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Identification of Vitamin D Potential, Oral Cavity Ecosystem and Its Relationship with Cytokine Expression and Bacterial Profile of *Tannerella forsythia*

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Abstract

Background: Oral microorganisms have an important role, especially in maintaining physiological balance, such as bacterial communities and host cell immunity in the oral mucosal epithelium and saliva. If there is a disturbance in homeostasis, it can cause certain diseases such as periodontal disease. Periodontal disease is generally caused by certain bacteria such as *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*.

Content: *Tannerella forsythia* is one of a group of red complex anaerobic bacteria that can mediate and bind to a number of other bacteria. In addition, *Tannerella forsythia* Lipopolysaccharide (LPS) is one of the virulence factors and also an inflammatory factor that plays a role in inducing cytokines such as Interleukin (IL)-1β, (IL)-6, and (IL)-8 so that it can aggravate the development of periodontitis. The progression of periodontitis can be controlled by proinflammatory cytokines and antimicrobial peptide secretion which is modulated by vitamin D in the oral cavity. Vitamin D has two mechanisms in suppressing periodontitis, namely first as an anti-microbial by inducing the production of β-defensins and cathelicidin which have strong antimicrobial activity, one of which is against *Tannerella forsythia* bacteria. Then the second as anti-inflammatory which occurs through decreased production of cytokines Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α which are inflammatory factors of *Tannerella forsythia*.

Summary: Therefore, it can be concluded that vitamin D has a close relationship with the oral ecosystem as well as the cytokine expression and bacterial profile of *Tannerella forsythia*.

Keywords: Cytokine Expression; *Tannerella forsythia*; Vitamin D

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Introduction

Microorganisms in the human body, especially in the oral cavity area, have an important role, especially their influence on various physiological functions such as the digestive process and immunity in hosts such as mucosal epithelium and saliva. If there are environmental changes in the microbial community, such as temperature and pH, it will certainly greatly affect the balance of microorganisms which can cause various diseases, one of which is periodontal disease [1].

Periodontal disease can generally be caused by certain bacteria such as *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*. *Tannerella forsythia* is a group of red complex anaerobic bacteria that can mediate and bind to a number of other bacteria found in the oral cavity. This can be influenced such as surface charge factors, electrostatic or hydrophobic interactions so that they can form biofilms through the Bacteroides surface protein A (BspA) protein which involves a cell-to-cell attachment process both with the same species and with *Fusobacterium nucleatum* bacteria. In addition, the bacteria can induce gingipain through the gingival epithelial host [2].

Based on the World Health Organization (WHO) report in 2022, it is estimated that around 19% of people over the age of 15 have more than 1 million cases of severe periodontal disease and the highest prevalence is at the age of 55 years and the rest at an older age. Of course, this can be caused by poor oral hygiene and other factors can be exacerbated if there is vitamin D deficiency. These factors can certainly trigger damage to periodontal tissue [3].

Vitamin D is a fat-soluble vitamin that can be categorized as a steroid hormone. Humans get 80% to 90% of vitamin D from sun exposure and a small portion can be obtained through food intake and supplements. Until now, vitamin D has been widely studied, one of which is related to

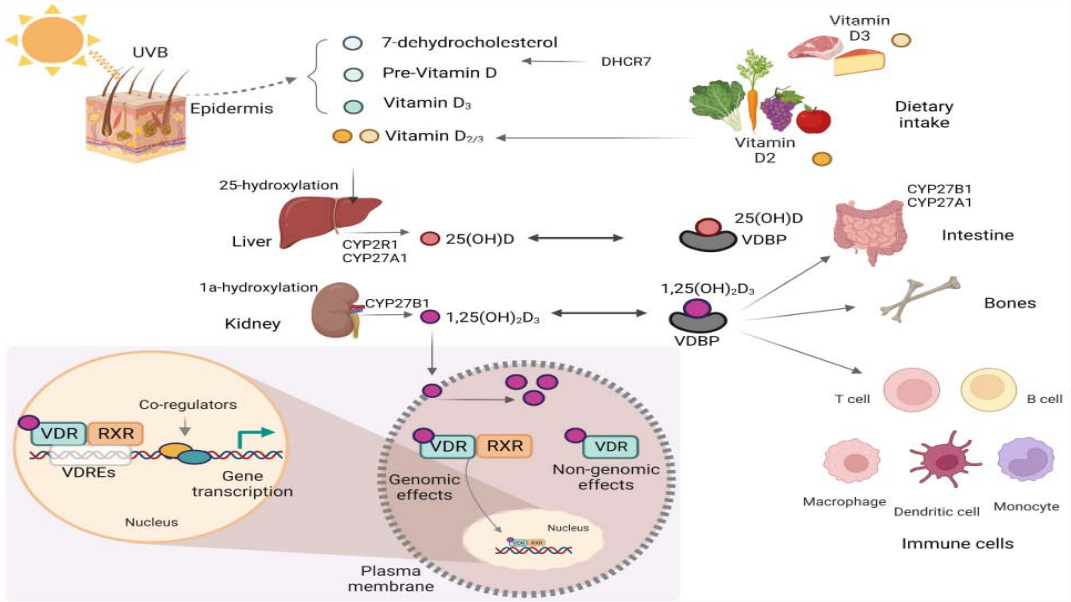

Figure 1: Biosynthesis and metabolism of vitamin D [6].
This figure was created using BioRender (https://biorender.com, accessed February 13, 2023).
UVB: Ultraviolet B; CYP2R1: Cytochrome P450, family 2, subfamily R, polypeptide 1; CYP27A1: Cytochrome P450, family 27, subfamily A, polypeptide 1; CYP27B1: Cytochrome P450, family 27, subfamily B, polypeptide 1; VDR: Vitamin D Receptor; VIDRE: Vitamin D Response Element; RXR: Retinoid X Receptor; DHCR7: 7-Dehydrocholesterol Reductase; VDBP: Vitamin D-Binding Protein

the balance of microorganisms in the oral ecosystem. The reason is because vitamin D has an antibacterial effect that can control a number of oral microorganisms so that if vitamin D deficiency occurs, it can increase the risk of periodontal disease through decreased activity of immune cells in gingival host cells [4,5].

Based on the description above, this review article will further discuss the identification of vitamin D in the oral ecosystem and its relationship with cytokine expression and bacterial profiles of *Tannerella forsythia* due to the effect of vitamin D which is able to act as an antibacterial and anti-inflammatory.

Vitamin D

Vitamin D is a fat-soluble vitamin that is classified as a secosteroid and is similar in structure to steroids. Humans obtain 80% to 90% of vitamin D from sun exposure and the rest comes from dietary intake. Vitamin D has many benefits, one of which is in the process of bone formation. Vitamin D is also very important in helping the body absorb calcium to maintain the integrity of the bone skeletal structure. In addition, vitamin D also plays a role in various biochemical processes in the extracellular fluid and cytosol to keep it balanced [4,5] (Figure 1).

Vitamin D function is influenced by parathormone and calcitonin from the parathyroid glands in maintaining calcium homeostasis by enhancing calcium absorption in the small intestine, mobilization of calcium from bone and regulation of calcium excretion in the kidney [7,8]. In general, vitamin D deficiency does not only occur in areas with little sun exposure such as in Antarctica or other parts of the earth, but is also commonly experienced especially in Indonesia. This condition is associated with lifestyles such as people who do not work outdoors, wear clothes that cover parts of the body so that the skin is not exposed to sunlight or due to insufficient vitamin D intake [9].

Recent studies have shown that vitamin D can affect the homeostatic conditions of microorganisms in the oral cavity [10]. In addition, vitamin D can affect the autophagy process to suppress osteoclast proliferation and induce differentiation. On the other hand, vitamin D also mediates osteoclastogenesis by inducing autophagy through Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL). Vitamin D supplementation showed a decrease in cytotoxic T cells, pro-inflammatory cytokines, and an increase in autophagy-related proteins in peripheral blood mononuclear cells especially in periodontitis patients [11].

Oral Ecosystem

The oral ecosystem has a diverse community of microorganisms commonly referred to as the oral microbiota which can be influenced by several factors, such as host, medication, age, and general behavior of the individual such as dietary habits, namely carbohydrate intake can determine the type of bacteria that inhabit the oral cavity. The activity of microorganisms in the oral cavity takes place as soon as the individual is born and continues to develop over time. As teeth erupt, new tooth structures allow for different microorganisms to inhabit the oral cavity, such as the enamel and gingival sulcus [12,13].

The microbiota consists of autochthonous (resident) and allochthonous (transient), where resident bacteria consist of bacterial species that are relatively constant and have specific habitat characteristics, for example on teeth, periodontium, oral mucosa and lips while the transient microbiota consists of non-pathogenic or opportunistic microorganisms that inhabit the oral cavity for a limited period of time without causing disease. However, if disruption occurs it can subsequently contribute to pathological development [14,15].

In a healthy oral environment, commensal bacteria are in symbiotic mutualism with the host and are also most commonly found in a diversity of microorganisms such as *Streptococcus*, *Prevotella*, *Fusobacterium*, and *Veillonella*. This indicates that a balance is achieved not only between the bacteria and the individual's immune system but also between the commensal bacteria themselves.

This balance is called homeostasis and is an important characteristic of a healthy mouth. It is important to understand that maintaining oral homeostasis is a multifactorial process that primarily depends on the host and microorganism environment created at various sites in the oral cavity [12,13].

Tannerella forsythia

Tannerella forsythia is one of the Bacteroides group which is one of the causes of periodontitis. This bacterium is included in gram-negative anaerobic bacteria and does not have surface fimbriae, capsules and is non-motile but exclusively has a unique surface layer in the form of glycoprotein or layer S. The virulence factors of *Tannerella forsythia* bacteria consist of lipopolysaccharides, Bacteroides surface protein A (BspA) (adhesin), sustain (trypsin-like proteinase), and layer S protein (immune stimulator). BspA is involved in the metabolism of bacterial protein secretion to the outer membrane and also the glycosylation process. In addition, BspA can also support oral bacterial colonization [2,16].

The S-layer is a water-insoluble protein that is intrinsically capable of assembling itself into a collection of crystals on the surface of bacterial cells and can help bacteria in selective self-defense. The S-layer consists of two glycoproteins with molecular weights of 220 and 210 kDa encoded by the *T. forsythia* cell Surface (S-) layer (tfs)A and (tfs)B genes. The S-layer also helps bacteria to increase adhesion and functions as a receptor ligand for bacterial coaggregation, which promotes biofilm formation and can lead to increased disease severity [16,17].

Tannerella forsythia cytokine expression

Tannerella forsythia bacteria require certain mechanisms to trigger cytokine expression in the body. Bacteroides surface protein A (BspA) is one of the most common target proteins found in patients with periodontitis, not only plays a role in biofilm colonization but can also induce cytokine production. In cellular activation, BspA can trigger the release of bone-resorbing proinflammatory cytokines from monocytes and the chemokine Interleukin (IL)-8 from gingival epithelial cells by activating the Toll-Like Receptor (TLR)-2-dependent pathway. In addition, methylglyoxal is a bacterial mediator produced by *Tannerella forsythia* which is a metabolic by-product that has cytotoxic effects on the host and is widely detected in patients with periodontal disease [2,18].

Tannerella forsythia Lipopolysaccharide (LPS) is one of the virulence factors and also an inflammatory factor that plays a role in inducing cytokines such as Interleukin (IL)-1β, (IL)-6, and (IL)-8 [19]. In a previous study, lipopolysaccharide was extracted from *Tannerella forsythia* and co-cultured with other bacteria such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis*. The results showed that under the condition of 1% human serum, the induction of cytokine expression between *Tannerella forsythia* LPS cultured alone or co-cultured with *Fusobacterium nucleatum* showed no difference, while when co-cultured with *Porphyromonas gingivalis*, there was a lower level of cytokine expression compared to *Tannerella forsythia* LPS cultured alone [19,20].

Vitamin D association with cytokine expression and bacterial profile of *Tannerella forsythia*

The influence of vitamin D on the immune response in periodontal tissues plays several important roles, including modulating proinflammatory cytokines, stimulating the secretion of antimicrobial peptides, and activating the release of hydrogen peroxide in monocytes. Antimicrobial peptides including β-defensins and cathelicidin are essential for neutralizing endotoxin and lipopolysaccharide products especially in periodontal bacteria, such as *Tannerella forsythia*. Pathogen Associated Molecular Patterns (PAMPs) and Toll-Like Receptor 1 or 2 (TLR 1/2) interactions of monocytes, macrophages and keratinocytes in periodontal tissues have been shown to induce Vitamin D Receptor (VDR) expression and production of the active form of vitamin D, $1,25(OH)_2D$ by these cells [21,22].

The protective mechanism of vitamin D against periodontitis occurs through two biological pathways, namely anti-microbial and anti-inflammatory pathways. The anti-microbial effect of vitamin D occurs from the binding of $1,25(OH)_2D3$ with VDR which then induces cyclic 3′,5′-Adenosine Monophosphate (cAMP), beta-defensin-2 (b-def-2) and beta-defensin-3 (b-def-3) peptides by macrophages, monocytes, gingival epithelium and periodontal ligament epithelium. Vitamin D also exerts strong antimicrobial effects against periodontal pathogens by directly inhibiting bacterial growth and LPS-induced inflammation or facilitating the production of β-defensins and cathelicidin which have strong antimicrobial activity against gram-positive and gram-negative bacteria, one of which is *Tannerella forsythia* bacteria [23].

In addition, the anti-inflammatory effect occurs through decreased production of proinflammatory cytokines such as Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α which are inflammatory factors of *Tannerella forsythia*, inhibiting Nuclear Factor kappa B (NF-kB) and upregulating Mitogen-activated protein Kinase Phosphatase-1 (MKP)-1. This decrease in proinflammatory cytokine production will inhibit periodontal tissue damage by reducing the stimulation of Matrix Metalloproteinases (MMPs). Decreased production of IL-6 and TNF-α will reduce the ratio of Receptor Activator of Nuclear factor kappa-B Ligand or Osteoprotegerin (RANKL/OPG) on osteoblast stromal cells, thus inhibiting osteoclast progenitor differentiation as a cause of alveolar bone resorption. In addition, a recent study on human gingival fibroblasts showed that vitamin D exerts anti-inflammatory effects and reduces Reactive Oxygen Species (ROS) through activation of the nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathway [23].

Conclusion

Based on the review article, it was found that vitamin D has a close relationship with the oral ecosystem as well as the expression of cytokines and the bacterial profile of *Tannerella forsythia*. It has been explained previously that vitamin D can affect the homeostatic conditions of microorganisms in the oral cavity and has the potential to act as an anti-bacterial through the bond between $1,25(OH)_2D3$ and Vitamin D Receptor (VDR). In addition, vitamin D also functions as an anti-inflammatory by reducing the production of IL-6, TNF-α and Matrix Metalloproteinases (MMPs). This can cause the progression of periodontal disease to be inhibited.

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