneity in pooled effect sizes. Furthermore, some studies did not explicitly exclude smokers. Smoking is a confirmed CP risk factor (reduces local blood flow, impairs immune function, lowers bacterial sensitivity to antimicrobials), thereby reducing treatment responsiveness. The inclusion of smokers may have widened interstudy differences in treatment outcomes, serving as an additional source of heterogeneity.

Regarding outcome measurement methods, inconsistencies in sample types and detection kits for inflammatory cytokines exacerbated heterogeneity. Some studies measured cytokines in GCF, which directly reflects local periodontal inflammatory status and is highly sensitive to therapeutic changes. In contrast, a few studies used serum samples, which reflect systemic inflammatory levels and are influenced by overall immune status and other potential inflammatory foci. Differences in the dynamic changes of GCF versus serum cytokines may have contributed to heterogeneous results. Additionally, ELISA kits from different manufacturers were used across studies, and variations in detection sensitivity, specificity, and standard curve calibration may have led to fluctuations in measured values for the same indicator. For example, the large variability in pooled TGF-β MD is closely linked to differences in sample types (GCF vs. serum) across studies. These methodological inconsistencies

collectively amplified interstudy heterogeneity. Notably, a random-effects model was used for data pooling for all outcomes with significant heterogeneity, which accounts for true differences in effect sizes across studies and mitigates heterogeneity impacts through weighted averaging, ensuring the reliability of pooled results.

The cytokine regulatory pattern observed in this study—"systematic downregulation of proinflammatory factors and significant upregulation of anti-inflammatory factors"—is consistent with the immunopathological mechanisms of CP. The nonsignificant result for CRP (MD=−0.37; 95% CI, −3.91 to 3.16; p=0.84) requires rational interpretation based on its biological characteristics and study design limitations. Biologically, CRP is an acute-phase reactant that primarily reflects systemic inflammatory status, with low sensitivity to local periodontal inflammation. In CP patients without systemic complications, local treatment has minimal impact on serum CRP levels, making it difficult to detect significant changes. Methodologically, only 3 studies reported CRP data, with a total sample size of fewer than 200 patients—resulting in low statistical power and an increased risk of false-negative results for small-magnitude changes. Additionally, treatment duration may have influenced outcomes: some included studies had a short treatment course (4 weeks), while serum CRP changes typically require a longer duration (8 to 12 weeks) to become evident. Short-term intervention may not have induced detectable fluctuations in serum CRP, contributing to the nonsignificant result.

This study provides high-quality evidence-based support for minocycline hydrochloride combined with tinidazole in CP treatment by systematically integrating existing RCT data, offering complementary value and improvements over previous research. Prior studies on this combination regimen were mostly small-sample, single-center observational studies, and limitations in sample size and study design led to conflicting conclusions: some reported significantly higher total efficacy rates for combination therapy versus monotherapy, with superior improvements in clinical indicators and cytokines; others found no significant efficacy differences and even suggested that excessive combination medication may increase antimicrobial resistance risk. These inconsistencies left clinicians without a unified evidence base for treatment decision-making. This meta-analysis addressed these gaps by comprehensively searching domestic and foreign databases, strictly screening eligible RCTs, and using scientific statistical methods for data synthesis—minimizing individual study bias and enhancing conclusion reliability and persuasiveness. It is the first study to systematically confirm the significant advantages of the combination regimen in improving periodontal clinical indicators and regulating inflammatory balance, resolving inconsistencies in previous research.

Compared with existing related meta-analyses, this study offers 3 key innovations and supplementary values: first, comprehensive outcome indicators. It simultaneously included core clinical parameters (PPD, CAL, etc.) and inflammatory/immune indicators (TNF-α, IL-6, TGF-β, T_H17, Treg), not only evaluating therapeutic efficacy but also dissecting underlying mechanisms, enabling a discussion from "phenomenon" to "essence." Second, expanded research perspectives. By incorporating immune cell subsets (T_H17, Treg), it supplemented insights into the combination therapy's regulation of local periodontal immune balance, enriching mechanistic understanding. Third, meticulous heterogeneity analysis. It explored heterogeneity sources across intervention protocols, study populations, and detection methods, providing targeted suggestions for future study design and improving the scientificity and standardization of subsequent research.

The results of this study have important clinical implications, providing a clear evidence-based basis for optimizing CP treatment regimens. Based on the findings and clinical practice, we propose the following application suggestions: For moderate to severe CP patients, following standardized basic mechanical treatments (supragingival scaling, subgingival scaling, and root planing), minocycline hydrochloride combined with tinidazole is recommended as the preferred adjuvant therapy to eliminate residual pathogens, regulate inflammatory responses, and enhance treatment efficacy. Regarding administration, the regimen of local periodontal pocket injection of 2% minocycline hydrochloride ointment (once weekly for 4 to 6 weeks) combined with oral tinidazole (400 mg twice daily for 5 to 7 days) is preferred, as it achieves high local drug concentrations and systemic synergistic antibacterial effects, ensuring efficacy while minimizing systemic adverse reactions. For mild CP patients, the principle of "mechanical treatment as primary, drug therapy as adjuvant" should be adhered to, avoiding excessive

combination medication; short-term adjuvant therapy is only considered if mechanical treatment yields suboptimal results. During treatment, oral hygiene guidance should be strengthened to improve patients' self-plaque control ability—critical for maintaining efficacy and preventing recurrence. Additionally, active smoking cessation intervention should be provided for smokers, as smoking reduces treatment responsiveness; smoking cessation significantly improves therapeutic outcomes.

This study has several limitations. First, most included studies were single-center studies conducted in China, which limits the generalizability of the findings. Second, the methodological quality of the included studies was limited. Many studies did not clearly describe allocation concealment, blinding, trial registration, or protocol availability, and one study was reported as using a cohort method rather than a clearly randomized method. Third, substantial heterogeneity was observed across most outcomes. Differences in treatment duration, route of minocycline administration, baseline disease severity, sample source for biomarker detection, and study quality may have contributed to this heterogeneity. Fourth, publication bias could not be excluded, especially because most studies were small and regionally concentrated. Fifth, safety outcomes were insufficiently reported, and detailed information on gastrointestinal reactions, local irritation, allergic reactions, fungal overgrowth, drug discontinuation, and antimicrobial resistance was unavailable or incomplete. Finally, all included studies had short treatment or follow-up periods, with the longest follow-up not exceeding 2 months, which limits conclusions about long-term efficacy, durability of CAL improvement, recurrence prevention, antimicrobial resistance, and long-term safety.

In conclusion, minocycline hydrochloride combined with tinidazole may provide additional short-term benefits for improving periodontal clinical parameters in patients with chronic periodontitis and may be associated with favorable changes in several inflammatory and immune-related indicators. However, the current evidence is limited by substantial heterogeneity, unclear risk of bias in several methodological domains, incomplete safety reporting, possible publication bias, and short follow-up duration. Therefore, this regimen may be considered as an adjunctive option after basic periodontal treatment, but its long-term efficacy and safety still require confirmation through large-scale, multicenter, well-designed randomized controlled trials with standardized intervention protocols and extended follow-up.

STATEMENT OF ETHICS

Ethical approval and informed consent were not required because this systematic review and meta-analysis used data from previously published studies and did not involve the direct recruitment of human participants or animals.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

All data supporting the findings of this systematic review are contained within the published article and the studies cited in the reference list.

AI ASSISTANCE DISCLOSURE

No AI tools were used.

REFERENCES

1. Sethi G, Grover V, Gupta J, Jain A. Response to adjunctive antibiotic therapy along with nonsurgical periodontal therapy in the treatment of peri-implantitis and chronic periodontitis patients: An exploratory review. Journal of Indian Society of Periodontology. 2024;28(4):393-406.
2. Wielento A, Lagosz-Cwik KB, Potempa J, Grabiec AM. The Role of Gingival Fibroblasts in the Pathogenesis of Periodontitis. J Dent Res. 2023;102(5):489-96.
3. Cardoso EM, Reis C, Manzanares-Céspedes MC. Chronic periodontitis, inflammatory cytokines, and

interrelationship with other chronic diseases. Postgrad Med. 2018;130(1):98-104.
4. Carvalho-Filho PC, Gomes-Filho IS, Meyer R, Olczak T, Xavier MT, Trindade SC. Role of Porphyromonas gingivalis HmuY in Immunopathogenesis of Chronic Periodontitis. Mediat Inflamm. 2016;2016:7465852.
5. He S, Wei S, Wang J, Ji P. Chronic periodontitis and oral health-related quality of life in Chinese adults: A population-based, cross-sectional study. J Periodontol. 2018;89(3):275-84.
6. Akram Z, Abduljabbar T, Abu Hassan MI, Javed F, Vohra F. Cytokine Profile in Chronic Periodontitis Patients with and without Obesity: A Systematic Review and Meta-Analysis. Dis Markers. 2016;2016:4801418.
7. Zhang D, Liu W, Miao R, Wang L, Zhou X, Wang H, et al. Chronic Periodontitis is a Risk Factor of Renal Dysfunction in Patients with Type 2 Diabetes. Experimental and Clinical Endocrinology & Diabetes : Official Journal, German Society of Endocrinology [and] German Diabetes Association. 2021;129(6):407-12.
8. Bullon P, Newman HN, Battino M. Obesity, diabetes mellitus, atherosclerosis and chronic periodontitis: a shared pathology via oxidative stress and mitochondrial dysfunction? Periodontol 2000. 2014;64(1):139-53.
9. Lei D, Zhou Y, Tang S, Li Y. Effect of chronic periodontitis on quality of life and severity in patients with bronchiectasis. Shanghai Kou Qiang Yi Xue = Shanghai Journal of Stomatology. 2024;33(2):186-9.
10. Mkrtchyan S, Dunamalyan R, Sakanyan G, Varuzhanyan H, Hambardzumyan S, Mardiyan M. EFFECT OF CHRONIC PERIODONTITIS ON HEALTH-RELATED QUALITY OF LIFE AND ANXIETY AMONG PATIENTS IN YEREVAN, ARMENIA. Georgian Medical News. 2023;(335):36-40.
11. Mlachkova A, Popova C, Doseva V. Presence of IL-8 Gene Polymorphism and IL-8 Serum Levels in Patients with Chronic Periodontitis - Literature Review. Folia Medica. 2020;62(2):253-7.
12. Dosseva-Panova VT, Popova CL, Panov VE. Subgingival microbial profile and production of proinflammatory cytokines in chronic periodontitis. Folia Medica. 2014;56(3):152-60.
13. Wu Q, Cao Z, Wu S. Study on the Clinical Efficacy of Combined Therapy with Minocycline Hydrochloride Ointment and Tinidazole for Chronic Periodontitis: Retrospective Study. J Inflamm Res. 2025;18:4641-9.
14. Jervøe-Storm P, Bunke J, Worthington HV, Needleman I, Cosgarea R, MacDonald L, et al. Adjunctive antimicrobial photodynamic therapy for treating periodontal and peri-implant diseases. Cochrane Db Syst Rev. 2024;7(7):CD011778.
15. Abdullah AN, Al-Habib OAM, Mohammed SA. Changes in the level of cytokines in the saliva of hypertensive patients with chronic periodontitis after scaling and root planning. Prostag Oth Lipid M. 2023;169:106765.
16. Singh A, Vasudevan S, Palle AR, Atchuta A, Bhadauriya S. Comparative Evaluation of Scaling and Root Planing with and without Oxygen-releasing Gel in the Treatment of Chronic Periodontitis: A Split-mouth Study. The Journal of Contemporary Dental Practice. 2024;25(5):445-52.
17. van Steenberghe D, Bercy P, Kohl J, De Boever J, Adriaens P, Vanderfaeillie A, et al. Subgingival minocycline hydrochloride ointment in moderate to severe chronic adult periodontitis: a randomized, double-blind, vehicle-controlled, multicenter study. J Periodontol. 1993;64(7):637-44.
18. Yuan Y, Xu J. Application analysis of minocycline hydrochloride ointment combined with tinidazole in the treatment of chronic periodontitis. Minerva Surg. 2024;79(1):123-5.
19. Yan Q. Effect of minocycline hydrochloride ointment in the treatment of chronic periodontitis. Proceeding of Clinical Medicine 2024;33(10):742-4. DOI: 10.16047/j.cnki.cn14-1300/r.2024.10.019.
20. Wang H Y. Clinical effect and safety study of tinidazole tablets combined with minocycline hydrochloride ointment in the treatment of chronic periodontitis. Chinese Journal of Modern Drug Application 2023;17(19):124-6. DOI: 10.14164/j.cnki.cn11-5581/r.2023.19.033.
21. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical Research Ed.). 2011;343:d5928.
22. Chen H, Ma S, Liu X, et al. Clinical study on minocycline combined with tinidazole in the treatment of patients with severe chronic periodontitis. Chinese Journal of Clinical Pharmacology 2025;41(10):1373-8. DOI: 10.13699/j.cnki.1001-6821.2025.10.005.
23. Liu C X. Clinical effect of minocycline hydrochloride ointment combined with tinidazole in the treatment of patients with chronic periodontitis. Tianjin Pharmacy 2023;35(04):47-50.
24. He D W, Sun J. Clinical value of minocycline hydrochloride combined with tinidazole in the treatment

of patients with chronic periodontitis. Guide of China Medicine 2022;20(05):100-102+106. DOI: 10.15912/j.cnki.gocm.2022.05.029.

25. Liu H Y. Safety analysis of minocycline hydrochloride ointment combined with tinidazole in the treatment of chronic periodontitis. Journal of North Pharmacy 2023;20(11):118-20.
26. Xia T, Zhang T J, Dong P. Efficacy of minocycline hydrochloride ointment combined with tinidazole in the treatment of periodontitis and its influence on periodontal indexes of patients. Clinical Rational Drug Use 2023;16(13):19-21+26. DOI: 10.15887/j.cnki.13-1389/r.2023.13.006.
27. Xu C P, Tao Y. Clinical efficacy observation of minocycline hydrochloride ointment combined with tinidazole in the treatment of chronic periodontitis. Journal of Modern Medicine & Health Research 2022;6(21):59-62.
28. Ou S Z, Xu Y X. Clinical efficacy of minocycline hydrochloride ointment combined with tinidazole tablets in the treatment of chronic periodontitis. Journal of Clinical Rational Drug Use 2022;15(03):124-6. DOI: 10.15887/j.cnki.13-1389/r.2022.03.037.
29. Yan Z G. Effects of minocycline hydrochloride ointment combined with tinidazole on oxidative stress response and inflammatory factor levels in gingival crevicular fluid of patients with chronic periodontitis. China Medical Herald 2021;18(30):121-4. DOI: 10.20047/j.issn1673-7210.2021.30.030.
30. Liu Q Z, Pang Z Z, Li Y. Effects of minocycline hydrochloride ointment combined with tinidazole on IL-10, TGF-β levels in gingival crevicular fluid and Th17, Treg levels in peripheral blood of patients with chronic periodontitis. Journal of Clinical and Experimental Medicine 2019;18(09):966-9.
31. Jiang X X. Clinical effect analysis of minocycline hydrochloride combined with tinidazole in the treatment of severe chronic periodontitis. Clinical Medical Engineering 2020;27(03):321-2.
32. Zhang Z B, Zhang Y, Huang W L, et al. Clinical study on tinidazole tablets combined with minocycline hydrochloride ointment in the treatment of chronic periodontitis. Chinese Journal of Clinical Pharmacology 2018;34(03):248-50. DOI: 10.13699/j.cnki.1001-6821.2018.03.017.
33. Guo L, Lin T, Feng Y. Comparison of efficacy and safety of minocycline hydrochloride combined with metronidazole or tinidazole in the treatment of chronic periodontitis. Drug Evaluation Research 2017;40(09):1294-6.