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Review Article
Oral Candidiasis of Tobacco Smokers: A Literature Review

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Abstract

The mouth is a vital point of entry into the human body, the health of the mouth entails mental, physical as well as social well-being. Studying diseases, microbiota and environmental conditions of the mouth is important to maintain oral health and all body. The smoke of tobacco cigarettes is one of the worst habits that affect the health of the mouth and the body. Therefore, this review has been conducted to study the effect of smoking on the balance of the oral microbiota and the opportunistic organisms, one of the most important of them *Candida*. Although a few studies have found that cigarette smoking does not influence carriage by *Candida* significantly. However, most of the studies had results completely contrary to that, smoking cigarettes affect *Candida* pathogenic characteristics such as a transition from yeast to hyphal form, biofilm formation and, virulence-related gene expressions. Tobacco is not only an inducer of the transition process but it considers an excellent medium for this process. Furthermore, smoking was significantly associated with *Candida* pathogenicity in patients with clinically suspected oral leukoplakia and smoking worsens oral candidiasis and dampens epithelial cell defense response. Nicotine significantly altered the composition and proportion of yeast cells, as well as the extracellular polysaccharide amounts which increase biofilm matrix and thickness which could promote oral candidiasis. Smoking has the potential to alter the oral condition and cause severe oxidative stress, thereby damaging the epithelial barrier of the mouth. These oxidative molecules during smoking activate epithelial cells proteins called oxidative stress-sensing proteins. If some of these proteins induced, widely thought to have anti-inflammatory properties, inhibit the secretion of pro-inflammatory cytokines and are linked to inflammation and oxidative stress is thought to be a possible therapeutic objective and a crucial regulator for smoking-related oral diseases and mouth candidiasis for instance leukoplakia. Also, it is transported into the cell nucleus in the existence of additional electrophilic chemicals to activate antioxidant enzyme gene expression. Therefore, smoking cigarettes destroys oral health and consequently destroys the health of the whole body.

Key words: *Candida* species, *Candida albicans*, cigarette smokers, oral microbiota, oral candidiasis, virulence, tobacco smoking, mouth health

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INTRODUCTION

Mouth is a vital point of entry into the human body, consists of both soft (tongue and the gingival mucosa) and hard (hard palate, teeth and bone) tissues. These tissue structures are essential for oral health. Oral health entails mental, physical as well as social well-being[1].

Microorganisms can be found in every aspect of human life and have an impact on it. The human mouth microbiota is thought to be 2nd most complicated after a colon and it is more diverse than mucosal sites as well as human skin. There are numerous habitats in the human mouth cavity. The synergy and interaction of various oral microbes protect the human body from unwanted stimulation from outside. An imbalance of normal microbial flora contributes to oral and systemic diseases. Or, to put it another way, mouth microbiomes play a critical role in the health of humans and the microbiological community[2-6]. This normal mouth microbiota is made up of interactive, complex communities of microorganisms and nutrients, mostly bacteria that live in biofilms on oral cavity surfaces[4-9]. Almost microbial biofilm properties may actually preserve or improve oral health, in addition, to defending against the possible invasive pathogenic microbes, while others may enhance the virulence of possible microbes that are harmful and reduce the effectiveness of antimicrobials[9-11].

Microbiota in the mouth has been associated with a variety of oral diseases. Recent evidence suggests that the microbiota of the mouth is closely linked to human physical conditions for instance cancer, diabetes and obesity. Microbiota of the mouth will become one of the modern objectives aimed to achieve human physical health in the future[12]. Studies on oral microbiomes and their relationships with the other microbiomes in various human sites of the body and health conditions are crucial in our understanding of our bodies and how to improve health in human beings[3]. Alternatively, the microenvironment in the oral cavity varies in microbial composition and is influenced by hosts, external environmental variables and complex signaling. Undoubtedly, human health can be affected by the health state that affects the composition of oral bacteria, as well as microbial community destruction, which is linked to systemic diseases[13]. Antibiotics-induced changes in bacterial balance as the main component of oral microbiota, these bacteria may be crucial and upper hand in causing candidiasis and other human fungal infection, for instance, using of antibacterial antibiotics and immunosuppression (systemic or local) drugs make most infections especially Candidal and other fungal infection may require this to spread[2,9]. The microbiota in the mouth is a vital basic human microbiota component. Microflora balance disturbances occurring in the host oral cavity may be altered by *Candida* because it is an opportunistic fungus that remains harmless until this state changes for various reasons[12,14]. Yeast *Candida* is an organism that is frequently found on the mucosal surfaces of healthy people's genitourinary tracts, digestive systems and mouths. This yeast has the potential to be an opportunistic pathogen[15,16].

The smoke of tobacco cigarettes contains over four thousand chemicals, most of which are toxic, of which fifty are extremely cariogenic as well as contributing to dental caries[17]. Although several studies have found that cigarette smoking has no significant effect on *Candida* carriage[18-20], other studies have found that tobacco smoking significantly increases its prevalence[21,22]. Moreover additional studies have suggested that smoking, whether alone or in combination with other factors, maybe a significant risk factor for candidiasis in the mouth, this connection or its pathogenicity effects on *Candida* in the mouth is far from resolved. The precise mechanism by which cigarette or cigar smoke may affect dental candidal carriage is fully unknown[23].

Therefore, the goal of this review was to explain the oral microbiota, especially candidal mycobiota (fungal microbiota), oral candidiasis, factors that affect oral candidiasis, interactions between commensal *Candida* and cigarette smokers and mechanisms by which oral carriage of *Candida* may be influenced by tobacco cigarette smoking.

Human oral microbiota: Sometimes, the oral cavity is referred to as a mirror that reflects a people's health. The human mouth cavity is a unique environment that involves diverse microbial habitats. For example, the tongue, hard and soft palate, buccal mucosa and teeth, which make up a diverse ecological system with a lot of different species[24].

Oral microbiota is not like gut microbiota in changes of bacterial types. Environment and diet have a great influence on the gut microbiota but the same causes have a small effect on oral bacteria[25]. In the previous data collected about oral the human microbiome, about 150 genera, 400 oral taxa, 700 species and over 1300 microorganism strains[26]. Only prokaryotes in the buccal cavity contain about 700 species[3]. Saliva contains about more than 10^8 microorganisms/mL, which have been detected[27]. There are many microorganisms in the mouth, most of them bacteria, then fungi and then viruses. These bacteria are mostly Firmicutes, *Bacillus*, Proteobacteria and Actinomycetes[28,29]. The majority of bacterial microflora residents in the mouth are streptococci[30]. From oral bacterial classification, *Streptococcus* spp., are separated into four groups, mitis-group, *anginosus*-group,

sanguinis-group and *mutans*-group[31,32]. The members of the *salivarius*-group are associated with tongue mucosal surfaces and human mouth vestibular mucosa. The mutans-group is one of the causative agents of dental caries while anginosus-group members are frequently etiological agents of internal organs abscesses and it is also linked to the development of purulent human disease[31-33]. On the other hand, mitis-group members consider opportunistic bacterial pathogens linked to endocarditis infections[32].

Gomez *et al*.[34] found that bacteria are the primary constituents of the oral microbiota. *Lactobacillus* spp., *Staphylococcus* spp., *Porphyromonas gingivalis* and *Streptococcus mutans* are examples of common oral bacteria. The main constituent of oral bacterial microbiota is *S. mutans* which is considered an etiological agent disease of teeth hard tissues, the highest incidence among oral diseases and a major component of plaque on the teeth[35,36].

Whereas one of the most periodontal pathogens of Gram-negative anaerobic bacteria is *P. gingivalis*. If *P. gingivalis* is not treated, the gums can fall off the teeth. The lactic acid in large amounts is produced from sugar fermentation by *Lactobacillus* spp., which can easily cause caries. On the other hand, *Lactobacillus* spp., consider a probiotic in yogurt which has benefits to the host's health[37].

Human oral viruses, mostly phages, consider one of the oral microbiota members[38]. Throughout life, the oral type phage remains constant[39]. Other non-original viruses may appear in the oral cavity when certain diseases are present in the human body, mumps and HIV are two of these viruses[40,41].

In general, different studies from various countries concluded that microbial compositions of healthy Oral microbiota are similar. There are eighty-five fungal species to be found in oral microbiota, one of the most crucial fungi of oral microbiota is *Candida* spp.[42]. If the oral microbiota is balanced, *Candida* doesn't invade oral tissues but if the balance changes, *Candida* becomes opportunistic, in addition, *Candida* interacts with *Streptococcus* to form biofilm as a pathogenic role[43]. *Candida* species are oral normal microflora that is most commonly found in the dorsum (end part) of the tongue but can also be found on the digestive tract and vagina[44].

Oral mycosis: There are many fungal contaminants and etiological agents isolated from cases infected by oral cavity mycoses *Acremonium* spp., *Aspergillus* spp., *Cryptococcus* spp., *Candida* spp., *Fusarium* spp., *Malassezia* spp., *Rhodotorula* spp. and *Trichosporon* spp. On the other hand, *Candida* spp., as well as *Cryptococcus* sp., are the main factor in primary infections by colonization, especially *Candida* spp. In the case of biofilm formation in the mouth, usually, spores of more than one microbe come or accumulate on the epithelial cells' upper part and form a suitable environment for growth and microbial survival[45]. Colonization of oral cavity candidiasis can occur not only by Albicans but also by non-albicans e.g. *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. lusitaniae* and *C. parapsilosis* but CA is the most common and virulence species[46,47].

Candida spp. is one of the mycobiota, in immunocompromised individuals, it can cause oral candidiasis in oral mucosa according to an overgrowth in the site of infection[2,9]. Xu and Dongari-Bagtzoglou[2] noted that "A functional immunodeficiency in the Th17 $CD4^+$ cell subset is the underlying link that connects all known systemic conditions of the host related to mouth candidiasis".

Oral candidiasis: Out of two hundred known *Candidal* spp., only forty species can cause Candidal diseases but remain CA is the most commonly known species that cause infection[44].

Oral mycoses is a microbial-oriented efficient disease that was probably initially started by biofilm formation of the mouth lining tissues and its surrounding. Several studies concluded that *Aspergillus* spp. and *Candida* spp., are regularly isolated fungal species[48]. The percentage of presence of *Candida* spp., in the oral cavity is equivalent to 53% of mankind as a normal microbiota, 80% of isolated *Candida* is albicans species that it can colonize alone or with other microbial species[49].

Transformation of candidal pathogenicity from commensalism is based on the intervention of various predisposing factors that alter the oral cavity microenvironment and favor the appearance of opportunistic infection. *Candida albicans* (CA) is a highly invasive and adaptive microbe among other species of *Candida* which it can cause mycosis at various anatomical sites. In recent years, we have gained an improved comprehension of the complex interlinkage between CA strains and hosts but after all these papers there are still significant gaps in our understanding of albicans pathogenicity, albican's role in human microbiota and conversion between two states as well as responses of host immune system[50].

Generally, *Candida albicans* (CA) live and colonize up to sixty percent of healthy people as a commensal yeast therefore the conversion to opportunistic candidiasis is easy[51]. The oral cavity is the house of an exclusive complexed ecosystem called oral microbiota which is constructed of

hundreds of fungal and bacterial species, one of the very important microbiota is CA. In addition, that CA is the most common opportunistic ubiquitous yeast which is the most etiological agent of invasive and mucosal human fungal infections[52,53].

The virulence factors of *C. albicans*: One of the most important virulence factors of CA strains is the capability to change or switch to a pseudohyphal shape from a yeast shape. Many factors can induce this transition e.g. glucose, serum, CO_2, proline, N-acetylglucosamine, starvation and temperature (37°C)[54-57]. During candidiasis development, CA begins to adhere to tissues as well as invade these tissues. This adhesion is promoted by yeast cell wall proteins[58,59]. Cell wall *Candida* contains mannans, glucans, chitins and glycoproteins[60-62]. The scientists discovered three genes of CA, encoding different chitin synthases (CHS 3, 2 and 1). The production of an amount of chitin is reliant on cultural conditions. Preferentially, two of three genes (CHS3 and CHS2) are expressed under hyphal culture conditions[63,64], while CHS1gene level continued as a small level in two forms of hyphae as well as yeast[65]. Remarkably, CHS1p was found to be necessary for virulence and cell integrity[65]. Any defects in chitin proteins by mutation make mutant yeast cells less dangerous than the parent strain in the experimental animal model. Consequently, with a high chitin level, CA can evade the effects of cigarette smoke and the immune system of the host[63].

Commensal fungi CA colonized healthy individuals and a pathogen of immunocompromised and immunocompetent patients with compromised barriers to spread. Adaptation and regulation to the microenvironment of the host are involved in both commensal and pathogenic states. Pathogenic potential can be down-regulated in order to maintain commensalism or upregulated in order to harm tissues of the host and obviate or alter immune surveillance negatively[66].

The virulence of CA according to the production of several enzymes lipases, phospholipases, esterases and proteases which it used in the cleavage of immune defense proteins, biodegrading of connective tissues and as a result, the pathogen's acquisition of nutrition, invade and evade of immune defense is aided[67,68].

The production of enzymes related to members of multigene families, pH optimum, yeast unique substrate specificity and expression profile. The produced aspartyl protease enzymes have been shown to play several roles. One of them inactivates factor-H and the complement receptors CR3 and CR4 on macrophages, allowing CA to avoid detection by the host's innate immunity[67-70].

In the species CA, virulence is a polygenic trait that includes morphogenetic, genetic, physiological and biochemical characteristics. These characteristics increase the virulence of *Candida* species, the most important of which are: The transition from yeast to pseudohyphae (in response to specific conditions), phenotypic conversion (to become protected from neutrophil engulfment), biofilm formation (to reluctant against antifungal agents and host immune defense), adherence to host surfaces and metabolic adaptability (stress resistance, cell surface changes and effective utilization of alternative carbon sources). In addition to the production of hydrolytic enzymes (for the cleavage of host immune factors, the degradation of host connective tissues, and the acquisition of nutrients), evade phagocytosis (pyroptosis, phagolysosomal neutralization and host cells lysis by fungal hyphae), combating host nutritional immunity (transporters of micronutrients and proteins that are redundant with alternate cofactors), the production of candidalysin (secretory cytolytic peptide causes harm to host immune system) and evasion from host surface changes immune system (PAMPs masking, changes in cell wall composition and architecture)[66]. These adaptive characteristics allow CA to thrive in a variety of host niches, overcome host immune defenses and establish itself as a viable pathogen[66].

Etiology and condition of oral candidiasis: The mouth cavity, as one of the most important human openings, is exposed to a large number of microbes through food, air and water. Some of them grow, multiply and establish, forming communities within the cavity. The physiochemical environment in the cavity influences both the selection and growth of these microbes[67].

The environmental conditions are caused by a variety of molecules produced by the host and resident microbe. Changes in the cavity's molecular content are likely to alter the community of microbe. As a result, changes in the microbial community inside the oral cavity may occur in the case of various diseased conditions and changed food habits or both. As a result, the presence of certain microbes or an increase in the microbial numbers in a cavity of the mouth may be a good indicator of disease diagnosis[68].

Factors that contribute to oral fungal infection are primarily caused by our ignorance of oral health care. Forming of acid in the mouth cavity occurs as a result of both alcohol consumption and smoking, as well as a high intake of carbohydrates and sugar in food. The high rate of alcohol consumption can disrupt the oral microflora and cause the formation of acetaldehyde, which results in mouth fungal colonization[48,71,72].

In the same context, epithelial changes, poorly fitting dentures, hormonal disorders, physiological disorders, endocrine disorders, poor oral hygiene, empirical drug therapy and immunologic disorders are some of the other difficult causative factors that cause oral mycosis. The CA is the most common colonizing fungi isolated from the mouth cavity[48]. Oral candidiasis especially symptomatic symptoms increases and is affected by numerous conditions and factors. One of the most important factors is the temperature which is the key to many parameters for example ion activity, pH, gas solubility and aggregation of molecules[73-76]. The mouth temperature varies depending on where you look and this can affect the proportions of bacterial species, the optimum temperature for bacterial growth is 37°C[31].

On the other hand, the tongue's upper surface (dorsum), palatal mucosa and buccal mucosa deliver oxygen to aerobic environments which enhance facultative anaerobic growth[76]. Generally, oral microbes according to aeration separated into anaerobes and aerobes, most of them are either obligate anaerobic or facultatively anaerobic. Facultative anaerobic microorganisms meaning they can grow in the absence or presence of O_2 while obligate anaerobic microorganisms meaning they cannot grow in the O_2 presence[76]. Fusobacteria, bacteroides, some actinomycetes and spirochaetes as anaerobic microbes can only reproduce in the reduced buccal areas and they can be found in dental plaque deeper layer and in the gingival crevice[77].

Undoubtedly the growth of microbes is affected by the pH of the oral environment, for optimal growth, some microorganisms have preferred neutral pH while others preferred acidic pH, e.g. *Actinomyces viscosus* and *Streptococcus sanguinis* (neutral pH), *Lactobacillus acidophilus* (acidic pH) while *Porphyromonas gingivalis* (alkaline pH)[31,78]. The optimum oral pH range is between 7.3 to 6.7 which is adjusted by salivary secretion[76]. Aframian *et al.*[79] recorded that the mean oral pH value is 6.78. Changes in oral cavity pH are affected by the presence and consumption of food, e.g. usually after consuming sugar, the pH decrease towards acidic under 5.0, while bicarbonate food consumption increase towards alkaline pH 8.06[76,78,80]. Oral microbes are usually affected by extreme values of alkaline or acid. Plaque microbes are affected by pH fluctuating by sugar daily consumption, but slight pH changes may not affect plaque microbes. Microbial growth nutrients are separated into two kinds, exogenous and endogenous nutrients. Salivary secretions are the main components of endogenous nutrients[76,81]. The gingival crevice fluid that surrounds the teeth provides albumin as well as other host proteins as endogenous nutrients and its reasons for the variation of oral microbiota[75,82]. Also during metabolism, carbohydrates biodegrade, acid is produced then the pH degree decrease, which it allows some bacteria to grow at a rapid pace e.g. *Streptococcus mutans* and lactobacilli while *Streptococcus sanguinis* decreases[31,76].

Diseases and habits that may increase oral candidiasis: Oral candidiasis has three forms angular cheilitis, acute candidiasis and chronic candidiasis[48]. The CA is one of the commensal microbes in the digestive, genitourinary tracts and mouth. The most common yeast cause oral candidiasis is CA strains, which have fluconazole-resistant between lymphoma and gastrointestinal cancer patients[46].

In some immune diseases, an effect on T lymphocytes (CD4 and CD8) make a higher risk of fungal infection in the mouth because it provides primary and secondary immunity[48]. In the same context, suppressive factors of the immune system by opium addiction exhibit a high risk of mycosis in addicts[83]. Furthermore, consuming alcohol, smoking, food containing a high level of carbohydrates, immunosuppression, extreme age of the patient and decreasing salivary function are predisposing and colonizing factors for oral mycosis and it has the potential to progress to the chronic stage[48]. It is not hidden from anyone, smoking and chewing tobacco may cause health hazards involving cancer in mouth tissues. For this reason, oral candidiasis by CA as oral normal flora and opportunistic pathogen in immunocompromised patients especially cancer patients[16].

Tobacco plant and health effects: *Nicotiana tobacum*, a type of tobacco plant, produces tobacco by curing its leaves. Smoking and chewing are two common uses for *Nicotiana tobacum*. Tobacco includes more than three thousand different compounds, whereas cigarette smoke contains more than four thousand different chemicals, including hazardous substances, of which fifty are particularly cariogenic and cause dental cavities. Nicotine, an alkaloid found in cigarette smoke, makes up about 6-30% of cigarettes. The amount of nicotine in a cigarette ranges from 9 to 30 mg however, the body only absorbs 0.5-2 mg of nicotine each cigarette through respiration[84-86].

In tobacco, there are approximately 28 carcinogenic agents[16,87]. The DNA can be alkylated by tobacco carcinogenic chemicals, which can result in cancer. Chewing and smoking tobacco are linked to a number of health issues in people, including pancreatic, esophageal, mouth and lung cancers. Additionally, it causes teeth to decay and fall out, nicotine addiction, strokes, cardiovascular disorders, an increase in heart rate and nicotine poisoning in youngsters. It also causes

digestive issues and a rise in stomach acidity[88-90] and early delivery in pregnant women[91,92]. Catecholamines, free fatty acids and blood pressure can all be raised by nicotine smoking[16,93].

It can prevent the production of prostacyclin, which can cause platelets to clump together and cause blood clotting. The amount of nicotine in cured tobacco ranges from 0.2-4.75% by weight, depending on the level of ripeness, plant's variety, growing environment, leaf position and fertilizer application[94,95]. The buccal mucosa is able to freely absorb non-ionized nicotine. Nicotine absorption from chewing tobacco is facilitated by buffering it to an alkaline pH. Compared to nicotine found in cigarettes, nicotine found in chewing tobacco is more readily absorbed[16,96].

Oral candidiasis is one of the illnesses of the mouth that can be aggravated by a number of risk factors, for instance, the use of exogenous substances like tobacco and cannabis[23,97].

The use of cigarettes is a significant risk factor for symptomatic infection in immunocompromised persons, according to epidemiological research. Additionally, smokers were reported to have a greater rate of oral candidal carriage than non-smokers. This could be the reason why 98% of smokers in Indian villages get *Candida* leukoplakia, which can be treated by quitting the habit[18,21,98-101].

Tobacco smoking and oral health: It is said that a person's oral health is a mirror that reflects their overall health. Erythema, inflammation and edema of the denture-bearing mucosa that may be together with burning or pain are the telltale signs of denture stomatitis[102]. There are multiple patient factors that affect the onset and severity of denture stomatitis, but still, microbiological factors continue to be one of the most important predisposing factors[103]. Denture stomatitis's primary cause is not entirely understood, according to other studies, although various risk factors associated with it have been discovered, such as *Candida* infection, immune system flaws, mucosal damage, inadequate denture cleanliness and a pattern of wearing dentures[83,104].

Basically, buccal Candidal growth is linked to the majority of denture stomatitis cases and vice versa. On the other hand, cigarette smoking is the sole factor or with other factors as a result of oral candidiasis[23,50,105]. Smoking of tobacco cigarettes was linked to a greater risk of denture stomatitis, with an adjusted odds ratio of 95%. Furthermore, for denture stomatitis, there was a dose-response increase with the highest probability ratio in the fourth quartile[92]. Tobacco smoking use in other forms, for instance, hookah (nargileh, water pipe, ghalyan, or shisha), has been linked to changes in the component of the microbiome of mouth, the proliferation of *Candida* spp., as well as immune system cell suppression[83,106,107].

Smoking and the presence of oral candidiasis: Galai *et al.*[20] demonstrated that, *Candida* species were found in 84 % of smokers and 74 % of nonsmokers and also CFU mL^{-1} averages were reported to increase in smokers more than persons who do not smoke tobacco. Also, Muzurović *et al.*[108] denoted that, smoking influences *Candida* spp. in oral colonization and both have an adverse effect on dental health. Cigarette smoking and the presence of *Candida* spp. in the oral cavity both have a negative impact on oral hygiene. Smokers' microbial colonization was more diverse than that of nonsmokers. Tobacco use influences bacterial acquisition and oral mucosal colonization in favor of periodontal pathogens. Smokers' microbial colonization was more diverse than that of nonsmokers this achieved by tobacco smoke had a statistically significant effect on smokers' oral flora. While, in the other study, tobacco consumption did not appear to increment *Candida* numbers for oral colonization in healthy subjects[20,108,109].

Effects of tobacco smoke on oral condition to enhance oropharyngeal candidiasis: Several studies exhibit that, smoking results in a decrease innate immunity by inducing Candidal colonization as well as host infection[110]. Because of aromatic hydrocarbon compounds found in cigarette tobacco smoke can be transformed by different *Candida* spp., to carcinogenic compounds, this could imply that CA uses tobacco compounds as nutritional factors[111]. In the same context, CA may induce the production of N-nitroso(benzyl) methylamine, which contributes to smokers' high *Candida* leukoplakia levels[112].

Cigarette smoking has been linked to localized epithelial changes that allow Candidal colonization[25]. Tobacco cigarette smoking may provide nutritional support for *Candida* growth[113]. This idea has significant implications because the aromatic and heterocyclic hydrocarbon compounds found in the smoke of tobacco cigarettes can be transformed into carcinogenic compounds as an end product by inducible enzyme systems found in *Candida* species[111,112]. These theories and ideas provide a partial demonstration of why smokers can be extra vulnerable to candidal leukoplakia, which has a greater risk of malignant transformation than other types of leukoplakia[114].

One of the primary virulence factors of CA strains is the ability to change pseudohyphal shape from yeast shape. Many factors can induce this transition e.g. glucose, serum, CO_2, proline, N-acetylglucosamine, starvation and temperature (37°C)[54-57].

Research in the genus CA approved that this genus has the ability to invade and adhere to the tissues during the development of candidiasis[58,59]. This adhesion is promoted by yeast cell wall proteins[115]. Cell wall of *Candida* contains mannans, glucans, chitins and glycoproteins[60-62]. The scientists discovered three genes of CA, encoding different chitin synthases (CHS 1 to 3). Any defects in chitin proteins by mutation make mutant yeast cells less virulent than the non-mutant strain studded in an animal model. Overexpression of Sap2, EAP1 and HWP1 genes, which are considered the main virulence factors in CA, increased yeast growth, adhesion and formation of biofilm[116,117]. Consequently, with a high chitin level, CA can evade the effects of cigarette smoke and the immune system of the host[63]. In the same context, pretreatment of cigarette smoke condensate CA (CSCCA) was sensitive to oxidative stress while heat or osmotic stress is elevated in resistance. The CA pretreated with cigarette smoke condensation (CSCCA) also had increased chitin content, especially under hyphal culture conditions. During hyphal culture conditions, CA pretreated with cigarette smoke condensate (CSCCA) had a two to eight-fold increase in chitin content[116]. Smoking causes changes in the conditions of the buccal cavity and raises the likelihood of mucosal infections by oral candidiasis-CA. Cigarette smoke has a significant effect on CA[118].

On the other hand, gingival fibroblasts (GF) are important for tissue function and structure. Furthermore, gingival fibroblasts (GF) play an important role in the host immune response against oral candidiasis[119,120]. In response to stimuli like periodontal pathogenic microbes, GF are activated during the inflammatory process, releasing pro-inflammatory cytokines for instance IL-8, IL-6 and IL-1[121,122]. The secretion of some inflammatory cytokines modulated by fibroblasts is exposed to tobacco cigarette smoke.

Toxic chemicals derived from smoke have been linked to immune dysfunction. Moreover, pretreatment of cigarette smoke condensate CA (CSCCA) adhere better to the GF, propagated and adapted 3 times the amount than non-treated species. Contact with CA pretreatment of cigarette smoke condensate (CSCCA) affected fibroblasts, causing them to grow at a slower rate and secrete more IL-1. Tobacco smoking may contribute to the pathogenicity of CA, by enhancing the severity of Candidal pathogenicity, fungal virulence and the pathogen's persistence in cigarette smokers[116].

Tobacco users are thus more likely to contract invasive diseases due to several pathogenic bacteria[123-125]. Tobacco users have also been shown *in vitro* to induce biofilm formation by a variety of oral/respiratory pathogens, inclusive *Streptococcus mutans*, *Streptococcus pneumoniae*, *Streptococcus aureus*, *Pseudomonas aeruginosa*, *Pseudomonas gingivalis* and *Klebsiella pneumoniae*[123-125]. Tobacco smoking has also been linked to an increase in CA growth, adhesion and biofilm formation[117,126].

***In vitro* and *in vivo* studies of tobacco effects on virulence of *C. albicans*:** Avşar *et al*.[16] demonstrate that, prepared methanol and water cold extracts of smoking and chewing tobacco were tested *in vitro* for their effect on CA morphological changes. These extracts have been shown in studies to enhance switching, hyphal form from yeast form, implying that tobacco may increase the pathogenicity of CA in the human buccal cavity. Tobacco is not only an inducer of the transition process but it considers an excellent medium for this process, this means it may increase the virulence of CA by transitioning to a pathogenic form.

Nicotine is one of the main smoking products, it has a significant impact on the human microflora of the oral cavity, which results in microbiome changes and instability and as well as encourages the unchecked growth of harmful microorganisms. A biofilm is the most frequent type of microbial growth that leads to clinical infection on both hard and soft surfaces. Recent *in vitro* research recorded the link between tobacco smoking and dental caries, including how nicotine affects the growth of biofilms and the metabolic products of *S. mutans* and *S. sanguinis*[127-131].

Oral mycosis by *Candida* species as an etiological agent possesses virulence aspects for instance tooth surfaces adhesion and oral epithelial cells making enhance biofilm formation, swapping phenotypes and morphological transitions, which contribute to the fungal pathogenicity[131-135]. The onset of oral candidiasis is significantly influenced by the capacity of *Candida parapsilosis* and CA to cling to both soft and hard oral tissue[136].

Some species of *Candida* especially CA and *C. parapsilosis* have the ability to phenotypic switching, colonize and production of excess polysaccharide extracellular. These extracellular polysaccharides enhance attachment to human epithelial cells as well as biofilm formation[137-139]. All of these characteristics make *Candida* an etiological agent of nosocomial infection, the 4th most common infection[140]. Yeast adhesion processes to endothelial and epithelial human cells are controlled by Candidal agglutinin like sequences genes 1, 3 and 5 (CALS 1, 3, 5) which produced specialized proteins that enhance initiation, colonization and dental plaque development processes, in addition to Candidal adhesion like hyphae wall protein gene 1 (CALHWP1) make cell surface hydrophobic[141-143]. Researchers notice that the main component of nicotine enhances extracellular

polysaccharides production as well as Candidal colonization. One to two mg per milliliter encourages Candidal biofilm formation. Furthermore, CALHWP1 and CALS 3 expression elevated when nicotine concentration was elevated. Nicotine significantly altered the composition and proportion of yeast cells, as well as the extracellular polysaccharide amounts which increase biofilm matrix and thickness which could promote oral candidiasis, especially CA as well as *C. parapsilosis* species[144]. Moreover, several results explain candidiasis and tobacco smoking, such as smoking was significantly associated with *Candida* pathogenicity in patients with clinically suspected oral leukoplakia and smoking worsens oral candidiasis and dampens epithelial cell defense response studied in experimental animals[145,146].

Over seven thousand identified molecules in tobacco cigarette smoke, these molecules may be free radicals and/or oxidants[147]. It has the potential to alter the oral condition and cause severe oxidative stress, thereby damaging the epithelial barrier of the mouth[148].

These oxidative molecules during smoking activate epithelial cells proteins called oxidative stress sensing proteins, especially nuclear factor erythrocyte 2-related factor 2 (NFERF2)[149]. The induction of NFERF2 is widely thought to have anti-inflammatory properties. Also, NFERF2 is transported into the cell nucleus in the existence of additional electrophilic chemicals to activate antioxidant enzyme genes expression, for instance, haem-oxygenase-1 and NAD(P)H dehydrogenase quinone-1[150,151]. Furthermore, NFERF2 inhibits the secretion of pro-inflammatory cytokines such as interleukin IL-1β and (IL)-6 in response to lipopolysaccharide[152]. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome recognizes several pathogens and is critical in the fight against CA infection[153].

In the oral mucosa, smoking caused redox dysfunction and oxidative stress. The NLRP3 inflammasome was negatively regulated by smoking-induced NFERF2, which impaired the oral mucosal defense response and exceed susceptibility to CA. The NFERF2 pathway may be engaged in the pathogenicity of mouth by mediating an antioxidative response to cigarette smoke exposure and suppressing human immunity against CA. The NFERF2's negative regulatory effect on NLRP3 is involved in smoking-induced oral mucosa immunosuppression, increasing susceptibility to CA. The NFERF2, which has been linked to inflammation and oxidative stress, is thought to be a possible therapeutic objective and a crucial regulator for smoking-related oral diseases and mouth candidiasis for instance leucoplakia[154].

Smoking causes disruptions in the buccal cavity and increases the risk of mucosal infections caused by CA[118]. Nicotine influenced CA pathogenic characteristics such as morphology, biofilm formation and hyphal growth, as well as virulence-related gene expressions, which were found to be differentially expressed according to cigarette nicotine concentration. Pure nicotine at MIC (4 mg mL^{-1}) inhibited CA growth, while 0.1 mg mL^{-1} enhanced biofilm formation. Cigarette smoke condensate, on the other hand, has no effect on CA biofilm formation at this nicotine below MIC concentration which it recorded at 0.10 mg per milliliter in the same study. Furthermore, both pure nicotine and cigarette smoke condensate increased the expression of the genes secreted aspartyl proteinase 2 as well as hyphal wall protein 1. Pure nicotine has a different effect on the formation of CA biofilms. An *in vitro* study found that antifungal treatments (below MICs) against CA reduce nicotine's effect on the expression of virulence-related gene. However, there is a chance that smoking will interfere with various concentrations of antifungal (amphotericin and fluconazole) treatments[118].

CONCLUSION

Numerous articles have studied the link between smoking and oral *Candida* carriage, but it is important to understand the relationship's fundamental mechanisms clearly from different sides especially when few researchers question the negative impact of smoking. This review has emphasized how smoking cigarettes affects the expression of genes related to virulence, the change from yeast to hyphal form and other pathogenic characteristics of *Candida*. Smoking tobacco is not only thought to speed up the transition process, but it is also a great medium for it. Smoking has the potential to worsen oral health conditions and increase oxidative stress, which can harm the mouth's epithelial barrier, prevent the release of pro-inflammatory cytokines and make *Candida* more pathogenic in people with clinically suspected oral leukoplakia. Moreover, smoking increased the oral mucosa susceptibility to *Candida*, suppressed host immunity against *Candida* and caused oxidative stress, redox dysfunction and oral mucosal defense response impairment. Furthermore, nicotine affects thickens and increases the biofilm matrix, which may encourage oral candidiasis. Thus, beyond any doubt that smoking cigarettes harm oral health, which harms overall health as a result.

SIGNIFICANCE STATEMENT

The effect of smoking on *Candida* as one of the most important opportunistic organisms and evidence of the balance of the oral microbiota. This study introduces a complete view of the relationship between tobacco smoking and oral candidiasis and explains how tobacco smoking enhances oral candidiasis by promoting Candidal

pathogenic characteristics. This study will help the researcher to uncover the role of tobacco smoking in Candidal vorticity and pathogenicity in addition to the understanding negative impact on the oral cavity and immune response of the host.

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