Klotho in periodontitis: Mechanisms, biomarker potential and therapeutic implications (Review)

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Abstract. Periodontitis is a chronic inflammatory disease characterized by the destruction of tooth- supporting tissues, driven by microbial dysbiosis and an exaggerated host immune response. Beyond its local effects, periodontitis has been increasingly associated with systemic conditions, such as cardiovascular disease, diabetes mellitus, chronic kidney disease and stroke, highlighting its broader clinical relevance. Klotho, an anti-aging and regulatory protein primarily expressed in the kidneys, has emerged as a key regulator of inflammation, oxidative stress and cellular homeostasis. Both circulating soluble Klotho and locally expressed Klotho are considered to contribute to periodontal tissue homeostasis, although the relative contribution of each remains under investigation. Recent evidence suggests that Klotho plays a protective role in periodontal tissues by suppressing inflammatory signaling pathways, including NF-κB, reducing oxidative stress through antioxidant mechanisms, and supporting cell survival, regeneration and preserving alveolar bone homeostasis Experimental and clinical studies suggest that decreased levels of Klotho may be linked to the progression of periodontal disease, while restoring Klotho levels may offer therapeutic benefits. In addition, Klotho has been shown to function as a potential as a biomarker for disease activity and as a target for regenerative and precision-based periodontal therapies. Although current evidence remains limited, Klotho represents a promising link between systemic regulation and periodontal health. The present mini review summarizes the biological functions of Klotho, its mechanistic role in periodontitis and its potential diagnostic and therapeutic implications.

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Contents

1. Introduction

Periodontitis is a chronic inflammatory disease affecting the supporting structures of the teeth, resulting from complex interactions between microbial biofilms and the host immune response (1). It is characterized by the progressive destruction of periodontal tissues, including alveolar bone loss and may ultimately result in tooth loss (2). Beyond its local effects, periodontitis is increasingly recognized as a condition with systemic implications rather than being confined to the oral cavity. A growing body of evidence indicates that periodontal inflammation is associated with several systemic disorders, including cardiovascular diseases, diabetes mellitus, chronic kidney disease and cerebrovascular events, such as stroke (3-5). These conditions share common risk factors, such as age, smoking, obesity and socioeconomic status, which may contribute to their coexistence. Furthermore, periodontal infections can facilitate the dissemination of pathogenic microorganisms and inflammatory mediators into the systemic circulation, thereby promoting a chronic inflammatory state that may contribute to systemic inflammation and affect distant organs. This bidirectional association highlights the importance of understanding periodontitis within the broader context of overall systemic health (3-5).

Klotho is a multifunctional protein that has gained considerable attention due to its role in aging and systemic regulation.

Initially identified as an anti-aging gene, Klotho exists in both membrane-bound and soluble forms and is predominantly expressed in the kidneys (6). Its detailed molecular biology is discussed in the following section. Briefly, Klotho exists in membrane-bound and soluble forms that exert distinct biological functions (7,8). Beyond its role in mineral metabolism, Klotho exerts pleiotropic anti-inflammatory, antioxidant and cytoprotective effects that are particularly relevant to chronic inflammatory diseases (9,10).

Given the central role of inflammation, oxidative stress and alveolar bone resorption in the pathogenesis of periodontitis, molecules that regulate these processes have gained increasing research interest. Klotho, with its well-established anti-inflammatory, antioxidant and cytoprotective properties, represents a promising candidate in this context. It has been shown to modulate key inflammatory signaling pathways, including the suppression of NF-κB activation, thereby reducing the production of pro-inflammatory mediators (11). In addition, Klotho enhances cellular resistance to oxidative stress through the activation of antioxidant defense mechanisms, thereby limiting tissue damage (12). Emerging evidence also suggests that Klotho plays a role in maintaining periodontal tissue homeostasis by reducing oxidative stress–induced apoptosis and supporting regenerative capacity in periodontal ligament stem cells (13). Although emerging evidence suggests that Klotho supports periodontal homeostasis, it remains unclear whether these protective effects are mediated predominantly by circulating soluble Klotho or by local Klotho activity within resident periodontal tissues. While experimental studies have demonstrated Klotho-associated protective effects in periodontal ligament stem cells (PDLSCs), evidence for local expression and function in other resident periodontal cells, including gingival fibroblasts and osteoblasts, remains limited (9,10). Addressing this distinction is essential for understanding the translational potential of Klotho as a biomarker and therapeutic target in periodontitis (9,10,14). However, the role of Klotho in periodontitis remains underexplored, particularly in relation to its mechanistic pathways and clinical applications. Accordingly, the present mini review aimed to summarize the current understanding of Klotho in periodontitis, focusing on its biological functions, underlying mechanisms, and its potential as a biomarker, therapeutic target and contributor to personalized medicine approaches.

2. Biology of Klotho

Klotho is a transmembrane protein that exists in multiple biologically active forms, including a full-length membrane-bound form and a soluble form generated through proteolytic cleavage. The membrane-bound form is predominantly expressed in the kidneys, parathyroid glands and brain, where it functions as a co-receptor for fibroblast growth factor (FGF)23 (FGF23), while the soluble form is released into circulation and exerts systemic hormone-like effects (6,12). Although membrane-bound Klotho is predominantly expressed in the kidneys, parathyroid glands and brain, accumulating evidence suggests that Klotho signaling contributes to periodontal tissue homeostasis by both circulating soluble Klotho and local Klotho activity within periodontal tissues. Experimental studies have demonstrated Klotho-associated protective effects in PDLSCs (10,13,15), whereas evidence for local expression in other resident periodontal cells, including gingival fibroblasts and osteoblasts, remains limited (9,14) and requires further investigation. Consequently, periodontal protection is likely mediated through complementary actions of systemic soluble Klotho and local tissue-associated Klotho, although their relative contributions have yet to be fully elucidated (9,10,16). A key function of Klotho is its role in FGF23-mediated signaling, where it forms a complex with FGF receptors and enhances their specificity for FGF23 (7,8). This interaction is critical for maintaining phosphate homeostasis by promoting renal phosphate excretion and regulating vitamin D metabolism. Beyond its role in mineral metabolism, Klotho exhibits pleiotropic biological functions, including anti-aging, anti-inflammatory, antioxidant and cytoprotective effects that are increasingly recognized as being relevant to chronic inflammatory diseases, including periodontitis (9,14,17). It enhances cellular resistance to oxidative stress through activation of pathways, such as Forkhead box O (FoxO) and the upregulation of antioxidant enzymes, thereby reducing reactive oxygen species (ROS) generation and cellular damage (11). In addition, Klotho suppresses inflammatory signaling pathways, including NF-κB, and reduces apoptosis and cellular senescence, contributing to improved tissue homeostasis and cellular protection. These biological activities provide a mechanistic basis for the proposed role of Klotho in periodontal disease, where excessive inflammation, oxidative stress, dysregulated bone remodeling and impaired regenerative capacity collectively drive periodontal tissue destruction (9,10,15).

3. Pathophysiology of periodontitis

Periodontitis is a multifactorial inflammatory disease initiated by microbial dysbiosis within the subgingival biofilm and driven by a dysregulated host immune response. The transition from periodontal health to disease is characterized by a shift in the composition of the oral microbiota, favoring pathogenic species that promote a pro-inflammatory environment (18). Among these pathogens, *Porphyromonas gingivalis* is considered a keystone pathogen that disrupts host-microbial homeostasis by modulating immune responses, promoting chronic inflammation, and enhancing the production of pro-inflammatory cytokines and matrix-degrading enzymes, thereby accelerating periodontal tissue destruction (19,20). Rather than the direct effect of bacteria alone, it is the host-mediated inflammatory response that plays a central role in tissue destruction. This dysbiotic interaction leads to the activation of both innate and adaptive immune responses, resulting in the release of pro- inflammatory mediators and the amplification of tissue damage.

Inflammation and oxidative stress are key contributors to periodontal tissue breakdown. Activated immune cells produce high levels of pro-inflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor-α (TNF-α) and IL-6, which contribute to connective tissue degradation and promote osteoclastogenesis (21,22,23). In parallel, the excessive production of ROS during the inflammatory response leads to oxidative stress, causing damage to cellular components such as lipids, proteins and DNA (22). The combined

effects of inflammation and oxidative stress further exacerbate periodontal tissue destruction and impair the regenerative capacity of periodontal cells.

At the molecular level, several signaling pathways are involved in the progression of periodontitis. Among these, the NF-κB pathway plays a central role in regulating inflammatory responses by controlling the expression of cytokines, chemokines and other mediators of tissue destruction (23). Additionally, the receptor activator of nuclear factor-κB ligand (RANKL) pathway is critical in mediating osteoclast differentiation and activation, leading to alveolar bone resorption. This process is largely driven by an increased RANKL/osteoprotegerin (OPG) ratio, in which elevated RANKL expression together with reduced OPG levels promotes osteoclastogenesis and progressive alveolar bone loss. As the maintenance of the RANKL/OPG balance is essential for bone homeostasis, the disruption of this axis represents a hallmark of periodontal disease progression (24,25). Together, these molecular pathways contribute to the chronic inflammatory environment and progressive tissue and bone loss characteristic of periodontitis. Collectively, persistent inflammation, oxidative stress, dysregulated bone remodeling, and impaired regenerative capacity establish a pathogenic microenvironment that drives periodontal tissue destruction. These interconnected mechanisms provide a strong biological rationale for investigating Klotho as a potential regulator of periodontal homeostasis through its anti-inflammatory, antioxidant and osteoprotective properties (9,10).

4. Mechanistic role of klotho in periodontal disease

Klotho plays a multifaceted role in modulating key pathogenic processes involved in periodontitis, including inflammation, oxidative stress, cell survival and bone metabolism. Its regulatory effects on these pathways suggest a protective role against periodontal tissue destruction (Fig. 1). Although both circulating soluble Klotho and membrane-bound Klotho have been implicated in tissue protection, their respective contributions to periodontal homeostasis remain incompletely understood (9,26). Current evidence suggests that soluble Klotho exerts systemic anti-inflammatory and antioxidant effects, whereas local Klotho activity within periodontal tissues, particularly in PDLSCs, may contribute to tissue repair and regeneration (10,13,15). However, further studies are warranted to clarify the relative roles of systemic and local Klotho in periodontal disease (9,14,26).

Anti-inflammatory effects. Klotho exerts significant anti-inflammatory effects primarily through inhibition of the NF-κB signaling pathway, a central regulator of inflammatory responses. The suppression of NF-κB activation leads to the reduced transcription of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6, thereby limiting periodontal inflammation and tissue damage (11,27). By modulating cytokine production, Klotho helps maintain immune homeostasis and prevents excessive host-mediated destruction of periodontal tissues. Experimental evidence further suggests that Klotho may attenuate inflammatory responses induced by *Porphyromonas gingivalis* by suppressing NF-κB activation and reducing the production of pro-inflammatory cytokines (9,11,14,27). Although these findings are promising, the majority of evidence has been derived from experimental models, and additional studies are required to confirm these mechanisms in human periodontal tissues (9,14).

Antioxidant and cytoprotective functions. Klotho also plays a critical role in protecting cells against oxidative stress, which is a key contributor to the progression of periodontal disease. It enhances antioxidant defenses through the activation of FoxO transcription factors and the nuclear factor erythroid 2-related factor 2 pathway, leading to the upregulation of antioxidant enzymes and the reduction of ROS levels (10,12,17,28). This reduction in oxidative stress limits cellular damage, preserves tissue integrity and supports the survival of periodontal cells under inflammatory conditions. Beyond limiting oxidative damage, Klotho preserves mitochondrial function, enhances cellular resistance to oxidative injury and promotes the osteogenic differentiation of PDLSCs, thereby supporting periodontal tissue regeneration under inflammatory conditions (10,13,15,27).

Role in ferroptosis and cell survival. Recent evidence suggests that Klotho may influence ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation (9,15,29). The majority of evidence supporting Klotho-mediated regulation of GPX4, SLC7A11 and ferroptosis has been obtained from experimental models (15,29). Recent evidence in periodontal ligament stem cells demonstrates that Klotho protects osteogenic function by inhibiting NOX4-mediated ferroptosis; however, additional studies are required to determine whether these mechanisms operate broadly across periodontal cell populations (9,10).

Bone metabolism and alveolar bone loss. Klotho plays an essential role in bone metabolism through its interaction with the FGF23 signaling axis, which regulates phosphate balance and vitamin D metabolism (7). In addition, Klotho regulates alveolar bone remodeling by influencing the RANKL/OPG signaling axis. Experimental studies suggest that Klotho suppresses RANKL expression while preserving or enhancing OPG expression, thereby reducing osteoclast differentiation and activity and limiting alveolar bone resorption (9,10,24). Through these actions, together with its regulation of FGF23-mediated phosphate metabolism, Klotho contributes to the maintenance of bone homeostasis and periodontal structural integrity (9,10,24), which regulates phosphate homeostasis and vitamin D metabolism.

5. Evidence from experimental and clinical studies

In vitro studies. *In vitro* studies suggest that Klotho plays a protective role in periodontal cells, particularly PDLSCs. Klotho has been shown to enhance antioxidant capacity, reduce oxidative stress-induced damage and preserve osteogenic differentiation under inflammatory conditions (28). The reduced expression of Klotho has been observed in periodontitis-affected tissues, while its restoration decreases apoptosis and improves cellular function (13). Additionally, Klotho may inhibit ferroptosis and support regenerative potential in PDLSCs, highlighting its role in maintaining

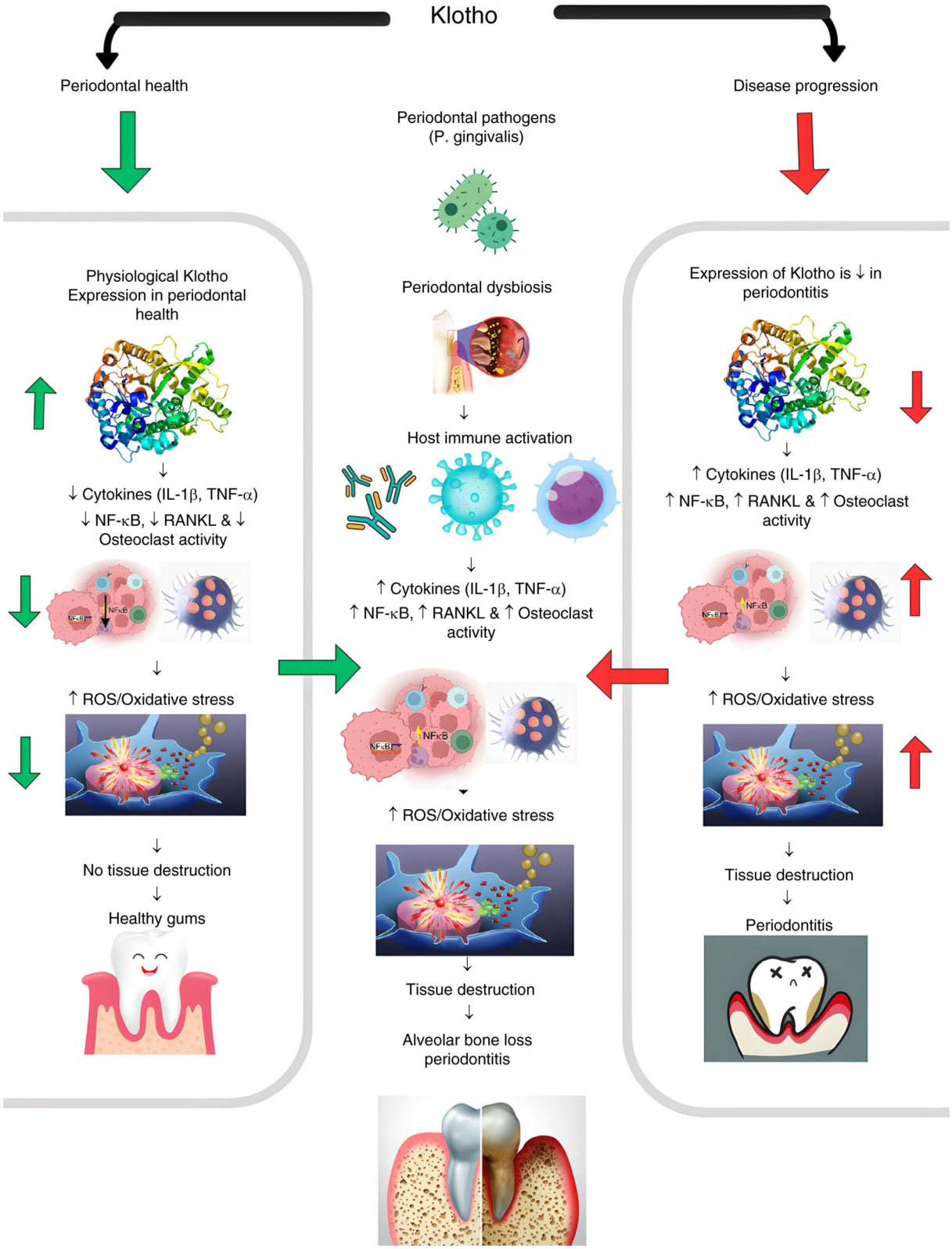

Figure 1. Klotho in periodontal health and disease progression. Schematic representation of Klotho in periodontal health and disease. In health, Klotho reduces pro-inflammatory cytokines (IL-1β and TNF-α), inhibits NF-κB signaling, decreases RANKL-mediated osteoclast activity and limits oxidative stress, maintaining tissue homeostasis. In periodontitis, reduced Klotho expression due to microbial dysbiosis (e.g., *Porphyromonas gingivalis*) and host immune activation leads to increased inflammation, NF-κB activation, RANKL-driven osteoclastogenesis, oxidative stress and periodontal tissue destruction. IL, interleukin; TNF-α, tumor necrosis factor α; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species.

periodontal tissue homeostasis. Recent studies have further demonstrated that Klotho preserves the osteogenic potential of periodontal ligament stem cells by attenuating oxidative stress, maintaining mitochondrial function, and inhibiting NOX4-mediated ferroptosis (10,13,15,27). These findings suggest that Klotho not only protects periodontal cells from

inflammatory injury but also promotes their regenerative capacity under pathological conditions (10,17).

Animal studies. Animal models further support the role of Klotho in periodontal and bone health. Klotho deficiency has been associated with an altered periodontal structure, increased inflammation and enhanced alveolar bone loss (29). By contrast, Klotho supplementation or overexpression has demonstrated regenerative effects, including improved cell survival, reduced osteoclast activity and enhanced bone formation in experimental models (30). These findings indicate that Klotho contributes to maintaining periodontal integrity and bone homeostasis by suppressing inflammatory responses, limiting oxidative stress, reducing osteoclastogenesis and promoting alveolar bone regeneration. Although encouraging, the majority of the available evidence has been generated in experimental animal models, highlighting the need for validation in well-designed human clinical studies (14,30).

Human studies. Clinical and epidemiological evidence suggests a potential association between Klotho and periodontitis, although findings remain inconsistent. Previous studies have reported lower serum levels of Klotho in individuals with periodontitis, with progressively lower levels observed as the severity of the disease increases (31,32). However, other research has demonstrated that this association may not remain significant after adjusting for confounding factors, such as age, smoking and systemic conditions (33). Overall, while the local expression of Klotho appears to play a clearer role in periodontal pathology, the utility of serum Klotho as a biomarker requires further investigation. The inconsistent findings reported across clinical studies may reflect heterogeneity in study design, sample size, periodontal disease classification and inadequate adjustment for confounding factors, including age, smoking, renal function, diabetes and other systemic conditions that influence circulating Klotho concentrations (33,34). Future prospective studies are required to evaluate both local periodontal and systemic Klotho levels in well-characterized, age- and renal function-matched cohorts. Furthermore, combining Klotho with established periodontal biomarkers, such as IL-6 and matrix metalloproteinase-8 (MMP-8), may improve diagnostic accuracy and facilitate its translation into precision periodontal care (34,35,36).

6. Klotho as a biomarker in periodontitis

Klotho has gained attention as a potential biomarker in periodontitis because of its association with inflammation, oxidative stress and tissue homeostasis. Both systemic and local measurements of Klotho have been explored, although their clinical significance appears to differ. The levels of serum soluble α-Klotho are easier to measure and have been evaluated in population-based studies; however, the interpretation of its levels is limited by the influence of age, kidney function and systemic inflammatory status. As a result, serum Klotho may reflect overall systemic health rather than periodontal status alone (31-33).

By contrast, local Klotho expression in gingival tissues, gingival crevicular fluid and PDLSCs may better represent the biological processes occurring within periodontal lesions. Studies have reported the reduced expression of Klotho in gingival tissues and periodontal cells affected by chronic periodontitis, supporting the notion that local Klotho is more directly linked to periodontal inflammation, oxidative damage and impaired regeneration (13,27). These findings suggest that the local assessment of Klotho may provide greater disease specificity than systemic measurement. Compared with established periodontal biomarkers, such as IL-6 and MMP-8, Klotho may provide complementary rather than replacement diagnostic information. Whereas IL-6 and MMP-8 primarily reflect active inflammation and connective tissue degradation, Klotho additionally reflects oxidative stress, cellular senescence, regenerative potential and tissue homeostasis. Consequently, combining local Klotho assessment with established inflammatory biomarkers may improve the diagnostic and prognostic accuracy of periodontal disease compared with the use of individual biomarkers alone (9,14,34-36).

Despite these promising findings however, several limitations hinder the clinical application of Klotho as a periodontal biomarker. The majority of available human studies are cross-sectional, involve relatively small sample sizes, and report inconsistent findings due to variations in periodontal case definitions, disease severity, analytical methods and inadequate adjustment for confounding factors, such as age, smoking, diabetes, chronic kidney disease and renal function. Furthermore, standardized methods for measuring the levels of Klotho in serum, saliva, gingival crevicular fluid and gingival tissues have not yet been established. Future longitudinal studies are thus required to evaluate both local and systemic Klotho levels in well-characterized, age- and renal function-matched cohorts, and determine whether combining Klotho with established periodontal biomarkers, such as IL-6 and MMP-8, improves diagnostic accuracy and prognostic value. Therefore, although Klotho exhibits considerable promise as a biomarker for periodontitis, particularly at the local level, further multicenter prospective studies are required before its routine clinical application can be recommended (34-36).

7. Therapeutic potential of klotho

Klotho has emerged as a promising therapeutic target in periodontitis due to its ability to modulate key pathogenic mechanisms, including inflammation, oxidative stress and bone metabolism. Recombinant Klotho therapy has demonstrated protective effects in experimental studies by suppressing inflammatory signaling pathways, particularly the NF-κB signaling pathway, reducing oxidative stress, enhancing antioxidant defenses and promoting cellular survival (11,12,14,27). These properties suggest that exogenous Klotho supplementation may help limit periodontal tissue destruction and promote healing under inflammatory conditions (12,28). In addition to recombinant Klotho protein, several therapeutic strategies aimed at enhancing endogenous Klotho expression have been explored in experimental studies. Pharmacological agents, gene delivery approaches, and epigenetic modulators capable of upregulating Klotho expression have demonstrated anti-inflammatory, antioxidant, and tissue-protective effects in preclinical models. However, these strategies remain at an early stage of development, and their safety, optimal dosage,

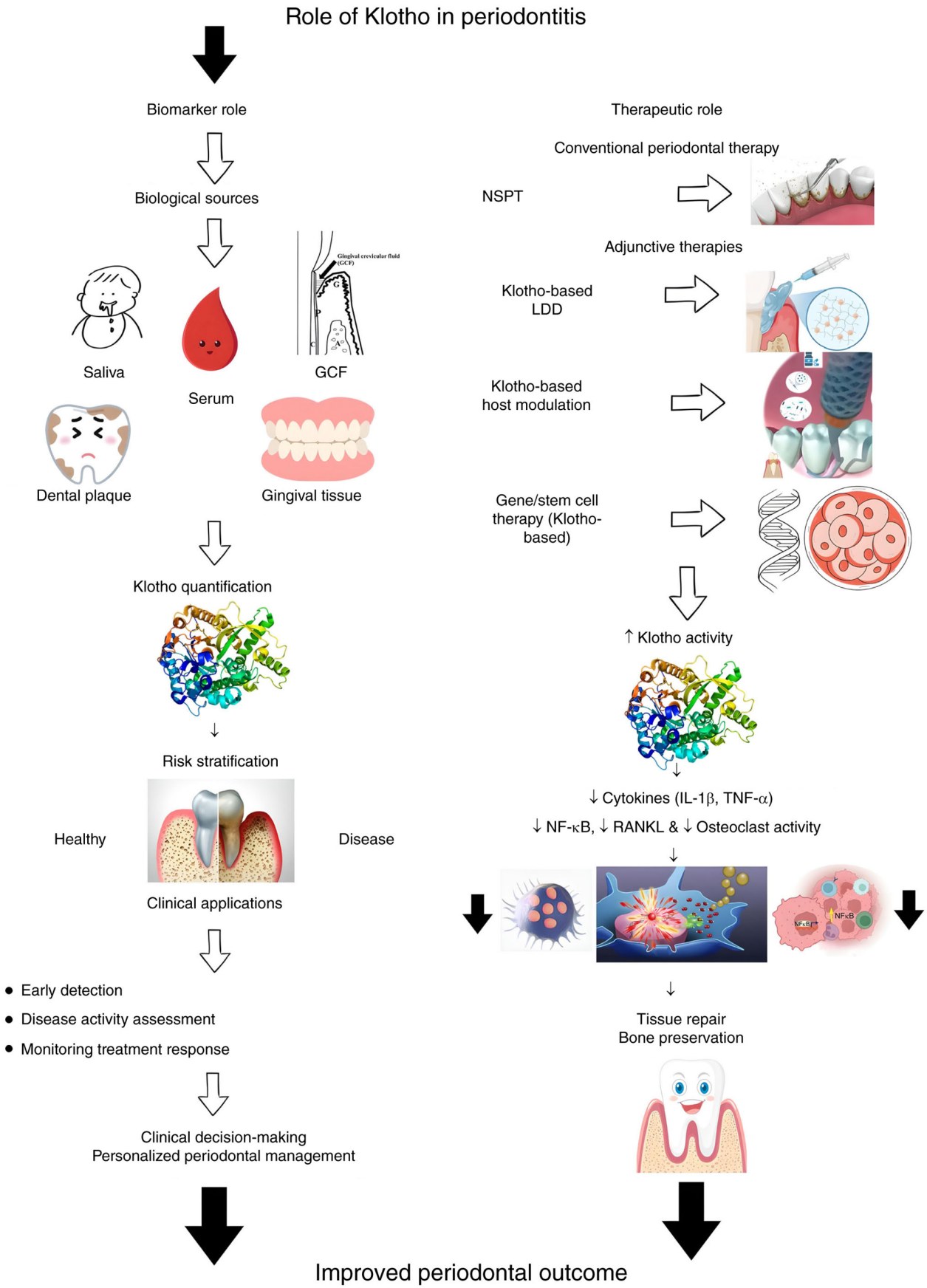

Figure 2. Klotho in periodontitis: Biomarker and therapeutic roles. Overview of Klotho as a biomarker and therapeutic target in periodontitis. Klotho can be detected in saliva, serum, gingival crevicular fluid, dental plaque and gingival tissue for risk stratification, early detection, disease assessment, and treatment monitoring. Therapeutically, nonsurgical periodontal therapy may be complemented by Klotho-based local drug delivery, host modulation, and gene therapy-based or stem cell-based approaches. Increased Klotho activity reduces inflammatory cytokines, NF-κB signaling, RANKL expression, and oxidative stress, promoting tissue repair, bone preservation, and improved periodontal outcomes. IL, interleukin; TNF-α, tumor necrosis factor α; RANKL, receptor activator of nuclear factor-κB ligand; GCF, gingival crevicular fluid; NSPT, non-surgical periodontal therapy; LDD, local drug delivery.

long-term efficacy and potential off-target effects require comprehensive evaluation before clinical translation (9,14,34).

Stem cell-based approaches further enhance the therapeutic potential of Klotho in periodontal regeneration. The pre-treatment of PDLSCs with recombinant Klotho has been shown to improve viability, reduce oxidative damage and enhance osteogenic differentiation. In addition, upregulation of Klotho expression in PDLSCs has been associated with decreased apoptosis and improved regenerative capacity, indicating its role in supporting periodontal tissue repair (13,37). Recent studies have further suggested that Klotho enhances the regenerative potential of PDLSCs by preserving mitochondrial function, inhibiting NOX4-mediated ferroptosis and maintaining osteogenic differentiation under inflammatory conditions, thereby supporting periodontal regeneration (10,13,15,27).

Advances in biomaterial-based delivery systems provide additional opportunities for the localized application of Klotho. The incorporation of Klotho into hydrogels, scaffolds, or nanoparticle-based carriers may enable controlled and site-specific delivery to periodontal tissues. However, successful local therapy must overcome the continuous outward flow of gingival crevicular fluid (GCF), which can rapidly remove therapeutic agents from periodontal pockets. Therefore, an ideal delivery system should possess strong mucoadhesive properties and sustained-release characteristics to maintain effective local Klotho concentrations, maximize therapeutic efficacy and minimize systemic exposure (38-40).

Klotho also holds potential in personalized medicine approaches for periodontitis. Given its involvement in inflammation, oxidative stress and bone metabolism, variations in Klotho expression may influence disease susceptibility, progression, and treatment response. As a biomarker, Klotho may help stratify patients based on molecular and inflammatory profiles, enabling more individualized treatment strategies. Although current evidence remains largely preclinical, integrating Klotho into precision-based periodontal care may improve patient stratification, diagnostic accuracy and individualized treatment strategies (9,34). Nevertheless, well-designed clinical trials are required to establish the efficacy, long-term safety, optimal delivery methods, and cost-effectiveness of Klotho-based therapies before their routine clinical application (Fig. 2) (9,34,41).

8. Limitations and future directions

Despite increasing evidence supporting the role of Klotho in periodontitis, several limitations need to be addressed. The majority of available studies are cross-sectional or experimental in nature, limiting the ability to establish causal relationships between Klotho expression and periodontal disease progression (9,34,37). Therefore, well-designed longitudinal and interventional human studies are required to clarify the temporal association between Klotho levels and disease onset, progression and treatment outcomes (13,41). In addition, the majority of clinical studies involve relatively small sample sizes and heterogeneous patient populations, limiting the generalizability and reproducibility of the available evidence (9,34). Another key limitation is the lack of standardized diagnostic criteria and measurement protocols across studies. Variability in periodontal case definitions, disease severity, sampling methods and Klotho detection techniques in serum, saliva, GCF and gingival tissues, contributes to inconsistent findings and limits direct comparison between studies. The standardization of these parameters is essential to improve reproducibility and clinical applicability.

Furthermore, the relative contribution of local vs. systemic Klotho in periodontal disease remains unclear. While local expression appears to be more directly associated with periodontal tissue changes, systemic Klotho levels are influenced by multiple confounding factors, including age, renal function, and systemic inflammation. Future studies are required to simultaneously evaluate local and systemic Klotho concentrations in well-characterized, age- and renal function-matched cohorts to clarify their respective contributions to periodontal disease and determine whether local-to-systemic Klotho ratios improve disease specificity. Finally, although preclinical studies highlight the therapeutic potential of Klotho, its clinical translation remains in the early stages. Further research is warranted to evaluate the long-term safety, efficacy, optimal dosage, delivery strategies and cost-effectiveness of Klotho-based therapies in well-designed multicenter clinical trials. Furthermore, integrating Klotho with established periodontal biomarkers, including IL-6 and MMP-8, may improve diagnostic and prognostic performance and facilitate its translation into precision periodontal care (35,36). Addressing these gaps will be critical for establishing Klotho as a reliable biomarker and therapeutic target in periodontitis.

9. Conclusion

Klotho has emerged as a key regulatory protein with significant relevance in the pathogenesis and potential management of periodontitis. Its ability to modulate inflammation, oxidative stress, cell survival and bone metabolism highlights its protective role in maintaining periodontal tissue homeostasis. Experimental and clinical evidence suggests that the reduced expression of Klotho is associated with periodontal disease, while its restoration may provide therapeutic benefits through anti-inflammatory and cytoprotective mechanisms. Although current findings are promising, the clinical translation of Klotho into periodontal practice remains in its early stages. Further well- designed longitudinal and interventional studies are required to validate its role as a reliable biomarker and therapeutic target. In addition, advances in biomaterials, regenerative therapies, and precision-based approaches may facilitate the translation of Klotho into clinical practice. Overall, Klotho represents a promising link between systemic regulation and periodontal health, with potential implications for early diagnosis, targeted therapy, and personalized medicine in periodontitis.

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Authors' contributions

All authors (GVP, JM and DP) contributed to the conception and design of the study. GVP performed the literature search and was responsible for the acquisition, analysis and interpretation of the data from the literature. GVP drafted the manuscript. JM and DP critically reviewed and edited the manuscript for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (Grammarly) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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