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REVIEW ARTICLE

Beyond Antibiotics: Exploring Alternative Adjuncts for Periodontitis

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ABSTRACT

Background: Periodontitis is a chronic, microbially-driven inflammatory disease affecting the gingiva and supporting structures of the teeth. Clinically, periodontitis is characterized by inflamed gingiva, clinical attachment loss, bleeding on probing, deep periodontal pockets, and alveolar bone loss. The pathogenesis involves an intricate interaction between specific gram-negative anaerobic bacteria particularly the “red complex” species (Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola) and a compromised host immune response. The primary method for nonsurgical periodontal therapy is scaling and root planning to remove supra- and subgingival calculus; however, advanced cases may require adjunctive systemic antibiotics. But due to the current global surge in antibiotic resistance, alternative non antibiotic therapies are under investigation.

Objective: This study aims to explore novel, non-antibiotic therapeutic approaches for the management of periodontitis.

Materials and methods: A comprehensive literature search was conducted using keywords such as periodontitis, non-antibiotic, bacteriophages, phytotherapy, nanoparticles, and metallic salts across databases including PubMed, ScienceDirect, and Google Scholar.

Results: The reviewed literature indicates that phytotherapy, manuka honey, metallic salts, nanoparticles, bacteriophages, photodynamic therapy, probiotics, and vaccine-based strategies can significantly reduce inflammation, bacterial load, and gingival bleeding.

Conclusion: In the context of multidrug resistance, these novel therapies present promising potential for periodontal treatment.

Keywords: Periodontitis; Non-antibiotic; Bacteriophages; Phytotherapy; Nanoparticles; Metallic salts

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1. INTRODUCTION

Periodontitis is a chronic inflammatory disease often associated with the accumulation of dental plaque and calculus, characterized by progressive loss of tooth-supporting structures that includes the periodontal ligament and alveolar bone.[1] Certain factors such as bacterial pathogens, compromised host immune response, and other contributing factors such as smoking, diabetes mellitus, metabolic syndrome, and obesity are responsible for its pathogenesis.[2] Its characteristic features include inflamed gingiva, clinical attachment loss, bleeding on probing, deep periodontal pockets, and alveolar bone loss.[3]

Periodontitis is caused by a group of specific Gram-negative anaerobic species referred to as the “red complex” which are strongly associated with disease initiation and progression.[2] These “red-complex” bacteria include Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, which are predominantly found in deep periodontal pockets of patients with periodontitis.[4]

Although bacterial infection is the main etiologic agent in periodontal disease, other possible risk factors (RF) have been identified by various researches that include modifiable RF like tobacco smoking, Type 1 and 2 diabetes mellitus, and non-modifiable (RF) that include genetic factors, like host responses, e.g., IL-1 gene polymorphism, which have been linked to periodontal disease, osteoporosis linked with alveolar bone loss, and systemic diseases like “Chediak-Higashi syndrome, cyclic neutropenia, lazy leukocyte syndrome, agranulocytosis, leukocyte adhesion deficiency, Down syndrome, and Papillon Lefevre syndrome”. [5]

The initial cause-related therapy considered to be the gold standard for periodontitis is scaling and root planning, which aims to remove supra gingival and sub gingival calculus. [6] In certain cases, however, this does not suffice, particularly when there are deep periodontal pockets, furcation involvement, or when bacteria possess the ability to invade host tissue, necessitating additional treatment to eradicate all pathogenic bacteria, such as prescription of systemic antibiotics. Amidst global antibiotic resistance, alternative therapies aimed at achieving a similar result are being explored. So far, the following list of treatments has been promising antimicrobial peptides (AMPs), bacteriophages, herbal extracts, manuka honey, metallic salts, nanoparticles, photodynamic therapy, probiotics, and vaccines.[6] While some of the treatment options are still being studied and undergoing clinical trials, these alternatives offer a potential solution in the face of global multidrug resistance.

2. MATERIALS AND METHODS

A comprehensive literature search was conducted using keywords such as periodontitis, non-antibiotic, bacteriophages, phytotherapy, nanoparticles, and metallic salts across databases including PubMed, ScienceDirect, and Google Scholar.

2.1 Non-Antibiotic therapy for periodontitis

Phytotherapy

The term ‘phytotherapy’ comes from Latin: ‘phyto’ means plant, and ‘therapy’ means treatment. Hence, it refers to the use of herbs with medicinal properties for the treatment of various diseases.[7] Natural herbs have been effective in managing oral health issues, including gingivitis, periodontitis, halitosis, and dental caries.[8] The main benefit of using medicinal herbs over synthetic chemotherapeutic drugs is that they generally have fewer adverse reactions, such as hypersensitivity reactions and bacterial resistance.[9] Additionally, they are non-alcoholic and non-cariogenic,[8] and are often preferred due to their complex biological activity, better safety profiles, cost efficiency, and minimal environmental damage. In contrast, synthetic drugs may cause more adverse effects and contribute to issues like antibiotic resistance due to their misuse.[10]

2.2 Useful Herbs in Periodontics:

Guava: Guava contains quercetin, which exhibits potent antibacterial activity against key periodontal pathogens such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, and Fusobacterium nucleatum. In addition, guava helps prevent gingivitis, fight periodontal pathogens, and reduce inflammation by inhibiting prostaglandins, kinins, and histamines, as well as modulating NF-kβ signaling to prevent inflammatory bone loss.[7]

Aloe Vera: Aloe vera has varying pharmacological benefits, including antiviral, antifungal, antibacterial, and anti-inflammatory. It is effective in reducing gum swelling, inflammation, and bleeding. Aloe vera toothpaste and mouthwashes have been associated with lower plaque scores and prevent gingivitis, and aloe vera gel has proved to have antibacterial activity against Aggregatibacter actinomycetemcomitans, Clostridium bacilli, S. mutans, and Staphylococcus aureus, portraying its potential in preventing and managing periodontal diseases.[11]

Neem: It contains compounds like azadirachtin and nimbin, which provide antibacterial, antifungal, and anti-inflammatory benefits. Toothpaste and gels containing neem are effective in treating gingivitis and periodontitis by combating plaque-forming bacteria such as Streptococcus mutans and Lactobacillus species, helping prevent caries, and combating halitosis. Moreover, gallotannins in neem inhibit bacterial adhesion and glucosyltransferase activity, making it a valuable antiplaque agent.[11]

Pomegranate: Pomegranate's antioxidant property is helpful in treating periodontitis, as it scavenges free radicals, lowers oxidative stress on macrophages, and reduces lipid peroxidation. Its antibacterial action targets bacteria associated with gingivitis such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, and Prevotella intermedia; hence, pomegranate mouthwashes are effective for anti-plaque and anti-gingivitis purposes.[10]

Turmeric: It is well known for its anti-inflammatory, antioxidant, antimicrobial, and antiseptic properties. According to a study on 0.1% turmeric mouthwash, it works well as an antiplaque agent and has a beneficial impact on reducing gingival inflammation; thus, it can serve as an effective adjunct to mechanical plaque control for preventing plaque buildup and gingivitis.[12]

Eucalyptus: It possesses anticariogenic and antiplaque effects. Research has demonstrated the ability of eucalyptus to inhibit virulence factors of Porphyromonas gingivalis, such as Arg- and Lys- specific cysteine proteinases. Ethanol extracts from eucalyptus leaves, preferably at a concentration as low as 10 mg/ml, exhibit strong antibacterial activity against periodontopathic bacteria, including P. gingivalis and Prevotella intermedia.[13]

Tulsi leaves: They are found to be effective in treating common oral infections and maintaining oral hygiene. Chewing raw tulsi leaves, which contain antibacterial agents including carvacrol, terpene, and the FDA-approved sesquiterpene beta-caryophyllene, helps combat oral health issues. Tulsi is also efficacious against halitosis, and its anti-inflammatory properties increase its effectiveness for treating gingivitis and periodontitis.[14]

Green and Black Tea leaves: It has been demonstrated that the active microbial components in black tea, theaflavin and theaflavin-3,3′-digallate, and in green tea, epigallocatechin3-gallate, inhibit the growth of Porphyromonas gingivalis and Prevotella intermedia. Furthermore, when extracts are combined with metronidazole and tetracycline, they show a synergistic antibacterial activity against P. gingivalis, enhancing their effectiveness in oral health management.[6]

Plant-Based Essential Oils: Recent research highlights the antimicrobial effectiveness of plant-based essential oils, including clove, eucalyptus, lemon, orange, basil, tea tree, and myrrh, against dental pathogens such as Streptococcus mutans, Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum. Volatile oils like turmerone, atlantone, and zingiberene also improve gum health through subgingival irrigation.[9] Essential oil mouthwashes offer multiple benefits: they reduce plaque and aid healing post-surgery, control plaque and caries, manage bad breath with no adverse effects, lower bacterial levels before dental procedures, and minimize the risk of bacteremia.[15]

Herbal Mouthwashes: Gingivitis and periodontitis can be managed with extracts from Matricaria recutita, Salvia officinalis, Acorus calamus, Mentha piperita, Arnica sp., Quercus sp., and Thymus sp. Another formulation, which includes Salvadora persica, Terminalia bellirica, Piper betle, and essential oils from Elettaria cardamomum and Gaultheria fragrantissima, effectively targets various pathogens such as Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Porphyromonas gingivalis, Streptococcus mutans, and Streptococcus sanguinis. Additionally, mouthwashes containing Ocimum sanctum extracts are noted for their ability to reduce gingival inflammation.[6]

Bacterial resistance is a growing concern in medicine. Studies suggest that plants offer valuable antibacterial compounds, and their effectiveness can be increased when combined with conventional antibiotics and can be helpful against periodontal infections.[16]

2.3 Bacteriophages

Bacteriophage, a virus that parasitizes the bacterium by infecting and replicating inside it, has recently gained popularity in terms of a possible therapeutic solution for various bacterial actions.[17]

Bacteriophages comprise a significant portion of viruses in oral biofilms, which can either exist as free virions (phage particles) or as dormant prophages within bacterial lysogens.[18] Studies estimate, there may be up to 100,000 viruses in a 1 μl volume of saliva, the majority of which are phages.[18]

Several advantages of phage therapy have been reported in different research that includes 1. Phages can penetrate dense biofilms and destabilize the structure by separating the tightly adhered neighboring cells, which cannot otherwise be achieved with antibiotic therapy. 2. Unlike the broad-spectrum antibiotics, they are strain-specific and target the selective bacteria responsible for the formation of biofilm (Fusobacterium nucleatum playing a central role in biofilm formation) 3. Cause minimal damage to commensal flora. 4. At the infection site, they have the potential to self-replicate.[19] Few disadvantages are also observed with the phage therapy that includes 1. The possibility of the immune system treating them as foreign bodies leads to the activation of the adaptive immune response. 2. High risk of phage acquiring bacterial resistance genes.[20]

Therefore, extensive studies are required to achieve a comprehensive understanding of bacteriophages at the genetic level to assess the safety and efficacy of this potential therapy.

Regarding the phage therapy, multiple in vitro studies confirmed the effectiveness of various phage isolates against periodontal bacteria: JD-Fnp4 exhibited significant pathogenicity and a broad host spectrum against Fusobacterium nucleatum,[21] novel vB_AacS_1/Dc-1 was active against Aggregatibacter actinomycetemcomitans; " vB_AorP_1/G-12, vB_AorP_2/Ch-28, and vB_AorP_3/Bl35" demonstrated activity against Actinomyces oris;[22] and novel SAM-E.f 12 showed promising results against antibiotic-resistant Enterococcus faecalis infections.[23] However, extensive research, particularly through clinical trials, is necessary to establish its efficacy.

2.4 Metallic salts

Antimicrobial in vitro tests have demonstrated that low molecular weight metal compounds like copper chloride, silver diamine fluoride (SDF), silver nitrate, and zinc chloride possess bactericidal and bacteriostatic activity.[6]

Silver diamine fluoride (SDF):

SDF is an efficient and economical alternative for various dental issues such as tooth caries, gum disease, and oral infections.[24] It is a unique mixture of silver, which possesses antimicrobial properties, and fluoride, which strengthens enamel and helps combat caries.[25] One of the major drawbacks of SDF treatment is tooth discoloration.[24] All SDF dilutions completely prevented the growth of S. mutans and A. actinomycetemcomitans, although P. gingivalis was still viable with 0.197% and 0.098% SDF; however, their growth was inhibited by higher concentrations [26].SDF treatment suppresses red- and orange-complex periodontal bacteria in subgingival biofilms, indicating a promising potential for SDF in preventing periodontal infections. The only red- and orange-complex species found in SDF-treated samples were P. micra and S. constellatus.[27] The main isolates from SDF-treated specimens were particularly Streptococcus spp., S. Oralis. No significant differences in antimicrobial efficacy were observed between 19% and 38% SDF in treating subgingival biofilm, suggesting their resistance to SDF irrespective of the concentration.[28]

Silver nitrate, copper chloride and zinc chloride:

Other metal ions, such as silver nitrate, copper chloride, and zinc chloride, have been tested for their potential as antimicrobial agents for treating periodontitis. Copper and zinc salts had limited and inconsistent effectiveness, whereas silver at 0.5 μg/mL exhibited a significant 3 log10 reduction in colony-forming units for the tested periodontal pathogens, including Eikenella corrodens, Campylobacter rectus, Prevotella intermedia, Fusobacterium nucleatum subspecies (incl. subsp. vincentii), Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Porphyromonas gingivalis, Prevotella denticola, and Campylobacter gracilis. Oral streptococci showed resistance to even higher concentrations of silver nitrate.[29] While some studies have proven that zinc and copper ions have increased adhesion and accumulation of salivary and serum proteins on P. gingivalis cells while inhibiting their coaggregation and hemagglutination. Therefore, these cations could prevent the settlement of P. gingivalis in the gingival sulcus, aiding in the prevention of periodontal disease.[30]

2.5 Nanoparticles (NPS)

Metal-based nanoparticles (NPs) unique mechanism of action presents a potential strategy for combating bacteria and biomolecules that have developed resistance to conventional antibiotics.[31] Metal NPs reported to exhibit antibacterial activity include silver, copper, iron, titanium dioxide, and zinc oxide.[32] NPs offer several key advantages for targeted drug delivery, especially in antimicrobial treatments. Their small size allows them to easily penetrate bacterial cell walls and biofilms. In addition, NPs can be designed to selectively target specific bacteria, improving treatment effectiveness. They also exhibit favorable pharmacokinetic properties, such as an extended plasma half-life, which enables prolonged drug circulation. Efficient renal excretion further helps reduce systemic toxicity, making NP-based therapies safer and more effective.[33]

NPs exert their antimicrobial effects primarily through the generation of reactive oxygen species (ROS), which damage microbial DNA, RNA, and proteins.[34] In addition to this, metal NPs release positively charged metal ions that interact with the negatively charged components of microbial cell membranes. These ions disrupt the membrane structure, allowing the NPs to penetrate bacterial cells. Once inside, the metal ions interfere with cellular processes by binding to the sulfhydryl groups (–SH) on microbial proteins, thereby inhibiting protein and nucleic acid synthesis. This combination of oxidative stress and direct interference with cellular machinery contributes to the antimicrobial action of nanoparticles.[34]

Zinc oxide nanoparticles:

Zinc oxide nanoparticles (ZnONPs) exhibited antibacterial efficacy against various bacterial strains, including S. aureus, S. mutans, P. gingivalis, and Fusobacterium nucleatum.[34] For the treatment of periodontitis, antibiotics incorporated with ZnONPs have shown superior effects. For example, oxytetracycline hydrochloride and ZnONPs were loaded into polycaprolactone nanofibers, resulting in the formation of PCL-OTCz as drug carriers.[35] This PCL-OTCz demonstrated significant antibacterial activity against four Gram-negative anaerobic bacteria— Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, and Treponema denticola—which was not achievable with the antibiotic and ZnO NPs alone.[35] Another combination of 0.2 mg/L of ZnO and 500 mg/L minocycline in serum albumin microspheres when loaded in Carbopol hydrogel also showed remarkable antibacterial activity against S. oralis, Porphyromonas gingivalis, S. sanguis, and Prevotella intermedia.[36]

Silver nanoparticles, titanium dioxide, and iron oxide nanoparticles:

Silver nanoparticles also demonstrated enhanced bactericidal activity against Gram-negative anaerobes, particularly P. gingivalis, B. pumilus, and E. faecalis.[37]

The growth of Porphyromonas gingivalis was also inhibited by tetracycline-loaded TiO_2 nanotubes, [38] but superparamagnetic iron oxide nanoparticles (SPIONs) when coated with polyglucose sorbitol carboxymethyl ether (PSC) does not directly kill Porphyromonas gingivalis; rather, they control periodontal inflammation by protecting human gingival fibroblasts (hGFs) against P. gingivalis invasion and inflammatory stimulation.[39]

2.6 Honey

For centuries, honey has been valued in traditional medicine for its anti-inflammatory, antibacterial, antioxidant, and wound-healing effects.[6] Compounds such as chrysin, quercetin, hydrogen peroxide, ferulic acid, β-defensin, methylglyoxal, ellagic acid, and chlorogenic acid contribute synergistically to the potent antimicrobial properties of honey.[40] Honey has been shown to be effective against several pathogens, including Campylobacter spp. Aggregatibacter actinomycetemcomitans, Campylobacter rectus, Eubacterium nodatum, Porphyromonas gingivalis, and Streptococcus gordonii.[41] A Randomized Controlled Trial (RCT) on patients suffering from periodontitis revealed that using the Manuka honey for 21 days significantly reduced plaque levels and bleeding sites.[42] Another clinical trial conducted with honey produced by Imtenan Co. Ltd. in Egypt showed significant effectiveness against Streptococcus mutans and Porphyromonas gingivalis.[43] Flavonoids,[44] hydrogen peroxide,[45] and the increased sugar concentration in honey create a hypertonic environment in the oral cavity that results in plasmolysis of microbial cells, leading to their growth inhibition and death.[46] Manuka honey has shown potential for use in mouthwashes because it has also demonstrated anti-inflammatory properties by dramatically lowering IL-8 and TNF alpha levels.[47]

Medical grade Manuka honey (NPA > 20) is highly effective against gingivitis-associated with gram-negative anaerobes, but its high sugar content, S. mutans resistance, and low pH risk to hard tissues limit its sub-gingival use, necessitating further research for safe dental applications.[48]

2.7 Photodynamic therapy

Non-invasive antimicrobial photodynamic therapy (APDT) complements scaling and root planing by not only eradicating periodontal bacteria but also preventing their recolonization.[49] Evidence from a systematic review and meta-analysis indicates that APDT may serve as an adjunct to scaling and root planing (SRP) in mild-to-moderate periodontitis cases with clinical attachment loss (CAL) < 5 mm. However, no improvement in clinical outcomes was observed in patients with severe periodontitis (CAL ≥ 5 mm), highlighting the limitations of APDT in advanced disease.[50]

A recent analysis has shown a significant reduction in the colonies of Porphyromonas gingivalis, Fusobacterium nucleatum, and Aggregatibacter actinomycetemcomitans (key bacteria involved in periodontitis) when susceptible to APDT.[51]

APDT operates through the coordinated action of three primary components: photosensitizers, light with appropriate wavelength, and oxygen. Photosensitizers are activated by light of a specific wavelength, leading to the generation of ROS. These reactive species induce irreversible oxidative damage to microbes. Importantly, photosensitizers selectively target and accumulate within microbial cells without causing harm to host tissues.[52]

Traditionally, photosensitizers included organic dyes and aromatic hydrocarbons, such as xanthene derivatives (e.g., Rose Bengal and eosin) and methylene blue. Over time, the field progressed from first-generation porphyrins, including hematoporphyrin derivatives, to second-generation chlorins and related compounds. These include Chlorin e6 (Ce6), temoporfin (m-THPC), Protoporphyrin IX (PpIX), 5-aminolevulinic acid (ALA), naphthalocyanines, and purpurins. Subsequently, third-generation photosensitizers were developed through nanostructure conjugation, such as nanoparticles, micelles, and liposomes. More recently, fourth-generation photosensitizers have emerged that are based on porous carrier systems, including mesoporous silica and metal–organic frameworks.[53]

2.8 Vaccines

Currently, no vaccine is approved for the treatment of periodontal diseases in clinical practice.

However, recent animal trials have shown success using different antigens from periodontal bacteria. This includes Porphyromonas gingivalis, Fusobacterium nucleatum, and Aggregatibacter actinomycetemcomitans as potential vaccine candidates. In addition to this, the potential vaccine candidates found against P. gingivalis include the following: "heat-killed whole bacteria, capsular polysaccharide and fimbriae, outer membrane proteins (PG32 and PG33), recombinant hemagglutinin B (HagB), hemagglutinin/adhesion domain from gingipain, and cysteine protease porphypain-2".[6] While no human vaccine trials have been conducted to date to evaluate whether this approach can prevent alveolar bone loss or inhibit bacterial colonization by targeted pathogens, the existing preclinical evidence indicates considerable therapeutic potential.[54]

2.9 Probiotics

Probiotics are beneficial live microorganisms that, when consumed in appropriate amounts, support the host by preventing the growth and colonization of harmful pathogens.[55] They have been employed in the treatment of various conditions, including diarrhea, inflammatory bowel disease, and allergies.

Additionally, they have been used in managing cardiovascular and cerebrovascular disorders, urogenital infections, and respiratory tract infections. Their applications also extend to cancer prevention and treatment, as well as the management of anemia.[56] Research interest in probiotics has started to grow, and initial human clinical trials have shown promising results for periodontal disease prevention.

Studies have shown that certain probiotic bacteria, such as Lactobacillus and Bifidobacteria species exhibit antimicrobial effects against oral pathogens and that this may help in managing periodontal infections.[6,57] Reuterin, an antimicrobial substance produced by Lactobacillus reuteri, has demonstrated potential in alleviating gingivitis and gingival bleeding.[58]

Clinical studies have confirmed that these probiotics can reduce plaque, gingival inflammation, and the proliferation of periodontal pathogens. Consuming fermented milk that contains the probiotic L. rhamnosus SD11 along with maltitol illustrates this effect.[59] Furthermore, improvements in periodontal pocket probing depth and plaque index were observed with daily intake of L. Salivarius probiotics, taken three times a day for a duration of 8 weeks.

CONCLUSION

The exploration of non-antibiotic alternatives has become increasingly essential due to the alarming rise in antibiotic resistance. The potential alternatives that include phytotherapy, bacteriophages, metallic salts, nanoparticles, honey, photodynamic therapy, vaccines and probiotics all have shown promising results yet still need further clinical trials to prove their long-term efficacy and safety. The integration of these non-antibiotic approaches may play a crucial role in reshaping the future of periodontal therapy.

ABBREVIATIONS	FULL FORM
RF	Risk factor
AMPs	Anti- microbial peptides
SDF	Silver diamine fluoride
NPs	Nanoparticles
ROS	Reactive oxygen species
(-SH)	Sulfhydryl
ZnONPs	Zinc oxide nanoparticles
SPIONs	Superparamagnetic iron oxide nanoparticles
PSC	Polyglucose sorbitol carboxymethyl
HGFs	Human gingival fibroblasts
RCT	Randomized Controlled Trial
APDT	Antimicrobial photodynamic therapy
SRP	Scaling and root planning

Authors contribution

HAA: Contributed to the conception and design of the study, participated in data collection, and contributed to drafting and revising the discussion and conclusion sections of the manuscript.

AID: Contributed to the development of the methodology, performed data analysis, and drafted the results and literature review sections of the manuscript.

TH: Contributed to the conception and design of the study, supervised the research project, and critically reviewed the manuscript.

AO: Participated in methodology, data collection and assisted in data organization.

RS: Contributed to the conception and design of the data analysis and provided critical revisions to the manuscript.

SA: Contributed to methodology, data analysis, drafting and revising the manuscript.

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Availability of data and materials

No primary datasets were generated or analyzed in this study. All data supporting the findings are derived from previously published articles, which are cited within the manuscript.

Consent for publication

Not applicable.

Disclaimer of using AI tools

The authors confirm that no artificial intelligence-assisted technologies were used in the development or preparation of this manuscript.

Conflict of interest

The authors declare that they have no conflict of interest related to this study.

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