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REVIEW

A Review of the Relationship between Oral Bacteria, Immunity, and Cognitive Function Targeting Drug Discovery

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ABSTRACT

Introduction: **The tripartite interaction between oral bacteria, the immune system, and cognitive function (the oral-brain axis) has increasingly garnered attention as a drug discovery target. Advanced biopharmaceutical technologies are used in addition to conventional vaccine technologies for developing preventive drugs. Regarding drug discovery, in addition to conventional improvements in the oral biome, the GAIN trial using gingipain inhibitors released by *Porphyromonas gingivalis* (Pg bacteria) has also attracted attention, as well as the serious effects of *Treponema denticola* (Td bacteria). Currently, there are no preventive drugs for these conditions; conventional oral hygiene management such as probiotics and scaling is the mainstay of treatment. Given this situation, developing preventive drugs is extremely important; we conducted this review for accelerating drug discovery.**

Method: **Electronic search of PubMed, CENTRAL, MEDLINE, EMBASE, Google, and CINAHL was performed. This period comprised the most recent five years (2020–2025). Based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 statement, the screening of selected databases involved evaluating data by titles and abstracts, and the eligibility analysis involved organizing methodologies and key results by reading the full documents, followed by result evaluation and final analysis.**

Results: **Clinical trials of gingipane protease inhibitors have confirmed their efficacy. However, newly discovered hepatotoxicity hinders drug development; moreover, the development of new drugs with improved safety is still in progress. Although probiotics and postbiotics have proven to be effective, antimicrobial resistance associated with conventional antibiotics is problematic. Phage therapy showed superior antimicrobial activity compared with conventional antibiotics, infecting and lysing only the target bacteria without affecting beneficial commensal bacteria.**

Conclusion: **Developing preventive drugs focusing on the tripartite interaction between oral bacteria, the immune system, and cognitive function, new drugs are currently in the development stage and their safety needs to be established. Oral care is evolving from a conventional and uniform approach into a precise one based on individuals' genetic background, microbiome, and systemic disease status. The use of Artificial Intelligence and induced pluripotent stem cells in regenerative medicine is progressing.**

Keywords: Advanced technology, oral bacteria, preventive drugs.

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1. Introduction

The tripartite interaction between oral bacteria, the immune system, and cognitive function (the oral-brain axis) is rapidly gaining attention targeting drug discovery. Advanced biopharmaceutical technologies are utilized in addition to conventional vaccine technologies for developing preventive drugs. The goal of drug discovery is holistic care; there has been a shift towards an approach that considers the entire disease process, from conventional post-symptomatic treatment to diagnosis, prevention, and pre-disease stages. In the case of oral bacteria, bacteria that enter the bloodstream from periodontal pockets cross the blood-brain barrier and reach the brain, where the neurotoxic enzymes produced by the bacteria cause chronic inflammation and nerve damage.

Regarding drug discovery, in addition to conventional improvements in oral biome, the GAIN trial of gingipain inhibitors released by *Porphyromonas gingivalis* (Pg bacteria) attracted attention. The primary objective of this clinical trial was to suppress cognitive decline in the general population, which was not achieved. However, in patients with Pg bacterial DNA-positive saliva, cognitive decline was suppressed by approximately 30%–50% [1]. Furthermore, although Pg bacteria have been targeted as core bacteria, the serious impact of *Treponema denticola* (Td bacteria) also increasingly garnered attention. Td has extremely high motility and exhibits neurotropism, meaning that it directly migrates to the brain along the nerve fibers. Clusters of Td have been identified in brain tissue samples from patients with AD; cases of coinfection with multiple spirochete species have also been reported. These bacteria form a symbiotic relationship with *P. gingivalis*, creating a red complex where they mutually promote growth, amplifying neuroinflammation and directly inducing apoptosis and tau protein hyperphosphorylation in nerve cells [2].

Currently, there are no preventative medications for Td bacteria; treatment relies solely on general hygiene care such as commercially available antibacterial mouthwashes, probiotics, and scaling. Given this situation, developing preventive drugs is of paramount importance; we conducted this review to facilitate drug discovery.

2. Methods

2.1. Target Literature and Search Period

Electronic search of PubMed, CENTRAL, MEDLINE, EMBASE, Google, and CINAHL was performed. This period comprised the most recent five years (2020–2025).

2.2. Selection and Exclusion Criteria

Results regarding the Correlation between oral bacteria, the immune system, and cognitive function were described. Treatment and prevention methods and results of inflammation caused by oral bacteria were described.

Opinion pieces, editorials, articles without empirical data, and publications consisting only of abstracts were excluded.

2.3. External Frames of Reference

Based on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement, the screening of selected databases involved evaluating data using titles and abstracts, and the eligibility analysis involved organizing methodologies and key results by reading the full documents, followed by result evaluation and final analysis.

3. Results

Considering the 11 studies presented in Table I, prevention or reduction of inflammation severity related to oral bacteria was demonstrated.

In clinical trial 1, the efficacy was confirmed; however, newly discovered hepatotoxicity hindered drug development. As a result, development was shifted to a new drug, "COR588," with improved safety. In trial no. 2, curcumin was effective; in clinical trial no. 3, curcumin was effective as a complementary therapy to scaling and root planing. Drug susceptibility testing of *T. denticola*, trial no. 4 revealed resistance to metronidazole, which was effective against anaerobic bacteria, highlighting the risk of resistance to conventional antibiotics. In trial no. 5, the value of personalized periodontal treatment is underscored, noting that customized care could improve patient outcomes. All three treatment methods (full mouth scaling [FMS], quadrant-specific scaling and root planning, and full-mouth disinfection [FMD]) showed notable improvements. These results indicated that each approach was effective in addressing severe periodontitis and provides clinicians with a variety of strategies that could be adjusted to suit the unique circumstances of individual patients. The results from trial no. 6 suggested that moxifloxacin might be a promising antimicrobial agent against *P. gingivalis*, *T. forsythia*, and *A. actinomycetemcomitans* for the treatment of periodontitis. However, these isolates showed reduced susceptibility to other antibiotics. Amoxicillin, azithromycin, and metronidazole were ineffective against A. actinomycetemcomitans in vitro.

The results in trial no. 7 suggested that o-Cymen-5-ol exhibited antibacterial properties without adversely altering the oral microbiome, making it an important component of oral care. Specifically targeting possible oral pathogens while encouraging the development of advantageous bacteria such as Rothia has been discovered, which might help control blood pressure. Experiment no. 8 investigated the anti-colitis effects of wheat-like arabinoxylan (WBAX) and symbiotic organisms derived from the probiotic strain *Rimosilactobacillus reuteri* WX-94, which exhibited tryptophan metabolic activity, as well as postbiotic WBAX. WBAX promoted the growth of *L. reuteri* and facilitated the microbial conversion of tryptophan to AhR ligands. It also promoted the reversal of DSS-induced colonic abnormalities and facilitated the regulation of essential proteins and genes involved in synthesis of amino acids.

TABLE I: Contents and Results of Clinical Trials

Authors	Population	Intervention	Results
1. Sabbagh and Decourt [1]	643 patients with mild-to-moderate AD dementia [1]	643 patients with mild-to-moderate AD dementia were administered placebo, 40-mg COR388 twice daily, or 80-mg COR388 twice daily	Atuzaginstat was the first gingipaneprotease inhibitor and has shown efficacy in some groups of patients exhibiting *P. gingivalis* DNA; however, drug development was hindered by newly emerging hepatotoxicity.
2. Izui *et al*. [3]	Human gingival epithelial cells (HGE): Immortalized cell lines are used [3].	The effects of curcumin on the expression of inflammatory cytokines were evaluated by a real-time reverse transcription polymerase chain reaction assay; its effects on cell migration were validated using a scratch wound assay.	In HGE cells stimulated with OMVs, the gene expression of IL-6, IL-1β, and TNF-α was significantly suppressed in a dose-dependent manner by curcumin, suppressing the cytotoxicity of OMVs on cell migration and dose-dependently inhibiting apoptosis by cells.
3. Kamil *et al*. [4]	Forty dental outpatients with moderate-to-severe gingivitis were randomly assigned to participate in the study [4].	Following baseline evaluation, all participants underwent SRP. Based on group allocation, the respective adjunctive intervention (curcumin gel, curcumin lozenges and chlorhexidine gel) were administered.	Curcumin gel and chlorhexidine gel (2%) significantly improved the clinical efficacy of scaling and root planing in patients with plaque-induced gingivitis. Curcumin gel demonstrated comparable clinical efficacy to chlorhexidine and was safe.
4. Pawar and Ramamurthy [5]	Plaque samples were collected from 30 participants who were diagnosed with periodontal disease [5].	A comprehensive antimicrobial agent panel commonly used for periodontal treatment was selected; in vitro antimicrobial susceptibility testing (AST) was performed on the isolated *T. denticola* strain using the antimicrobial gradient method.	*T. denticola* showed resistance to metronidazole and sensitivity to tetracycline, cefoperazone, chloranphenicol, clindamycin, and moxifloxacin.
5. Gaddam *et al*. [6]	In a randomized clinical trial including 180 patients with periodontitis, the patients were randomly allocated into three treatment groups [6].	Group I underwent full mouth scaling (FMS); Group II received quadrant-specific scaling and root planning (Q-SRP); and Group III received full mouth disinfection (FMD). Clinical parameters were evaluated at baseline and 3 months after intervention.	All three treatment modalities showed improvements in clinical parameters after three months. Intergroup comparisons revealed no significant differences in Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL) among the three groups. Plaque Index (PI) and modified Sulcus Bleeding Index (mSBI) changes were reduced significantly in the Q-SRP group compared with the other two groups.
6. Ardila and Bedoya-García [7]	76 patients were diagnosed with generalized periodontitis [7].	Subgingival samples were processed by culture. Etest was used for determining susceptibility to amoxicillin, metronidazole, azithromycin and moxifloxacin.	The isolates presented reduced susceptibility to the other antimicrobial agents investigated. The *P. gingivalis* samples showed relatively similar rates of resistance to amoxicillin (24.6%), azithromycin (21.3%), metronidazole (24.6%). Similarly, 25.6%, 21.0% and 25.6% of the *T. forsythia* isolates were resistant to amoxicillin, azithromycin, and metronidazole, respectively.
7. Pascual *et al*. [8]	A mouthwash formulated with o-cymen-5-ol and zinc chloride was administered to a cohort of 51 volunteers for 14 days, while another cohort of 49 volunteers received a placebo [8].	The evolution of the oral microbiome in both groups was analyzed using a metataxonomic approach.	Mouthwash containing o-cymen-5-ol and zinc chloride selectively targeted potential oral pathogens while maintaining the integrity of the rest of the microbiome.
8. Zhou *et al*. [9]	The study involved extracorporeal fermentation of WBAX and L. reuteri: Addition of glucose and WBAX to LB culture medium [9].	Heat-inactivated postbiotics derived from WBAX and *L. reuteri* modulated tryptophan-related gut microbiota and metabolism, improving chronic colitis in mice.	WBAX promoted the growth of *L. reuteri* and facilitated the microbial conversion of tryptophan to the AhR ligand. Oral gavage of the WBAX postbiotic promoted the reversal of DSS-induced colonic abnormalities and promoted the regulation of essential proteins and genes involved in synthesis of amino acids.
9. Kamitaki *et al*. [10]	In the study, integrated analysis of 12,519 oral microbiomes was performed [10].	DNA sequencing reads generated from whole-genome sequencing (WGS) of saliva samples from 12,519 participants in the Simons Foundation Powering Autism Research (SPARK) cohort were analyzed.	Eleven human gene regions directly controlled oral bacterial composition; in particular, "FUT2 mutations" influenced the abundance of 58 bacterial species.

TABLE I: (Continued)

Authors	Population	Intervention	Results
10. Zhu *et al*. [11]	The study demonstrated a nanocoating that rapidly altered the surface of *Escherichia coli Nissel* 1917 (EcN), a probiotic widely used for the treatment of gastrointestinal diseases [11].	The process involved decorating probiotics with multifunctional nanoarmor and layer-by-layer coating of HMW-HA, based on the mechanism of synergistically enhanced biotherapy for inflammatory targeting and colitis.	Applying therapeutic nanocoatings to probiotic bacteria preserved drug efficacy and enhanced therapeutic effects.
11. Xiang *et al*. [12]	*E. faecalis* YN771 was isolated, identified, and cultured from a patient requiring root canal retreatment in the oral surgery department of a hospital [12].	120 Sprague Dawley rats were divided into six groups: a blank group, a control group, an *E. faecalis* group, an *E. faecalis* + phage group, an *E. faecalis* + penicillin group, and an *E. faecalis* + clindamycin group, for comparison.	Phage therapy could prevent *E. faecalis* YN771 and RYN771 infections, and PEf771 showed the best antibacterial activity compared with common antibiotics.

Study no. 9 revealed that multiple human genes were significantly associated with the abundance of specific bacterial groups in a large-scale genome-wide association study. A single gene change could trigger coordinated fluctuations in multiple bacterial species, indicating that the oral cavity is not merely a collection of bacterial species but an interactive network. It was a co-evolutionary ecosystem in which the host creates the environment, and microorganisms adapted to it. In trial no. 10, the focus shifted from conventional sterilization therapy to a "preventive treatment using probiotics" that increased beneficial bacteria and restored balance. However, owing to drug retention problems, the key feature of this approach was the extended duration of the drug effects achieved through nanotechnology. Comparative experiments with phage therapy (no. 11) demonstrated superior antibacterial activity compared with common antibiotics, infecting and lysing only the target bacteria without affecting beneficial commensal bacteria.

4. Discussion

Tripartite interactions between oral bacteria, the immune system, and cognitive function (the oral-brain axis) are highly promising targets for drug discovery [1]. However, Atuzaginstat, the only drug that focused on the link between periodontal bacteria and Alzheimer's disease, warrants further research, including improvements in hepatotoxicity. Furthermore, *Treponema denticola* in the oral cavity is a type of bacteria known as the "red complex," and because it is associated with severe periodontal disease, it is extremely important for preventing its proliferation. However, antibiotic resistance is a major problem; the essence of oral diseases clearly lies not in the presence or absence of specific bacteria but in the disruption in the overall balance of bacterial communities (dysbiosis). Killing all commensal bacteria could lead to the proliferation of antibiotic-resistant and harmful bacteria [5], [7].

Traditional treatment methods involved SRP, which involved scaling different sections of the mouth for several weeks. Recently, FMS has emerged as a method for treating the entire oral cavity within 24 h. When an antiseptic (such as chlorhexidine) is added to the FMS, this intervention is called FMD; the reason for using the full-mouth method is to reduce the possibility of reinfection in previously treated areas. Therefore, accurate comparisons cannot be made without tracking changes over time after treatment [6].

In addition, curcumin, cetylpyridinium chloride, and isopropylmethylphenol are used as adjunctive therapies [3], [4], [8].

Therefore, our initial goal was to suppress the bacterial growth and prevent gingivitis. However, disruption in the balance of oral bacteria (dysbiosis) has attracted attention as a risk factor for serious systemic diseases; furthermore, the objective has shifted from sterilization to balance adjustment. In response, preventive dentistry using bacterial therapy or probiotics has begun to gain popularity. Furthermore, postbiotics are a new approach to oral care that uses metabolites produced by beneficial bacteria rather than live bacteria (probiotics). Since they use inactivated products, they are less prone to quality changes and have longer shelf life [9]. Furthermore, there is a close relationship between human genes and oral bacteria; 11 human gene regions influence the composition of oral bacteria have been identified [10]. Coevolution has been confirmed, in which oral bacteria adapt by altering their own genes to match genetic differences in humans.

Therefore, the oral cavity is a symbiotic ecosystem; disease is primarily caused by an imbalance in this ecosystem. The goal of treatment is not to eliminate bacteria but to restore homeostasis. Bacteria should not be eliminated but rather treated as partners with whom we should maintain balance and coexistence. The notion that "oral bacteria are equivalent to local infections " has been completely rejected, and the goal is to maintain homeostasis from the oral cavity to the entire body by normalizing the balance between bacterial communities. Therefore, an approach such as improving the soil of the mouth by cultivating a high-quality bacterial flora, is aimed for, but in next-generation disease treatment using live bacteria; solving the technical challenges of survival rate and colonization ability is necessary.

To address this problem, an innovative drug delivery system has been reported to dramatically increase the survival rate of probiotics under harsh stomach acid and intestinal conditions by coating them with an environmentally responsive nanoarmor, allowing them to stably

colonize and treat inflammation [11]. This achieves super-resistance by encapsulating probiotics in the nanoarmor, protecting them from the harsh acidic and enzymatic environment and allowing them to reach the inflamed area of the intestines alive. Furthermore, the nanoarmor is specifically broken down and released in response to the inflammatory environment, allowing probiotics to specifically colonize the inflamed areas and exert a sustained therapeutic effect. This achievement represents a significant advance in solving the technical challenges of survival rate and colonization ability in next-generation disease treatments using live bacteria.

However, problems, such as biofilm formation and antibiotic resistance, remain. In contrast, phage therapy is a treatment method that uses bacteriophages, which are viruses that infect and kill only specific pathogenic bacteria. It is effective against drug-resistant bacteria, does not kill beneficial bacteria, and has few side effects, making it a next-generation antimicrobial strategy that could be a cure for multidrug-resistant bacterial infections [12]. Using a mouse model, it was confirmed that the bacteriophage can efficiently destroy and kill *E. faecalis* biofilms that are resistant to conventional antibiotics, and that the bacteriophage functions safely and effectively in vivo. The greatest significance lies in the fact that they can treat drug-resistant bacteria, such as superbugs that are unresponsive to conventional antibiotics, by lysing the bacteria, cases that are untreatable with existing drugs can be expected to be cured by administering phages. Unlike antibiotics that kill a wide range of bacteria, these drugs are thought to have very few direct side effects because they are less likely to disrupt beneficial commensal bacteria other than the target bacteria and do not infect human cells.

Research toward the implementation of phage therapy is expanding, including reports on the prevention of infection after root canal treatment using phage vB_ZEFP [13], effectiveness of phage therapy using PEf771 in preventing periapical inflammation after root canal treatment [12], and development of novel bacteriophage cocktails for MSSA and MRSA infections [14]. Phage therapy is a personalized medical approach for treating drug-resistant bacterial infections that targets specific pathogenic bacteria. Identifying the causative bacteria at the infection site and selecting a phage that is highly effective against this strain, achieving high therapeutic efficacy while minimizing side effects is possible. Furthermore, the presentation of optimal solutions based on individual data has accelerated. Based on the accumulated big data, an AI-driven approach provides early diagnosis and risk prediction of periodontal-systemic interactions, presenting individually optimized solutions [15]. Furthermore, Oral Reverse Aging technology is under development; moreover, personalized care techniques that use induced pluripotent stem (iPS) technology and other methods to rejuvenate the oral environment are attracting attention [16]. Artificial intelligence (AI) integrates vast amounts of clinical data with individual vital signs, enabling precise prognostic prediction and automated treatment optimization. Furthermore, cutting-edge techniques for stem cell transplantation, including methods for extracting and administering cytokines secreted during cell growth, are evolving.

5. Conclusion

Regarding the development of preventive drugs focusing on the tripartite interaction between oral bacteria, the immune system, and cognitive function, the new drug "COR588" is still under development, and its safety needs to be established.

Due to the problem of drug resistance, the value of personalized oral treatment is being emphasized.

Oral care is evolving from a conventional one-size-fits-all approach to a precise approach based on an individual's genetic background, microbiome, and systemic disease status.

The use of AI and regenerative medicine using iPS cells are progressing.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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