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Scientific Rationale for the Use of Proteolytic Enzymes in Tooth Whitening: A Clinical and Methodological Analysis of Efficacy and Risks

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Abstract: In recent years, enzymatic tooth whitening has been increasingly regarded as a scientifically substantiated and biologically oriented alternative to conventional peroxide-based methods for the correction of dental discoloration. The growing relevance of this approach is associated with the need to improve the safety of aesthetic dental procedures while maintaining clinically significant efficacy. Enzymatic whitening systems are based on the use of plant-derived proteolytic enzymes (papain, bromelain, ficin, etc.) capable of selectively degrading protein components of the acquired pellicle and pigmented organic complexes without causing pronounced oxidative effects on the mineral matrix of enamel and dentinal structures. Such a mechanism is presumed to provide a more conservative interaction with hard dental tissues and reduce the likelihood of pulpal irritation.

The aim of the present systematic review was to comprehensively evaluate current evidence regarding the mechanisms of action of enzymatic whitening formulations, analyze their clinical efficacy based on objective instrumental color parameters (CIELab, ΔE*ab, ΔE00, and the Whiteness Index for Dentistry — WI_D), and assess their safety profile with respect to enamel morphological alterations, microhardness parameters, and the incidence of post-procedural hypersensitivity.

The methodological basis of the review included an analysis of recent in vitro, in situ, and clinical studies employing standardized colorimetric methods and sensitivity assessment scales (Schiff, NRS/VAS). A comparative analysis was performed between the obtained findings and the outcomes associated with conventional peroxide-based whitening protocols.

The reviewed literature demonstrated that enzymatic formulations are capable of producing statistically significant and clinically perceptible improvements in tooth color parameters corresponding to established visual perception thresholds. In addition, the frequency and severity of hypersensitivity were generally lower compared with high-concentration peroxide systems. Morphological investigations indicated minimal alterations in enamel surface structure and no significant reduction in microhardness values when recommended application protocols were followed.

However, considerable variability in enzyme concentrations, exposure regimens, and instrumental assessment methodologies was identified, limiting the comparability of available findings and reducing the overall level of evidence of individual studies. Furthermore, the absence of long-term randomized clinical trials does not allow definitive conclusions regarding the stability of the achieved whitening effect and potential delayed biological consequences.

Thus, enzymatic tooth whitening may be considered a promising direction in personalized aesthetic dentistry, combining a favorable balance between efficacy and safety. Further integration of this technology into clinical algorithms requires protocol standardization, harmonization of objective color assessment criteria, and the implementation of multicenter controlled clinical studies.

Keywords: Enzymatic tooth whitening, proteolytic enzymes, papain, bromelain, peroxide-free technologies, CIELab, ΔE00, Whiteness Index for Dentistry (WI_D), post-whitening hypersensitivity, enamel safety.

Introduction: Contemporary aesthetic dentistry is characterized by a steady increase in patient demand for tooth color enhancement with minimal intervention into the structure of hard dental tissues [2]. The socio-psychological significance of smile aesthetics, the influence of media culture, and the increasing accessibility of dental services contribute to the growing number of patients seeking tooth-whitening procedures [3,4]. At present, clinical efficacy is considered not in isolation, but in the context of biological safety, predictability of outcomes, and long-term stability of the achieved results.

Conventional whitening systems are primarily based on peroxide-containing compounds capable of diffusing through enamel and dentin with the subsequent generation of reactive radicals that degrade organic chromophores. Although this mechanism provides pronounced whitening effects, it is associated with several potential adverse outcomes [12,17]. In clinical practice, transient hypersensitivity of varying severity is the most frequently reported complication. Furthermore, experimental studies have demonstrated alterations in enamel surface morphology, variations in microhardness, temporary fluctuations in mineralization parameters, and irritation of oral soft tissues. Despite the largely reversible nature of most of these changes, tolerability remains a clinically significant factor limiting the frequency of repeated whitening procedures [1,4,5].

In recent years, considerable attention has been directed toward the development of alternative peroxide-free technologies aimed at reducing treatment aggressiveness while preserving aesthetic efficacy [6]. One of the most promising approaches involves the incorporation of plant-derived proteolytic enzymes into whitening gels. Papain, bromelain, ficin, and related enzymes possess the ability to selectively hydrolyze protein structures forming the acquired pellicle and retaining pigmented organic complexes [7].

Theoretically, this mechanism is characterized predominantly by superficial activity without deep diffusion of active components into dentinal tubules and without pronounced oxidative stress affecting the mineral matrix of enamel. Consequently, enzymatic systems may be regarded as a biologically oriented alternative to conventional whitening protocols [8]. However, the currently available evidence is characterized by substantial variability in study design, enzyme concentrations, and methods of objective color assessment.

Instrumental colorimetry has gained particular importance in contemporary evidence-based dentistry. The transition from subjective shade guides to CIELab-based systems with calculation of ΔE*ab and ΔE00 values has enabled the standardization of whitening efficacy assessment [3]. Furthermore, the introduction of the Whiteness Index for Dentistry (WI_D) has improved the correlation between instrumental measurements and visual perception. Nevertheless, these parameters are inconsistently applied in studies investigating enzymatic whitening systems, thereby limiting cross-study comparability.

Systematization of the accumulated experimental and clinical evidence is therefore necessary for an objective evaluation of the role of enzymatic tooth whitening in modern aesthetic dentistry [8].

A systematic analysis of scientific publications published between 2015 and 2025 was conducted. The literature search was performed using international and national scientific databases with keywords related to enzymatic tooth whitening, proteolytic enzymes, and peroxide-free technologies. Inclusion criteria comprised in vitro and in situ experimental studies, randomized controlled clinical trials, investigations reporting quantitative color assessment according to the CIELab system, studies including ΔE*ab, ΔE00, or WI_D calculations, as well as publications evaluating enamel microhardness, morphological alterations, or hypersensitivity outcomes. Exclusion criteria included studies lacking instrumental colorimetric evaluation, investigations involving combined systems in which the specific contribution of the enzymatic component could not be isolated, publications without a clearly described application protocol, and review articles lacking primary data [11,14].

The selected studies were analyzed according to the following parameters: type and concentration of enzyme; formulation characteristics and exposure regimen; color alteration parameters (L*, a*, b*, ΔE, ΔE00, ΔWI_D); changes in enamel microhardness and morphology; frequency and severity of hypersensitivity; and duration of follow-up.

Qualitative analysis was performed with consideration of methodological comparability, instrumentation used, and criteria of clinical significance [12].

Discussion

The most extensively studied active components are papain and bromelain, which are plant-derived cysteine proteases. Their biochemical activity is

directed toward the hydrolysis of peptide bonds within protein structures constituting the acquired dental pellicle and organic deposits [7].

It is assumed that degradation of protein matrices facilitates the removal of adsorbed pigmented molecules, including tannin derivatives and food-related chromogens [1]. Unlike peroxide-based systems, enzymatic gels do not initiate free-radical oxidation reactions and do not promote deep penetration of active molecules into dentinal tubules.

Several studies have demonstrated the potential benefits of combining proteolytic enzymes with mild activators or photodynamic components, thereby enhancing the whitening effect without substantially increasing treatment aggressiveness [2].

Analysis of experimental and clinical investigations revealed statistically significant increases in the L* parameter and reductions in a* and b* values following the application of enzymatic whitening gels. In the majority of studies, ΔE00 values exceeded the threshold of clinical perceptibility, indicating a visually appreciable whitening effect.

Although the degree of whitening achieved after a single application may be inferior to that obtained with high-concentration peroxide protocols, enzymatic systems demonstrate comparable ΔWI_D values during course-based application, confirming their ability to provide clinically acceptable aesthetic outcomes [4].

A substantial limitation of the currently available evidence is methodological heterogeneity, including variations in exposure duration, concentrations of active agents, types of colorimetric instruments, and statistical processing criteria employed across studies [13].

Scanning electron microscopy findings indicate minimal alterations in enamel surface morphology following the use of enzymatic gels. Most investigations report no evidence of pronounced erosion, demineralization, or increased surface roughness.

Enamel microhardness values either remain stable or demonstrate only minor fluctuations within physiological limits. These findings support the assumption that enzymatic systems predominantly exert a superficial mechanism of action.

Post-procedural hypersensitivity remains one of the principal clinical outcomes in the evaluation of whitening safety. The analyzed publications indicate that enzymatic systems are associated with a lower frequency of sensitivity and reduced symptom intensity compared with peroxide-based approaches [16,19].

The absence of active diffusion of low-molecular-weight oxidizing agents into dentin may reduce pulpal irritation and explain the more favorable tolerability profile observed with enzymatic formulations.

However, evidence regarding long-term follow-up remains limited, necessitating further clinical investigations.

The literature analysis identified several methodological limitations: small sample sizes; insufficient number of randomized controlled trials; variability of application protocols; absence of standardized thresholds for clinical significance; short follow-up periods; heterogeneity of hypersensitivity assessment scales.

These factors reduce the overall level of evidence and limit the possibility of formulating universal clinical recommendations [20].

Future research directions in the field of enzymatic tooth whitening should adopt a systematic and interdisciplinary approach. First, the development of a standardized clinical protocol appears essential, including clearly regulated parameters regarding proteolytic enzyme concentrations, duration and frequency of exposure, formulation characteristics, as well as protocols for tooth surface preparation and post-procedural management. Standardization would minimize result variability and improve reproducibility of clinical findings.

Of particular importance is the implementation of multicenter randomized controlled trials with adequate sample sizes and extended follow-up periods. Such studies should incorporate standardized instrumental color assessment methods with mandatory use of contemporary colorimetric criteria, particularly ΔE00 and the Whiteness Index for Dentistry (WI_D), which demonstrate the strongest correlation with visual perception of tooth color alterations. In addition, standardized hypersensitivity assessment scales (Schiff, NRS/VAS) should be adopted to ensure comparability of safety-related data [3].

Special attention should also be directed toward the evaluation of long-term stability of the achieved whitening effect, including assessment of potential repigmentation over different observation intervals (3, 6, 12 months, and beyond). Such investigations would facilitate evaluation of the clinical feasibility of repeated treatment courses and contribute to the development of maintenance therapy recommendations [5].

Another promising direction involves the development of combined enzymatic–remineralizing systems capable of simultaneously providing whitening effects and strengthening enamel through the incorporation of calcium-phosphate complexes, hydroxyapatite

particles, or fluoride-containing compounds. Such an approach may enhance biological safety and reduce the risk of hypersensitivity development.

The creation of predictive models for hypersensitivity risk based on individual clinical and morphological characteristics of enamel, including enamel thickness, degree of mineralization, and the presence of non-carious lesions, may facilitate the implementation of personalized dentistry principles and optimize whitening method selection for individual patients [2,11]. In addition to clinical parameters, evaluation of the economic effectiveness of the technology, including cost–benefit analysis and patient satisfaction assessment, appears clinically justified as an integral indicator of successful aesthetic treatment.

Comprehensive implementation of these research directions will contribute to the establishment of a high-level evidence base and allow determination of the justified role of enzymatic tooth whitening within contemporary personalized aesthetic dentistry algorithms focused on balancing efficacy, safety, and predictability of clinical outcomes.

Conclusion

The conducted systematic analysis of contemporary experimental and clinical studies indicates that enzymatic whitening systems represent an independent and scientifically promising direction within minimally invasive aesthetic dentistry. The use of plant-derived proteolytic enzymes provides clinically significant improvement in tooth color parameters, confirmed by objective instrumental assessment methods, including CIELab, ΔE*ab, ΔE00, and the Whiteness Index for Dentistry (WI_D). In the majority of the reviewed studies, the obtained values exceeded the thresholds of visual perceptibility and clinical acceptability, thereby confirming the genuine aesthetic efficacy of this approach.

Comparative analysis demonstrates that, when applied in course-based regimens, enzymatic formulations are capable of producing whitening effects comparable to those achieved with moderate peroxide-based protocols, while exhibiting a more favorable tolerability profile. Morphological investigations, including scanning electron microscopy analyses, indicate the absence of pronounced enamel structural damage, erosive defects, or persistent increases in surface roughness. Enamel microhardness values generally remain within the limits of physiological variability, supporting the conservative nature of the treatment approach.

Of particular clinical importance is the lower frequency and intensity of post-procedural hypersensitivity compared with traditional high-concentration peroxide systems. This phenomenon is presumably associated with the absence of active radical diffusion through the enamel–dentin complex and minimal irritation of pulpal structures. The improved tolerability profile enhances patient satisfaction, broadens the indications for application, and potentially reduces the likelihood of refusal of repeated aesthetic procedures.

Nevertheless, it should be emphasized that the currently available evidence base remains limited by several methodological factors. Considerable variability exists in enzyme concentrations, exposure regimens, duration of treatment courses, and methods of objective colorimetric assessment. The absence of standardized thresholds for clinical significance and unified hypersensitivity assessment scales complicates cross-study comparison of results. Furthermore, most available investigations are characterized by relatively small sample sizes and short follow-up periods, preventing comprehensive evaluation of long-term color stability and potential delayed biological effects.

Future development of this field should therefore be associated with the standardization of enzymatic whitening protocols, implementation of unified instrumental efficacy assessment criteria (primarily ΔE00 and WI_D), performance of multicenter randomized controlled trials, and investigation of long-term color stability. Additional scientific interest is represented by the development of combined enzymatic–remineralizing systems, as well as predictive models for hypersensitivity risk based on individual clinical and morphological characteristics of enamel.

Thus, enzymatic tooth whitening may be considered a biologically oriented and potentially safe alternative to peroxide-based methods for the correction of dental discoloration. Final integration of this technology into clinical aesthetic dentistry algorithms will require further accumulation of high-level evidence and the development of scientifically substantiated application protocols.

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