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Review Article

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Chlorhexidine in Restorative Dentistry: Evidence, Controversies, and Clinical Implications

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Abstract

Chlorhexidine is widely used in restorative dentistry because of its broad-spectrum antimicrobial activity, substantivity, and low cost. Beyond its antiseptic properties, chlorhexidine has attracted considerable interest due to its ability to inhibit dentin-derived matrix metalloproteinases and its potential to stabilize the resin–dentin hybrid layer. Despite strong mechanistic and in vitro evidence supporting these biological effects, their translation into consistent long-term clinical benefits remains uncertain. This narrative review critically evaluates the role of chlorhexidine in restorative dentistry from the perspectives of rational drug use and health technology assessment. Evidence from laboratory studies, randomized controlled clinical trials, and systematic reviews was synthesized to examine the pharmacological properties of chlorhexidine, its effects on dentin bonding, cytotoxic potential, and overall safety profile. Particular emphasis is placed on the discrepancy between promising in vitro findings and inconsistent clinical outcomes, as well as on concerns related to cytotoxicity, antimicrobial resistance, and adverse effects. The available evidence does not support the routine use of chlorhexidine in restorative procedures, underscoring the need for selective, indication-based application guided by robust clinical data and principles of rational drug use.

Keywords: ***Chlorhexidine; Restorative Dentistry; Dentin Bonding; Matrix Metalloproteinases; Cytotoxicity; Drug Utilization.***

1. Introduction

Modern restorative dentistry increasingly incorporates adjunctive pharmacological agents with the intention of improving clinical outcomes and extending the longevity of restorations [1]. Alongside advances in adhesive materials and restorative techniques, such adjuncts are frequently adopted to enhance antimicrobial control, modulate biological processes at the tooth–restoration interface, or compensate for perceived procedural limitations [2]. Among these agents, chlorhexidine (CHX), a cationic bisbiguanide with well-established antimicrobial properties, has been widely used in restorative dental practice for several decades [2,3].

Owing to its broad antimicrobial spectrum, substantivity, accessibility, and relatively low cost, CHX has become a routine component of many restorative protocols, often applied as a cavity disinfectant or as a dentin pretreatment prior to adhesive procedures [4]. However, the widespread and often habitual use of CHX has raised increasing concerns regarding its rational and evidence-based application [5]. In many clinical settings, CHX is used reflexively rather than selectively, with limited consideration of its true contribution to long-term restorative success.

The World Health Organization defines rational drug use as the provision of medications appropriate to patients' clinical needs, administered in adequate doses, for an appropriate duration, and at the lowest cost to individuals and society [6,7]. When evaluated through this framework, the role of CHX in restorative dentistry becomes complex. On one hand, laboratory-based studies provide compelling mechanistic evidence supporting antimicrobial effects, inhibition of dentin-derived MMPs, and a potential capacity to stabilize the resin–dentin hybrid layer [4,8,9]. On the other hand, dose- and time-dependent cytotoxic effects on pulpal and soft tissue cells, concerns regarding biological safety in deep cavities, and adverse effects such as tooth staining and taste disturbances challenge its indiscriminate use [3,5,10-13].

Importantly, despite extensive experimental investigation, the translation of these biologically plausible mechanisms into consistent and clinically relevant long-term benefits has remained uncertain. High-quality clinical studies have failed to demonstrate reliable improvements in restoration survival, marginal integrity, or secondary caries prevention associated with routine CHX use [4,14-17]. This discrepancy highlights a translational gap between laboratory efficacy and clinical effectiveness that warrants critical reappraisal.

The aim of this narrative review is to critically evaluate the role of chlorhexidine in restorative dentistry from the perspectives of rational drug use and health technology assessment [6,7]. The pharmacological properties of CHX, its biological interactions with dentin, its role in MMP inhibition, and its cytotoxic and safety profile are examined in relation to both experimental and clinical evidence [10,18]. Particular attention is given to the discordance between in vitro findings and clinical outcomes, with the goal of supporting evidence-based clinical decision-making rather than perpetuating habit-driven practice.

This review does not constitute an umbrella review. Although systematic reviews and meta-analyses were included, the objective was not to aggregate review-level data but to provide a

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critical narrative synthesis. A targeted, non-systematic literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science, covering publications from approximately 2000 to 2025. Peer-reviewed original studies, narrative and systematic reviews, meta-analyses, and randomized controlled clinical trials published in English were considered. Greater emphasis was placed on clinically relevant outcomes, long-term restorative performance, and evidence that elucidates discrepancies between experimental and clinical findings.

2. Chemical and Pharmacological Properties of Chlorhexidine

The clinical behavior of chlorhexidine in restorative dentistry is fundamentally determined by its chemical structure and resulting pharmacological properties [9,11,18]. CHX is a cationic bisbiguanide that remains positively charged across the physiological pH range, conferring a strong affinity for negatively charged biological substrates such as bacterial cell walls, oral mucosa, dental plaque, and demineralized dentin collagen [11,18-20]. These electrostatic interactions underpin its antimicrobial activity, substantivity, and biological behavior at the resin–dentin interface [5-7].

From a pharmacological standpoint, CHX exhibits concentration-dependent antimicrobial effects. At lower concentrations, it primarily exerts bacteriostatic activity by inducing reversible alterations in bacterial membrane permeability. At higher concentrations, it becomes bactericidal through irreversible membrane disruption and cytoplasmic coagulation [3,10,11]. While these mechanisms are well characterized, their relevance to restorative dentistry extends beyond short-term microbial reduction and depends on interactions with dental hard tissues and adhesive interfaces under clinical conditions [11].

A defining characteristic of CHX is its substantivity, defined as the capacity to bind to biological surfaces and be released gradually over time [17]. In restorative procedures, this property allows CHX to bind to collagen fibrils exposed following acid etching of dentin [5,18,21-23]. Retention of CHX within demineralized dentin and the hybrid layer has been demonstrated to persist for extended periods, forming the biological rationale for its proposed role in modulating dentin-derived enzymatic activity [18,21].

However, although these properties provide biological plausibility, they do not inherently constitute evidence of clinical benefit. Antimicrobial activity and substantivity alone do not guarantee improved restoration longevity, particularly in the complex oral environment where mechanical loading, thermal cycling, moisture, and biofilm dynamics act simultaneously [5,11]. Consequently, these pharmacological properties must be interpreted in conjunction with clinical evidence rather than extrapolated directly from laboratory observations [6,7].

3. Clinical Indications of Chlorhexidine in Restorative Dentistry: Claimed Benefits and Evidence

Chlorhexidine has been incorporated into restorative dental practice for several proposed indications, including cavity disinfection, reduction of residual bacterial contamination, and prevention of secondary caries [11,24]. Despite widespread adoption, the frequency of these applications does not consistently reflect the strength of the supporting clinical evidence [11]. From a rational drug use perspective, each claimed indication must be evaluated against demonstrated clinical outcomes rather than theoretical or surrogate endpoints alone [6].

Cavity disinfection following cavity preparation is the most commonly cited indication for CHX use. The rationale is the elimination of residual microorganisms to reduce postoperative sensitivity and the risk of secondary caries [3,11]. Although biologically plausible, high-quality clinical evidence does not support a consistent long-term benefit. Notably, a three-year randomized controlled clinical trial by Sartori et al.,[16] demonstrated that application of 2% CHX to acid-etched dentin did not improve restoration survival or clinical durability compared with controls. These findings directly challenge the routine use of CHX as a cavity disinfectant and suggest that short-term antimicrobial effects are insufficient predictors of long-term restorative success [11,16].

Similarly, although CHX effectively reduces bacterial counts immediately after application, this transient reduction has not been shown to influence restoration longevity or failure rates. Brookes et al.,[11] emphasized that residual bacterial presence alone is not a reliable determinant of restorative outcomes, which are influenced by multiple biological, mechanical, and procedural factors.

Another frequently cited indication is the prevention of secondary caries through plaque reduction at restoration margins. While CHX has well-documented effects on plaque control, a Cochrane review concluded that these effects do not translate into a significant reduction in caries incidence [11,14]. This disconnect illustrates the limitation of extrapolating surrogate outcomes, such as plaque indices, to clinically meaningful endpoints.

Compounding these uncertainties is the absence of standardized clinical protocols. Considerable variability exists in CHX concentration, application time, and mode of delivery across studies, limiting comparability and precluding evidence-based guideline development [2,4,11,15]. Collectively, current clinical evidence does not support routine CHX use for commonly claimed indications in restorative dentistry, highlighting the need to examine its biological mechanisms and their true clinical relevance.

4. Biological Mechanisms at the Resin–Dentin Interface

The proposed role of chlorhexidine in restorative dentistry extends beyond its antiseptic properties to include biological interactions at the resin–dentin interface [18,24]. During adhesive procedures, acid etching dissolves hydroxyapatite crystals on the dentin surface, exposing a three-dimensional collagen matrix that serves as a scaffold for resin infiltration and hybrid layer formation [1]. When this collagen network is incompletely infiltrated or protected, it becomes vulnerable to hydrolytic and enzymatic degradation over time [17,22].

Endogenous dentin proteases, particularly matrix metalloproteinases such as MMP-2, MMP-8, and MMP-9, play a central role in this degradation process [25-28]. These enzymes are present in a latent form within dentin and may be activated during adhesive procedures through acid etching or acidic primers via the cysteine-switch mechanism [29-31]. Once activated, they degrade exposed collagen fibrils in the presence of water, leading to progressive hybrid layer deterioration and time-dependent loss of resin–dentin bond strength [13,15,32,33].

Chlorhexidine exhibits strong affinity for dentin collagen due to its cationic nature, enabling ionic binding to exposed collagen fibrils and retention within the hybrid layer [18,23]. Its substantivity supports prolonged biological activity at the adhesive interface [18,22].

Mechanistically, CHX inhibits MMP activity primarily through chelation of metal ions such as zinc and calcium, which are essential for enzymatic function [22].

In vitro investigations consistently demonstrate that CHX application to acid-etched dentin delays hybrid layer degradation, reduces nanoleakage, and preserves bond strength over time [17,27,33-35]. These effects have been observed across both etch-and-rinse and self-etch adhesive systems, supporting the concept of CHX as a biomodulatory agent rather than a purely antimicrobial adjunct [4,17,35].

Despite the robustness of these mechanistic findings, the biological advantages observed under laboratory conditions have not been consistently reflected in improved clinical outcomes [16,17]. This discrepancy underscores a translational gap between experimental efficacy and clinical effectiveness, emphasizing the limitations of extrapolating in vitro mechanisms directly to routine clinical practice.

5. Cytotoxicity and Biocompatibility

The rational use of pharmacological agents in restorative dentistry requires careful consideration of potential toxic effects on vital tissues [6,36]. Because CHX can diffuse through dentinal tubules and potentially reach the pulp, its biological effects on pulpal cells are of direct clinical relevance, particularly in deep cavities [2,10].

In vitro studies have demonstrated pronounced dose- and time-dependent cytotoxic effects of CHX on odontoblast-like cells. Lessa et al.,[10] reported significant reductions in cellular viability and metabolic activity across clinically relevant concentrations, with limited evidence of complete cellular recovery. Prolonged exposure was associated with delayed cellular injury, suggesting progression toward apoptotic pathways rather than transient reversible damage [10,12]. Morphological alterations, including cell shrinkage, loss of adhesion, and suppression of protein synthesis, further support concerns regarding pulpal biocompatibility [10,12].

In addition to pulpal cells, CHX has been shown to adversely affect human gingival fibroblasts by inhibiting cell viability, proliferation, and migration—functions essential for soft tissue homeostasis and wound healing [5,12,37]. Although these effects are primarily documented under laboratory conditions, they raise concerns regarding repeated or unnecessary exposure of oral tissues during restorative procedures.

These findings are particularly relevant in clinical situations involving limited remaining dentin thickness, where diffusion of CHX toward the pulp may be increased [10,38]. Consequently, the biological safety of CHX must be carefully weighed against its proposed benefits, especially in deep cavities where potential harm may outweigh uncertain clinical advantages.

6. Translational Challenges Between In Vitro and Clinical Evidence

Chlorhexidine exemplifies the translational challenges commonly encountered in restorative dentistry, where biologically plausible mechanisms do not necessarily yield predictable clinical benefits [15,17]. Laboratory studies consistently demonstrate that CHX can delay hybrid layer degradation and preserve resin–dentin bond strength under controlled conditions [17,27,33,34]. However, these findings have not been reliably mirrored in clinical investigations.

The three-year randomized controlled trial by Sartori et al.,[16] found no significant improvement in restoration survival or clinical performance associated with CHX application. These results suggest that laboratory improvements in bond strength stability may not translate into clinically meaningful endpoints such as restoration longevity or marginal integrity [15,16].

Several factors likely contribute to this translational gap, including salivary dynamics, mechanical and thermal loading, pH fluctuations, bacterial challenges, and patient-related variables that are not fully replicated in laboratory models [22,25]. Moreover, bond strength represents only one aspect of restorative success, and statistically significant laboratory differences may not influence clinical outcomes [16,39].

7. Concentration, Protocol Variability, and Adhesive Compatibility

The clinical behavior of CHX is influenced by multiple factors, including concentration, application time, delivery strategy, and compatibility with adhesive systems. Substantial heterogeneity in study protocols complicates interpretation and contributes to inconsistent findings [15-17].

Although in vitro studies frequently employ CHX concentrations ranging from 0.2% to 2%, clinical investigations have not identified a concentration threshold associated with improved long-term restorative outcomes. Notably, application of 2% CHX failed to demonstrate clinical benefit in randomized trials [16].

Delivery strategy is another critical determinant. Externally applied CHX solutions and CHX incorporated into adhesive systems represent fundamentally different approaches with distinct pharmacological and mechanical implications [11,17]. Rinse application protocols may interfere with adhesive infiltration depending on the adhesive formulation and application mode [13]. In contrast, CHX-containing adhesives aim to release lower concentrations in a controlled manner, although their clinical superiority has not been conclusively demonstrated [35].

Given the absence of standardized protocols and consistent clinical benefit, CHX cannot currently be recommended as a uniform adjunct in restorative dentistry. Its use should instead be considered selectively, in relation to adhesive system characteristics, cavity depth, and patient-specific factors.

8. Safety Profile and Adverse Effects

Although chlorhexidine is widely perceived as safe, available evidence indicates that it is not biologically inert [11,40]. Local adverse effects such as mucosal irritation, tooth and tongue discoloration, and taste disturbances have been consistently reported [11,38,41]. Experimental studies further demonstrate a dose-dependent irritant potential on oral mucosal tissues, supporting the clinical relevance of these observations [12].

Beyond local effects, concerns have been raised regarding cytotoxicity to pulpal and soft tissue cells, potential alterations in the oral microbiome, and the development of antimicrobial resistance or cross-resistance mechanisms [11,38,42,43]. Although much of this evidence is derived from mechanistic or observational studies, the convergence of these findings suggests that CHX exposure is associated with measurable biological effects rather than complete biocompatibility. Within this context, a precautionary approach is warranted, particularly when CHX is used routinely or repeatedly without clear evidence of long-term clinical benefit. In parallel, recent discussions on pharmacovigilance in dental practice have highlighted that adverse drug reactions related to agents commonly used in dentistry may be underreported, underscoring the need for greater awareness and systematic monitoring of drug-related safety outcomes in routine dental care [44].

9. Health Technology Assessment and Rational Drug Use

From a health technology assessment perspective, CHX should be evaluated not only based on accessibility and antimicrobial activity but also on clinical effectiveness, biological safety, and overall cost–benefit balance [6,7]. Although CHX is inexpensive at the point of purchase, the absence of proven clinical benefit combined with measurable biological risks weakens the justification for routine use [15,16].

Routine application of CHX for cavity disinfection represents an example of overuse and misuse within the framework of rational drug use [6]. Evidence from randomized clinical trials and systematic reviews does not support improved restorative outcomes, and under certain conditions CHX may adversely affect adhesive performance [13,16].

Optimizing restorative outcomes is more reliably achieved through meticulous contamination control, effective isolation, and strict adherence to adhesive protocols rather than adjunctive pharmacological interventions [1,16,35].

10. Conclusion

Despite its long-standing use in restorative dentistry, the clinical benefit of chlorhexidine (CHX) remains uncertain. While mechanistic and in vitro studies consistently demonstrate antimicrobial activity and inhibition of dentin-derived proteases, these effects have not been reliably translated into improved long-term clinical outcomes.

Clinically, the available evidence does not support the routine use of CHX as a cavity disinfectant or bond-enhancing adjunct, particularly in deep cavities where concentration- and time-dependent cytotoxic effects may occur. Accordingly, future research should prioritize well-designed, long-term clinical studies that simultaneously evaluate restorative performance and biological safety, while accounting for delivery strategies and adhesive compatibility.

From a health technology assessment and rational drug use perspective, the routine incorporation of chlorhexidine into restorative dentistry is not sufficiently supported by current clinical evidence in the absence of demonstrable clinical benefit. Its application should instead be limited to clearly defined indications, guided by evidence-based risk–benefit considerations rather than established clinical habits. Importantly, the concerns discussed in this review are largely derived from associative and mechanistic evidence. These findings should not be interpreted as definitive proof of clinical harm.

11. Declarations

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Ethical Clearance

Not applicable

Conflict of interest

The author declares that there is no conflict of interest.

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Contributors

HGD solely conceived the study, conducted the literature review and analysis, wrote the manuscript, and approved the final version for publication.

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