Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Periodontology and Implantology

Journal homepage: https://www.ijpi.in/

Review Article

Filifactor alocis: A deleterious intruder into the oral cavity and its effect on periodontal status

P Swethaa[1]*, B Fathima Afzana[1], Arun Sadasivan[1], T.S Nilima[1], Chitra GirijaVallaban[1], Steffi Vijayakumar[1]

[1]Dept. of Periodontology, Sree Mookambika Institute of Dental Sciences, Kulasekaram, Tamil Nadu, India

Abstract

Filifactor alocis, a Gram-positive obligate anaerobic bacterium, is increasingly recognized as key player in periodontal disease. This review delves into the virulence attributes of *F. alocis*, from its capability to thrive in oxidative stress environment of periodontal pockets to its production of damaging proteases and collagenases. The interactions of *F. alocis* has with another oral bacteria and host immune system are also explored. Understanding these mechanisms may provide insights into novel diagnostic and therapeutic approaches for periodontal disease.

Keywords: Gram-positive obligate, Virulence attributes, Oxidative stress environment, Damaging proteases and collagenases, Host immune system

Received: 05-02-2025; **Accepted:** 01-03-2025; **Available Online**:25-04- 2025

1. Introduction

Periodontitis is a chronic inflammatory disease occurred due to complex interaction between certain pathogens in a dysbiotic sub gingival biofilm, developing in progressive and irreversible loss of periodontal tissues.[1,2] The etiology of periodontitis has been a field of extensive research and it is well established that unlike other infectious diseases, periodontal diseases are related with a consortium of organisms rather than individual pathogens at periodontal sites.[3] The quest to find specific periodontal pathogens has led to the discovery of a numerous candidates. In 1998, Socransky et al clustered these repeatedly occurring bacterial species into complexes among which, "the red complex" (*Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola*) and the "orange complex" (*Aggregatibacter actinomycetemcomitans, Porphyromonas endodontalis, Prevotella intermedia*, and *Fusobacterium nucleatum/periodonticum*) species has played an important role in the initiation and development of periodontal diseases.[4] Furthermore, *P gingivalis* had designated as a "keystone pathogen", orchestrating inflammatory disease by altering a normally benign micro biota into a dysbiotic one.

But a major drawback in all these paradigms is that a large extent of the studies on etiology of periodontal diseases have historically been limited to some cultivable bacteria that were strongly related with the diseased sites.[5] But recent advents in the evolution of culture-independent procedures has allowed the invention of as-yet unculturable and fastidious organisms in periodontitis patients like *Treponema lecithinolyticum, Solobacterium moorei, Cryptobacterium curtum, Mitsuokella dentalis, Porphyromonas endodontalis, Peptostreptococcus micros, Fusobacterium nucleatum* and it is likely that these appearing new pathogens may play a major role in the progression of periodontal disease.[5]

Among these, *F. alocis* deserves special attention due to its unique characteristics which allows them to modify multiple changes on the microbial community and host cells proteome, compatible with the polymicrobial synergy and dysbiosis (PSD) periodontal pathogenesis model.[6] *F. alocis* infections are portrayed by dysfunctional modulation of

*Corresponding author: P Swethaa
Email: swethaaraj98@gmail.com

https://doi.org/10.18231/j.ijpi.2025.003

neutrophils, adhesion to and invasion of epithelial cells, resistance to oxidative stress and inhibition of complement cascades.[7] Furthermore, in collation to other traditional periodontal pathogens, *F. alocis* is present in periodontal pocket in more numbers and it is less in healthy or periodontitis resistant patients, making them potential diagnostic indicator of active periodontal disease. This review focuses on *F. alocis*, the newest member of periodontal phylogeny and its role in periodontal diseases.

1.1. Incidence

Filifactor alocis (A thread like organism inhabiting in a furrow). Filum-thread; factor-a marker; alox-a furrow; referring to its separation from a crevice of the gums. The main site of *F alocis* is the gingival sulcus. *F. alocis* (ATCC 35896) was first isolated in 1985 from gingival sulcus in gingivitis and periodontitis patients and was originally arranged as *Fusobacterium alocis*,[8] then rearranged based on sequencing of 16s rRNA genes into the genus *Filifactor*.[9]

Recent years has seen an exponential rise in the studies highlighting the interrelation of *F. alocis* and periodontitis and it is now recognized as third most common pathogen in generalized aggressive periodontitis (45%), second most common in chronic periodontitis (90%) but shows the least occurrence in periodontitis resistant groups. In addition, *F. alocis* has also been obtained from infected root canals, particularly in cases of persistent or refractory periapical lesions. Its presence in these lesions suggests its capability to live and thrive in the anaerobic surrounding within the root canal system.[10]

There is documented evidence suggesting an association between *Filifactor alocis (F. alocis)* and peri-implantitis.[11] The sulcus around dental implants affected by peri-implantitis often contains significant levels of asaccharolytic anaerobic Gram-positive rods (AAGPRs), among which *F. alocis* is one of the most predominant species.[12] *F. alocis* has been associated to gingivitis and diabetes during pregnancy and oral squamous cell carcinoma. Furthemore, *F. alocis* has also been found in extraoral sites in conditions like thoracic emphysema, lung cancer and brain abscesses and is shown to help in aggression of periodontal disease in rheumatoid arthritis.[13]

1.2. General characteristics

Filifactor alocis is a non-spore forming, Gram-positive, asaccharolytic obligate anaerobic bacterium owning trypsin like enzymatic activity alike *P. gingivalis and T. denticola. F. alocis* pertain to domain: Bacteria, phylum: Firmicutes, class: Clostridia, order: Clostridiales, family: Peptostreptococcaceae, genus: *Filifacor*, species: *Alocis. F. alocis* typically presents as short rods measuring 1-2 μm in length, but at times, it may exhibit elongated forms, reaching lengths of 7-8 μm14 **Figure 1**. Transmission electron microscopic studies compared the ATCC 35896 strain of *F. alocis* with clinical isolates, revealing distinct surface differences. While the former displayed rudimentary markings and slender projections resembling pili, the latter displayed a thick slimy covering without external projections or markings.

Filifactor alocis (F. alocis) exhibits low gingipain-type activity, but demonstrates elevated non-gingipain protease activity. The asaccharolytic properties of *F. alocis* are reflected in genome, which encodes several proteins like arginine, lysine and cysteine, involved in amino acid metabolism. Despite potential shortcomings in its native amino acid synthesis pathways, the bacterium possesses a wide array of enzymes such as peptidases, proteases, and other variants. This suggests its capability to adapt and meet its nutritional needs by utilizing a diverse range of substrates.

F. alocis primarily utilizes the amino acids arginine and lysine, with cysteine being the next most used. These amino acids can be sourced from the destruction of numerous protein substrates by other bacteria and host-derived proteases in the periodontal pocket, providing *F. alocis* with nutritional support, aiding its existence and virulence.[15] In silico analysis of the *F. alocis* genome forecast a robust amino acid metabolism, including a well-developed arginine deiminase pathway, which metabolizes arginine into citrulline and ornithine.

F. alocis genome contains three annotated genes for the arginine deiminase pathway: arginine deiminase (HMPREF0389_ 001584), ornithine carbamoyltransferase (HMPREF0389_ 00791), and carbamate kinase (HMPREF0389_ 00535). In silico analysis of ornithine carbamoyltransferase reveals it has an ornithine/aspartate carbamoyltransferase domain, suggesting the enzyme may have a dual role. Studies by Uematsu et al., 1976 have suggested another possible enzymatic process without the intermediate step of citrulline formation, in the transmission of arginine to ornithine **Figure 2**.

Due to its gradual growing and fastidious nature, it is harder to detect *F.alocis* by conventional culture based methodologies. However, *F. alocis* have the potential for thriving in brain heart infusion broth enriched with yeast extract (0.5 mg/ml), L-cysteine (50 μg/ml), and 20% arginine, under anaerobic conditions at 37°C, with a gas composition of 10% H2, 10% CO2, and 80% N2 or sheep blood containing cysteine and arginine.[14] The existence of *F. alocis* in bacterial biofilms is confirmed by specific probes, indicating its role in the community. Visualization via FISH provides insights into microbial community dynamics.[0] *F. alocis* is predominantly found colonizing the apical and middle thirds of carriers, with occasional detection in the cervical third.[6] Notably, it exhibits a preference for settling on the carrier side adjacent to the soft tissues, placing it in direct contact with the host's immune defences. Those findings strongly imply that *F. alocis* actively contributes to both production and maintenance of the biofilms.[16] *F. alocis* might appear either scattered in the biofilm or in densely

packed groups as concentric bacterial aggregations or test tube brush formations. Radial alignment of F.alocis towards the surface of mushroom like protuberance of the biofilm are also observed. The capacity of *F. alocis* to establish microbial communities relies on the metabolic characteristics of these bacteria.

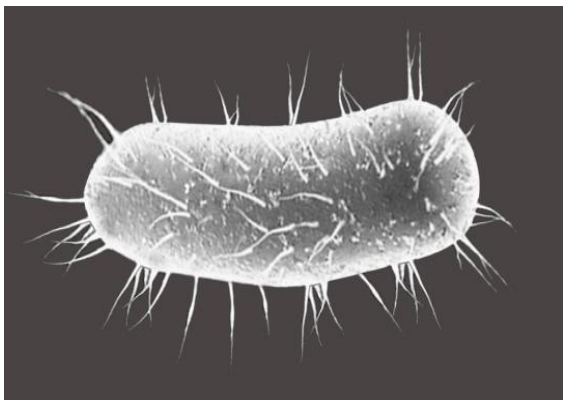

Figure 1: Structure of *F. alocis*

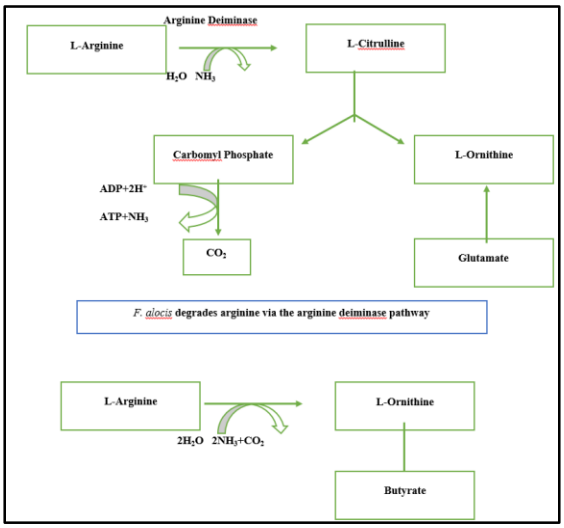

Figure 2: Enzymatic transmission of arginine to ornithine and ammonia

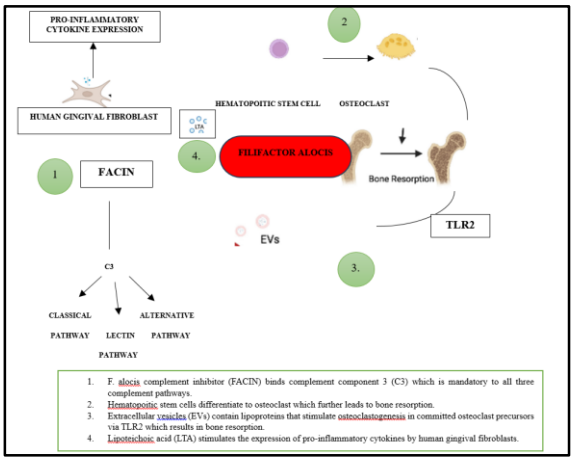

Figure 3: Mechanism of action of *F. alocis*

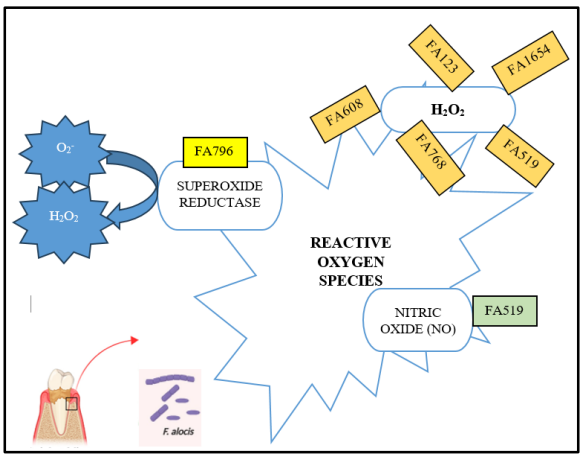

Figure 4: Oxidative stress resistance

2. Discussion

2.1. Virulence attributes

Filifactor alocis (F. alocis) possesses virulence properties that enable it to inhabit and live in the stressful environment of the periodontal pocket, akin to typical periodontopathogens. *F. alocis* can exacerbate the pathogenic process through various mechanisms like (1) Polymicrobial synergy (2) Enhanced invasive capacity (3) Oxidative stress resistance (4) Induction of chronic inflammation. Some unique virulence activities attributes of *F.alocis* are discussed below.

3. Virulence Factors Table 1

3.1. Proteases, collagenases and exotoxins

Proteases produced by major oral pathogens contribute significantly to their virulence by facilitating tissue degradation, immune evasion, nutrient acquisition, interference with host signaling, toxin activation, and biofilm formation. The genome of *F. alocis* contains 15 different proteases. Among these, the Caax protease (HMPREF0389_00590), which is a membrane-bound protease, is likely involved in the modification and secretion of proteins and/or peptides. This suggests a role for this protease in various cellular processes, potentially contributing to the virulence and pathogenicity of *F. alocis* infections.[18] The genome of *F. alocis* ATCC 35896 contains several uncharacterized proteases, the functions of which could be vital for understanding disease development, including tissue destruction and evasion of host defences. Investigating these proteases may offer insights into *F. alocis* pathogenicity and aid in developing targeted treatments for associated oral diseases.

Collagen, a key component of gingival connective tissue, is highly resistant to degradation and can only be cleaved by collagenases. The peptidase HMPREF0389_00504 (PrtFAC) produced by *F. alocis* has been shown to bind and degrade type I collagen and gelatin in a calcium-dependent manner.

This activity highlights the potential role of PrtFAC in tissue destruction associated with *F. alocis* infections. In addition PrtFAC, has the potential to induce both caspase-dependent and caspase-independent apoptosis in normal oral keratinocytes suggesting it may contribute to the pathogenesis of *F. alocis* by promoting host cell death.[19]

F. alocis can trigger the release of matrix metalloproteinases (MMPs), such as collagenase and gelatinase, from neutrophil granules, potentially leading to periodontal tissue damage. The genome contains a gene for alkyl hydroperoxide reductase subunit C (AhpC), which may help clear hydrogen peroxide. The lipoprotein-like molecules impede osteogenesis, reducing osteoblasts and impairing new bone formation while increasing osteoclast activity.[20] Membrane vesicles of *F. alocis* are lipoprotein-like molecules that affect osteoclasts and osteoblasts, leading to increased bone resorption typical of periodontitis.[21] The consequences on osteoclastogenesis and osteogenesis are mediated through Toll-like receptors (TLRs) on innate immune cells **Figure 3**.

3.2. Invasion and adhesion

Filifactor alocis (F. alocis) possesses the capability to adhere and penetrate epithelial cells, and this ability has further increased in the presence of Porphyromonas gingivalis.[0] The improved abilities seen with *P. gingivalis* likely result from bacteria communicating with each other, altering protein interactions. This inter-bacterial signaling can significantly affect microbial communities and host responses, particularly in environments like the oral cavity where *P. gingivalis* is involved in periodontal disease. Though, the exact mechanism by which *F. alocis* enhances invasion in the presence of other bacterial species, particularly *P. gingivalis* remains unclear, some potential mechanisms that could contribute to this phenomenon includes: (1) Synergistic interactions (2) Indirect effects (3) Competition and niche adaptation (4) Modulation of host immune responses. Filopodial projections originating from host microvilli were observed during the invasion by F. alocis, and it was believed that these projections played a role in mediating the organism's internalization.[22] As vesicle-mediated endocytic internalization of Gram-positive bacteria usually relies on type II and III exotoxins, it is plausible that exotoxins may leads to the heightened internalization noticed during co-infection with *F. alocis* and *P. gingivalis*.

Proteomic analysis of *Filifactor alocis* during co-infection with *Porphyromonas gingivalis* in epithelial cells by using tandem mass tagging disclosed an elevation of membrane adhesion proteins and Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs), suggesting enhanced bacterial adhesion and potential synergistic interactions that may exacerbate host tissue invasion. MSCRAMMs play a critical part in Gram-positive bacterial virulence by facilitating compliance and settlement of host tissues, a key early step in the development of clinically significant infections. The appearance of *F. alocis* MSCRAMMs has detected in both cell membrane and cell wall fractions.[23] In silico analysis of *F. alocis* collagenases reveals molecular similarity to collagenolytic MSCRAMMs found in other pathogenic bacteria. *F. alocis* can similarly aim the extracellular matrix (ECM) by interacting with collagenolytic MSCRAMMs.

3.3. Crispr genes

Regions of unusual DNA composition in bacterial genomes, such as the clustered regularly interspaced short palindromic repeats (CRISPR) locus and associated CRISPR-associated genes, are considered adaptive immunity systems in bacteria and have recently been linked to bacterial virulence.[24] The Type I CRISPR–Cas system is characterized by the signature Cas3 helicase/nuclease protein; the Type II system contains Cas1, Cas2, and Cas9, along with a predicted trans-activating crRNA (tracrRNA) and a small CRISPR/Cas-associated RNA (scaRNA); and the Type III system is defined by the presence of Cas10.[25] *F. alocis* is predicted to belong to the Type II-A CRISPR–Cas system. The upregulation of CRISPR/Cas system components through the co-infection of epithelial cells with *F. alocis* and P. gingivalis may indicate their involvement in virulence and pathogen synergy.

3.4. Oxidative stress resistance

Oxidative stress resistance is considered as a unique characteristic of *F. alocis*. And it is observed that, *F. alocis* infact experiences stimulated growth under such conditions. This likely explains the relative abundance of *F. alocis* in periodontal pockets compared to other organisms. *F. alocis* might also act as "oxidative sink," helping to stabilize the microbial community within the periodontal pocket's microenvironment. This is supported by the study by Aruni W et al., 2014, where it was observed that the presence of *F. alocis* enhances the existence of P. gingivalis when exposed to hydrogen peroxide-induced oxidative stress.[26]

The identification of the initial antioxidant enzyme known as "superoxide reductase" (SOR) in *F. alocis* highlights its significant role in defending against superoxide radicals, managing oxidative stress induced by exposure to air, and responding to hydrogen peroxide (H_2O_2)-related oxidative challenges **Figure 4**. SORs are enzymes containing iron that facilitate the transmission of superoxide radicals into hydrogen peroxide (H_2O_2).[21] The presence of sialidase activity in *F. alocis* serves dual functions. It not only fulfills its role as an asaccharolytic agent by breaking down sialated glycoproteins found in saliva, but also releases sialic acid, which acts as a scavenger for reactive oxygen species (ROS). This scavenging action helps to mitigate oxidative stress within the inflammatory environment of the periodontal pocket.[15]

When *F. alocis* is co-cultured with Porphyromonas gingivalis, it upregulates proteins involved in oxidative stress resistance, such as superoxide reductase, iron-sulfur cluster

proteins, iron permease, rubrerythrin, ferrous hydrogenase family proteins, and thioredoxin family proteins. This suggests an adaptive response to oxidative stress in the existence of *P. gingivalis*. Filifactor alocis has 3-methyladenine DNA glycosylase, an enzyme associated with stress resistance, but its specific function remains unclear. The *F. alocis* genome contains unique genes for iron-sulfur cluster proteins and a ferrous iron transport system not found in other "red complex" bacteria. *Filifactor alocis* also has a well-established protein sorting and transport system, indicated by the abundance of membrane proteins in its genome.[23]

3.5. Host microbe interaction

The initial encounter of periodontal bacteria occurs with the epithelial cells found in the gingival crevice. Filifactor alocis has ability to stimulate gingival epithelial cells to secrete proinflammatory cytokines such as Interleukin 1β (IL-1β), IL-6, and Tumor necrosis factor α (TNF-α).[27] Extracellular vesicles derived from *Filifactor alocis* have the capability to stimulate the expression of various cytokines including IL-1β, IL-1 receptor antagonist, IL-6, IL-8, and TNF-α in human monocytic cells. Additionally, they stimulate the expression of IL-6 and IL-8 in human oral keratinocyte cells. The cytokines induced by *Filifactor alocis*, such as IL-6, IL-1β, and TNF-α, can upregulate pathways that promote the generation of osteoclasts and contribute to increased alveolar bone loss, thereby facilitating progression of disease. In periodontal tissues, both resident and penetrating immune cells, such as monocytes and fibroblasts, may elevate the expression of another pro inflammatory mediator, cyclooxygenase 2 (COX-2). COX-2 is an inducible enzyme that is expressed specifically during inflammatory processes.[28] Neutrophils are recruited to periodontal pockets to form a protective barrier against microbial invasion. They migrate into the crevicular fluid, where they engulf and destroy bacteria, helping to prevent deeper tissue damage. *Filifactor alocis*, or *F. alocis*, has developed multiple strategies to resist the actions of neutrophils.[29] Phagocytosis of *F. alocis* results in minimal generation of reactive oxygen species, both internally and externally. *F. alocis* survive inside neutrophils by delaying the arrival of specific granules and preventing the fusion of azurophil granules with the phagosome. Phagosomes containing *F. alocis* also reduce the release of antimicrobial peptides like lysozyme and lactoferrin within the phagosome. *F. alocis* also downregulates neutrophil apoptosis pathways. Neutrophils challenged with *F. alocis* maintained their nuclear morphology, exhibited reduced phosphatidylserine externalization, and displayed decreased DNA fragmentation. Neutrophil extracellular traps (NETs) are antimicrobial defenses where neutrophils release their chromatin, coated in antimicrobial peptides, to trap and kill pathogens. Armstrong et al., 2018 observed that *F. alocis* does not trigger NET release from neutrophils, suggesting this bacterium has a virulence factor that helps it evade the immune response.[30]

Complement system subversion by periodontal bacteria is a hallmark feature of periodontitis which results in exacerbated inflammation and dysbiosis. In case of F. alocis, a key contributor in complement resistance is a unique cytosolic enzyme acetylornithine transaminase, named as FACIN or *F. alocis* complement inhibitor. Depending on the molecular trigger, there are 3 pathways of complement activation, and these merges at the stage of C_3 activation leading to opsonisation of the pathogen C_3b. FACIN binds to C_3 and captures C_3b within the complex with factor B, thereby locking in the convertase in an inactive state. These alterations result in downregulation of C_3b opsonisation on the pathogen surface which leads to inhibition of phagocytosis of the pathogen. In addition to its role in phagocytosis, C_3b is essential in other key processes, such as antibody generation and C_3 conversion always precedes C_5a generation. Thus, we can speculate that by shutting down C_3b opsonization, FACIN will disturb interaction of *F. alocis* with various immune cells.[31]

3.6. Biofilm formation and polymicrobial synergy

Oral biofilms, or dental plaque, consist of microorganisms adhering to tooth surfaces and are a primary contributor to the onset of periodontal disease. A co-occurrence group centered on *Filifactor alocis (F. alocis*), comprising eight potential pathogens associated with periodontitis across various oral habitats. These pathogens include *P. gingivalis, Porphyromonas endodontalis, T. forsythia, F. alocis, Eubacterium nodatum, Fretibacterium species, Lachnospiraceae species, and Peptostreptococcaceae species.*[28]

When P. gingivalis ATCC 33277 was co-cultured with F. alocis, there was a marked increase in biofilm formation. This increased capacity for biofilm formation may arise from the autoaggregation ability and unique component expression of both species.[16] This phenomenon potentially hints at a symbiotic association between *F. alocis* and *P. gingivalis*, *P. gingivalis* and *F. alocis* collaborated to form heterotypic communities, where the presence of *F. alocis* notably boosted the abundance of *P. gingivalis.* Under these conditions, proteins produced by *F. alocis* might provide nutritional support and promote adhesion for *P. gingivalis*, thereby enhancing its virulence. Within three-species communities consisting of *S. gordonii, F. nucleatum* and *F. alocis* the inhibitory impact of *S. gordonii* outweighed the collaborative effects of F. nucleatum on F. alocis. The relationship between *A. actinomycetemcomitans* and *F. alocis* showed that *A. actinomycetemcomitans* could either promote the accumulation of *F. alocis* or have no effect on it.[29]

4. Antibiotic Resistance

Cato et al., 1985 studied the susceptibility of 20 *F. alocis* isolates to breakpoint concentrations of five antibiotics - chloramphenicol [12 µg/mL], clindamycin [1.6 µg/mL], erythromycin [3 µg/mL], tetracycline [6 µg/mL], and penicillin 2 U/mL) and observed that all isolates of F.alocis were susceptible to the antibiotics except one, which was resistant to penicillin.[30] The study results indicate that *F. alocis* is highly susceptible to commonly used antimicrobials, with exceptions of isolate 30.27, which showed reduced susceptibility to clindamycin (CDM) and very high tolerance to azithromycin (AZM), and the ATCC 35896 strain, which has previously been reported to have reduced susceptibility to tetracyclines.[31] The ATCC 35896 strain has been associated with the tet(M) gene, which encodes a ribosomal protection protein (RPP) and is located within a mobile genetic element (MGE).[33] The genes tet(M) and tet(32) were the most commonly detected tetracycline resistance genes among subgingival isolates from patients with periodontitis.[34] Mobile genetic elements (MGEs), such as conjugative transposons, can spread tetracycline resistance genes widely, potentially making tetracyclines ineffective in the oral environment. The presence of the erm(B) gene may have given isolate 30.27 very high tolerance to azithromycin (AZM) (>256 µg/mL) and reduced susceptibility to clindamycin (CDM) (1 µg/mL). The erm(B) gene codes for a methyltransferase that methylates adenine in the 23S rRNA of the bacterial ribosome, preventing macrolides and lincosamides from binding and thereby conferring resistance.[35]

Table 1: Virulence factors of *F. alocis*

Protease	• RIP metalloprotease (HMPREF0389_00112) • Protease (HMPREF0389_00122) [Collagenase domain] • ATP-dependent protease La (HMPREF0389_00279) • Zinc protease (HMPREF0389_00298) • ATP-dependent zinc metalloprotease FtsH (neutral zinc metallopeptidase family protein) (HMPREF0389_01001) • Caax amino protease family protein (HMPREF0389_00590) • Caax amino protease (HMPREF0389_00677) • Metalloprotease (HMPREF0389_00692) • Glycoprotease family protein (HMPREF0389_01443) • Xaa pro dipeptidase (HMPREF0389_01538) • O-sialoglycoprotein endopeptidase (HMPREF0389_01445) • Serine protease HtrA (HMPREF0389_01460) • ATP-dependent Clp protease (HMPREF0389_01648) • Carboxy-processing protease (HMPREF0389_00522) • Oligoendopeptidase F (HMPREF0389_00926) (HMPREF0389_00527)
MSCRAMMs (putative)	• Fibronectin binding protein (HMPREF0389_00575) [Fibronectin binding domain] • Heparin binding protein 50S ribosomal protein L29(HMPREF0389_00839) • Collagenase U32 family (HMPREF0389_00504) [Collagenase domain] • Collagen adhesin/ binding protein - Collagen adhesin protein (HMPREF0389_01006) [Collagen binding domain] Gram positive anchor (HMPREF0389_01336) [Collagen binding domain] Hypothetical protein (HMPREF0389_01750) [Collagen binding domain]
Exotoxins	• FtxA (Putative exotoxin – large family of RTX proteins) • PrtFAC induces caspax-dependent and independent apoptosis of oral keratinocytes
Extracellular vesicles (EVS)	• Released by strain ATCC 35896. • EVs proteomics revealed 28 proteins including lipoproteins, autolysins, *F.alocis* complement inhibitor (FACIN), transporter and metabolism-related proteins and ribosomal proteins
Facin	• FACIN is a cytoplasmic enzyme acetylornithine transaminase involved is arginine catabolism, which serves as an additional role in evading complement cascade. • It acts as a Complement inhibitory protein, secreted or expressed on the cell surface which binds to C3, blocking all complement pathways.
Superoxide reductase	• Strain ATCC 35896 encode an antioxidant enzyme, superoxide reductase FA796, that reduces superoxide radicals into H_2O_2. • Glutathione peroxidase and alkyl hydroperoxide reductase subunit AhpC are found in the genome of *F.alocis* and function in clearing H_2O_2

5. Conclusion

F. alocis is emerging as a new oral bacterium with unique virulence characteristics. Its association with other significant periodontal bacteria and its potential as a diagnostic marker for periodontal disease are likely influenced by multiple factors. *F. alocis* could play a pivotal role in community dynamics by forming synergistic partnerships with other pathogenic oral bacteria, particularly during periods of activity. *F. alocis* possesses unique potential virulence characteristics, including resistance to oxidative stress and genes encoding a well-developed amino acid metabolic pathway. These attributes can collectively modulate changes in both the oral microbial community and the host cell proteome, potentially contributing to the disease process. *F. alocis* is distinguished by its association with both generalized and localized aggressive periodontitis (LAP), as well as peri-implantitis and endodontic infections, making it one of the few organisms linked to such a broad range of oral conditions.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Jiang Y, Song B, Brandt BW, Cheng L, Zhou X, Exterkate RAM et al. Comparison of red-complex bacteria between saliva and subgingival plaque of periodontitis patients: A systematic review and meta-analysis. Front Cell Infect Microbiol.2021;11:727732.
2. Hiranmayi KV, Sirisha K, Ramoji MVR, Sudhakar P. Novel pathogens in periodontal microbiology. J Pharm Bioallied Sci.2017;9(3):155–63.
3. Lee JS, Spooner R, Chowdhury N, Pandey V, Wellslager B, Atanasova KR, et al. In Situ Intraepithelial Localizations of Opportunistic Pathogens, Porphyromonas gingivalis and Filifactor alocis, in Human Gingiva. Curr Res Microb Sci.2020;1:7–17.
4. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontol.1998;25:134–44.
5. Edmisson JS, Tian S, Armstrong CL, Vashishta A, Klaes CK, Miralda I et al. Filifactor alocis modulates human neutrophil antimicrobial functional responses.Cell Microbiol.2018;20(6):e12829.
6. Schlafer S, Riep B, Griffen AL, Petrich A, Hübner J, Berning M, et al. Filifactor alocis--involvement in periodontal biofilms. BMC Microbiol.2010;10:66.
7. Jusko M, Miedziak B, Ermert D, Magda M, King BC, Bielecka E et al. FACIN, a double-edged sword of the emerging periodontal pathogen Filifactor alocis: A metabolic enzyme moonlighting as a complement inhibitor. J Immunol. 2016;197(8):3245–59.
8. Cato EP, Moore LVH, Moore WEC. Fusobacterium alocis sp. nov. and Fusobacterium sulci sp. nov. from the human gingival sulcus. Int J Syst Bacteriol. 1985;35(4):475–7.
9. Jalava J, Eerola E. Phylogenetic analysis of Fusobacterium alocis and Fusobacterium sulci based on 16S rRNA gene sequences: proposal of Filifactor alocis (Cato, Moore and Moore) comb. nov. and Eubacterium sulci (Cato, Moore and Moore) comb. nov. Int J Syst Bacteriol. 1999;49(4):1375–9.
10. Gomes BPF, Jacinto RC, Pinheiro ET, Sousa ELR, Zaia AA, Ferraz CC et al. Molecular analysis of Filifactor alocis, Tannerella forsythia, and Treponema denticola associated with primary endodontic infections and failed endodontic treatment. J Endod. 2006;32(10):937–40.
11. Tamura N, Ochi M, Miyakawa H, Nakazawa F. Analysis of bacterial flora associated with periimplantitis using obligate anaerobic culture technique and 16S rDNA gene sequence. Int J Oral Maxillofac Implants. 2013;28(6):1521–9.
12. Gogeneni H, Buduneli N, Ceyhan-Ozturk B, Gumus P, Akcali A, Zeller I et al. Increased infection with key periodontal pathogens during gestational diabetes mellitus. J Clin Periodontol.2015;42(6):506–12.
13. Eley BM, Cox SW. Cathepsin B/L-, elastase-, tryptase-, trypsin- and dipeptidyl peptidase IV-like activities in gingival crevicular fluid: a comparison of levels before and after periodontal surgery in chronic periodontitis patients. J Periodontol. 1992;63(5):412–7.
14. Aruni AW, Roy F, Fletcher HM. Filifactor alocis has virulence attributes that can enhance its persistence under oxidative stress conditions and mediate invasion of epithelial cells by porphyromonas gingivalis. Infect Immun. 2011;79(10):3872–86.
15. Aruni AW, Mishra A, Dou Y, Chioma O, Hamilton BN, Fletcher HM. Filifactor alocis--a new emerging periodontal pathogen. Microbes Infect. 2015;17(7):517–30.
16. Pei J, Grishin NV. Type II CAAX prenyl endopeptidases belong to a novel superfamily of putative membrane-bound metalloproteases. Trends Biochem Sci. 2001;26(5):275-7.
17. Chioma O, Aruni AW, Milford TA, Fletcher HM. Filifactor alocis collagenase can modulate apoptosis of normal oral keratinocytes. Mol Oral Microbiol. 2017;32(2):166–77
18. Kim HY, Song MK, Gho YS, Kim HH, Choi BK. Extracellular vesicles derived from the periodontal pathogen Filifactor alocis induce systemic bone loss through Toll-like receptor 2. J Extracell Vesicles. 2021;10(12):e12157.
19. Amano A, Furuta N, Tsuda K. Host membrane trafficking for conveyance of intracellular oral pathogens. Periodontol 2000. 2010;52(1):84-93
20. Wang Q, Wright CJ, Dingming H, Uriarte SM, Lamont RJ. Oral community interactions of Filifactor alocis in vitro. PLoS One. 2013;8(10):e76271.
21. Mishra A, Aja E, Fletcher HM. Role of Superoxide Reductase FA796 in Oxidative Stress Resistance in Filifactor alocis. Sci Rep. 2020;10(1):9178.
22. Inubushi J, Liang K. Update on minocycline in vitro activity against odontogenic bacteria. J Infect Chemother. 2020;26(12):1334–7.
23. Arredondo A, Blanc V, Mor C, Nart J, León R. Tetracycline and multidrug resistance in the oral microbiota: differences between healthy subjects and patients with periodontitis in Spain.J Oral Microbiol. 2020;13(1):1847431.
24. Roberts MC. Resistance to tetracycline, macrolide-lincosamide-streptogramin, trimethoprim, and sulfonamide drug classes. Mol Biotechnol. 2002;20(3):261–83.
25. Bhaya D, Davison M, Barrangou R. CRISPR-Cas systems in bacteria and archaea: versatile small RNAs for adaptive defense and regulation. Annu Rev Genet. 2011;45:273–97.
26. Aruni W, Chioma O, Fletcher HM. Filifactor alocis: The Newly Discovered Kid on the Block with Special Talents. J Dent Res. 2014;93(8):725–32.
27. Kim HY, Lim Y, An SJ, Choi BK. Characterization and immunostimulatory activity of extracellular vesicles from Filifactor alocis. Mol Oral Microbiol. 2020;35(1):1–9.
28. Zidar N, Odar K, Glavac D, Jerse M, Zupanc T, Stajer D. Cyclooxygenase in normal human tissues--is COX-1 really a constitutive isoform, and COX-2 an inducible isoform? J Cell Mol Med. 2009;13(9B):3753–63.
29. Ryder MI. Comparison of neutrophil functions in aggressive and chronic periodontitis. Periodontol 2000. 2010;53:124–37.
30. Armstrong CL, Klaes CK, Vashishta A, Lamont RJ, Uriarte SM. Filifactor alocis manipulates human neutrophils affecting their ability to release neutrophil extracellular traps induced by PMA. Innate Immun. 2018;24(4):210–20.

31. Jusko M, Miedziak B, Ermert D, Magda M, King BC, Bielecka E et al. FACIN, a Double-Edged Sword of the Emerging Periodontal Pathogen Filifactor alocis: A Metabolic Enzyme Moonlighting as a Complement Inhibitor. J Immunol. 2016;197(8):3245–59.
32. Chen H, Liu Y, Zhang M, Wang G, Qi Z, Bridgewater L et al. A Filifactor alocis-centered co-occurrence group associates with periodontitis across different oral habitats. Sci Rep. 2015;5:9053.
33. Wang X, Zhang X, Zong Z. Genome sequence and virulence factors of a group G Streptococcus dysgalactiae subsp. equisimilis strain with a new element carrying erm(B). Sci Rep. 2016;6:20389.
34. Arredondo A, Blanc V, Mor C, Nart J, León R. Tetracycline and multidrug resistance in the oral microbiota: differences between healthy subjects and patients with periodontitis in Spain. J Oral Microbiol. 2020;13(1):1847431.
35. Roberts MC. Resistance to tetracycline, macrolide-lincosamide-streptogramin, trimethoprim, and sulfonamide drug classes. Mol Biotechnol. 2002;20(3):261–83.

Cite this article: Swethaa P, Afzana BF, Sadasivan A, Nilima TS, GirijaVallaban C, Vijayakumar. *Filifactor alocis*: A deleterious intruder into the oral cavity and its effect on periodontal status**.** *IP Int J Periodontol Implantol* . 2025;10(1):9–16