Review

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Exploring the Impact of Tobacco Usage on Microbiome Dysbiosis and Associated Health Risks: A Comprehensive Review of Recent Advancements and Future Directions

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Abstract

All over the world, tobacco usage is quickly expanding. Though it presents a major health risk and is anticipated to have long-lasting impacts on the public and economic health of the country, its consumers are increasing with every passing day. Tobacco is being used in a variety of ways, with cigarettes being the most popular. Smoking affects the healthy oral, intestinal, and pulmonary microbiomes, often altering the dynamic equilibrium of the diverse bacteria that make up the human microbiome, or "dysbiosis". Smoking-induced dysbiosis can lead to developing conditions like asthma, chronic obstructive pulmonary disease, Crohn's disease, ulcerative colitis, and periodontitis. The purpose of the following article is to provide a better and more comprehensive overview of the key areas that the tobacco industry needs to investigate, such as microbiome manipulation, to provide a complete picture of recent advancements in tobacco research while also keeping public safety in mind, and the various diseases linked to tobacco use. ***Clin Ter 2023; 174 Suppl. 2 (6):119-125 doi: 10.7417/CT.2023.2478***

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Introduction

Tobacco use has grown and diversified substantially since its introduction in Europe, in the 15th century. Until the 18th century, the most widespread forms of tobacco intake were smokeless or sublingual tobacco (also known as snuff) and pipe smoking. Nowadays, approximately two billion individuals worldwide consume tobacco products, predominantly by smoking cigarettes—which emerged in the nineteenth century and has gained in popularity ever since (1). Moreover, it has been observed that annually a minimum of four million individuals across the globe suffer from diseases associated with tobacco use (2), which include chronic obstructive pulmonary disorder, (3, 4) cardiovascular disorders, (5, 6), autoimmune diseases (7, 8), and numerous forms of cancer, imposing a significant financial burden on the healthcare sector (9, 10).

Despite cigarettes being the most widely used tobacco product, there are still many alternative ways to consume tobacco: some of these have been around since the days before cigarettes were widely available and have managed to survive and keep a substantial user base ever since (11,12). On the other hand, also new alternatives have been developed in the last years: for instance, vaping (that is using electronic cigarettes or e-cigarettes) and heated tobacco products are two new ways to consume nicotine that have been created in response to the significant rise in smoking-related mortality (2, 13). These new forms of usage, which are promoted or portrayed as being safer or harmless, have attracted both the new generations and long-time smokers (14-16). Table 1 presents a list of commonly utilized tobacco forms.

The prevalence of tobacco usage among young individuals is widespread globally. Apart from adults, also children and young individuals in the US face a significant health hazard, which is expected to have enduring consequences on the social and financial well-being of the nation (17). It is indisputable and well-documented that tobacco accounts for 75% of healthcare expenditures in the US (18). Primarily, the initiation of tobacco consumption typically occurs

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Table 1. Various ways to consume tobacco for daily use

Product	Definition	pH
Cigarette	Paper-rolled tobacco for smoking.	5.5-6 (acidic)
Cigar	The process of air-curing and fermenting tobacco is followed by the use of a wrapping material that incorporates tobacco leaf in various manifestations.	Products might have a buccal or inhalable pH between 6.5 (acidic) and 8.0 pH (alkaline)
Blunt	Cigarillo shells held cannabis.	-
Heated tobacco	Electronic devices generate heat in order to produce an aerosol by treating reconstituted tobacco sticks with a humectant (glycerin).	5.5-6 (acidic)
Chewing tobacco	The act of placing tobacco between the lip and gum or inhaling it through the nasal passage.	Range from more acidic (5.2-7.1) to more alkaline (pH 7.6-8.6)
Waterpipe/hookah	The process involves using charcoal to heat flavored tobacco, which subsequently undergoes a cooling effect upon traversing a chamber filled with water.	3.8-5.8 (acidic)
Electronic cigarettes	Devices that use electricity to turn a liquid into a spray, usually containing flavorings, propylene glycol, and nicotine.	7-9 (alkaline)

during teenage years and adolescence (19): over 88% of adult daily smokers affirm that they initiated their smoking habit before reaching 18 (20). During this developmental phase, individuals exhibit heightened vulnerability to social influences, including the persuasive tactics employed by tobacco advertisements, which exert a disproportionately adverse effect on the vulnerable minds of the youth (21). According to Fagerström and Doll (YEAR), cigarettes are the exclusive consumer product globally recognized for its association with premature mortality, affecting around 50% of those who smoke regularly (22, 23). Furthermore, this epidemic continues to affect the US, as well as other countries with lower or moderate incomes, which are not equipped to handle the resulting health and economic consequences (24, 25).

Besides addressing Public Health issues, the tobacco industry works constantly for innovating and looking into ways to make tobacco use safer and develop substitute behaviors. New research directions must be investigated to accomplish these goals. Therefore, the following article aims to present a better and more thorough overview of the important areas that the tobacco business needs to explore—including microbiome manipulation—to give a thorough picture of recent developments in tobacco research while keeping public safety in view, and the different diseases associated with the usage of tobacco.

Tobacco Use and Microbiome Dysbiosis

Cigarette smoking or any other form of tobacco use have been associated with several severe illnesses (26); additionally, they can cause the colonization of pathogenic bacteria by altering immune responses and the microbial communities that are connected to human beings, which are sensitive to many environmental factors (27-29). Smoking can affect the human microbiome, which includes different groups of microbes like viruses, protozoa, bacteria, and fungi, in different diseases (30). The human microbiome has the ability to maintain homeostasis in any case of disturbance, which can be influenced by factors like alcohol, antibiotics, smoking, and diet (31). Table 2 displays the variations in the microbiome across various species.

Many clinical disorders and health conditions have been associated with various constituents of tobacco, including fine particulates, chemicals, and heavy metals (41-48). Recent studies have reported that the diseases linked to smoking can be caused by the microbes present in tobacco. The microbes that have been identified in tobacco flakes, fresh tobacco leaves, or fine tobacco particles are *Acinetobacter calcoaceticus*, *Pantoea agglomerans*, and species of Pseudomonadaceae like *Stenotrophomonas maltophilia* and *P. fluorescens*; these microbes have been studied because of the DNA sequencing technology, which help in their identification through microbes' culturing (47).

Tobacco has the ability to suppress our immune system: it can lead to impairment of the bacterial community in the smoker's organism and thus affect their antimicrobial defenses. Tobacco smoking can impact the peripheral immune system by decreasing the action of natural killer cells and increasing the number of leukocytes in the body, thus increasing its vulnerability toward infection (49). Research has shown that smoking impacts the functionality of neutrophils and macrophages, leading to a reduction in dendritic cells and increased numbers of lymphocytes, macrophages, neutrophils, and eosinophils. Dendritic cells are integral components of the immune system, fulfilling crucial functions (50, 51).

The Role of Tobacco in the Development of Periodontal Disease

A considerable body of research indicates a strong association between the occurrence of periodontal disorders and both tobacco use and the highly complex microbial populations residing inside the subgingival sulcus (52-54). Tobacco smokers had a notably elevated susceptibility to the development of severe periodontal disease (55). Current research examined the microbial configuration of patients

Table 2. Alterations in the diversity of the smokers' microbial community

	Source	Specimen	Enriched microbes	Diminished microbes	References
Oral	Human	Subgingival plaque	Species: Pseudoramibacter alactolyticus, Fusobacterium nucleatum, Pseudomonas pseudoalcaligenes, F. naviforme, A. haemolyticus, Filifactor alocis, A. baumannii, Dialister microaerophilus, A. schindleri, Desulfobulbus sp. Clone R004, A. guillouiae, Megasphaera sueciensis, Acinetobacter johnsonii, M. geminatus, M. micronuciformis, M. elsdenii	Species: Hemophilus parainfluenzae, Streptococcus sanguinis, Neisseria subflava, S. parasanguinis, A. dentalis, S. oralis, A. israelii, Granulicatella elegans, Actinomyces viscosus, G. adiacens	(32)
Oral	Human	Oral wash samples	Genera: Streptococcus, Atopobium, Lactobacillus, Bifidobacterium		(33)
Oral	Human	Mouth wash sample	Genera: Atopobium, Treponema, Prevotella, TG5 and Mycoplasma, Porphyromonas, Megasphaera, Paludibacter, Dialister Phyla: Bacteroidetes and Actinobacteria, Spirochaetes, Synergistetes and Tenericutes	Genera: Leptotrichia, Neisseria, Fusobacterium, Eikenella, Lautropia, Aggregatibacter, Haemophilus, Actinobacillus Phyla: Cyanobacteria, Proteobacteria, GN02, Fusobacteria and SR1	(34)
Airways	Human	Oropharyngeal and nasopharyngeal swabs	Nasopharynx Genera: Eubacterium spp. Eggerthella, Anaerovorax, Dorea, Erysipelotrichaceae I.S. Oropharynx Genera: Veillonella spp., Megasphaera	Nasopharynx Genera: Shigella spp. Oropharynx Genera: Neisseria spp., Capnocytophaga, Fusobacterium	(35)
Airways	Mice	Lung	Genera: Oxalobacteraceae, Escherichia-Shigella, Trichococcus	Genera: Caulobacteraceae-unclassified, Oceanospirillales, Raoultella, Lactobacillus, Caulobacteraceae-Phyllobacteriaceae-uncultured, Lactobacillaceae, Enterobacter, Acidimicrobiales-norank	(36)
Airways	Human	BALF	Virome: Haemophilus, Rhodoferax phages, Prevotella, Capnocutophaga, Xanthomonas, Aeromonas and Actinomyces	Virome: Spiroplasma phages, Lactobacillus, Enhydrobacter, Gardnerella phages, Morganella, Enhydrobacter, Holospora and Enterobacter	(37)
Gut	Rat	Caecal contents	-	Genera: Bifidobacterium sp.	(38)
Gut	Mice	Caecal contents	Genera: Clostridium sp.	Genera: Segmented filamentous bacteria, Lactococcus sp., Enterobacteriaceae sp. and Ruminococcus sp.	(39)
Gut	Mice	Colonic sample	Genera: Lachnospiraceae sp.	-	(40)

who suffer from moderately to severe prolonged periodontitis in smokers. The results of the study revealed significant variations in the prevalence of disease-causing bacteria and those that are linked to oral health. Specifically, there was a higher prevalence of *Fusobacterium*, *Treponema*, *Bacteroides*, *Parvimonas*, and *Campylobacter*, while *Veillonella*, *Streptococcus*, and *Neisseria* were found to be at lower levels (56). Many different mechanisms contribute to the increased risk, progression, and severity of periodontal conditions in smokers.

There are several elements that contribute to the negative impacts of tobacco use on dental health. Initially, tobacco use leads to decreased blood flow to the gums, resulting in limited delivery of essential nutrients and oxygen and impaired removal of waste products. Secondly, tobacco use suppresses the immune response, particularly the inflammatory response, which is crucial in maintaining oral health. It also hinders the periodontium's ability to recover, both structurally and functionally. Lastly, disrupting the balance of oral microbiota subsequently leads to heightened vulnerability to diseases. The confluence of these several factors hinders the process of wound healing, thus making the progression of periodontal disease faster (57).

Probiotic Interventions and Harm Reduction Perspectives

Within the broad spectrum of reported results, in vitro studies have demonstrated that: (i) The regulation of the immune system and inflammation is influenced by exposure to periodontal pathogens, which in turn affects the development of cellular mediators; (ii) There is an hindrance in the growth and attachment of infectious organisms to dental surfaces; (iii) The release of diverse antimicrobial agents modifies the surrounding environment (58, 59).

A potential player in overcoming microbiome dysbiosis could be a probiotic called *Lactobacillus reuteri* (*L. reuteri*), which has the ability to secrete certain antimicrobial compounds, including lactic acid, reuterin, and nitric oxide (NO) (60, 61). In particular, the last compound has bactericidal properties against anaerobic strains *F. nucleatum* and *P. gingivalis* (62, 63). Moreover, the antimicrobial molecules show a broader spectrum of inhibitory activity, including many types of microorganisms, like fungi and protozoa (64). Lactic acid bacteria can produce bacteriocins, bioactive chemicals that demonstrate inhibitory properties against particular periodontopathogens. There are examples in literature that show their use in the treatment of periodontitis, regardless of the concurrent use of chlorhexidine, which is a wide-spectrum antimicrobial substances (65, 66). Probiotics induce alterations in the activity of immune cells, thus indirectly influencing their impact on periodontopathogens: one such effect is the stimulation of macrophages to produce reactive oxygen species (ROS) (67). The presence of certain factors may result in adverse effects on anaerobic microorganisms, like *P. gingivalis*, that thrive in low oxygen conditions (68). Additionally, *L. reuteri*'s anti-inflammatory and cytokine-secretion-inhibiting properties are likely to be responsible for its positive impact on periodontal infections (69-71). The potential anti-inflammatory effects of *L. reuteri* may contribute to the regulation of the matrix metalloprotein and tissue inhibitor of metalloprotease-1 balance, as well as the inhibition of pro-inflammatory cytokines. These effects may potentially mitigate inflammatory processes and the degradation of periodontal tissues (72).

Harm reduction measures in the context of tobacco smoking is a subject that elicits different points of view. There are apprehensions over the potential impact of promoting smoking reduction on individuals' long-term cessation motivation. It is suggested that such efforts may inadvertently create a setting that would be beneficial to the promotion of "reduced risk" products by the tobacco industry, as well as to conducting biased studies aimed at demostrating their efficacy (73). The primary focus in addressing the negative consequences linked to tobacco smoking should be on promoting smoking cessation as the most impactful strategy (74). Using tobacco-related products in a way that is less detrimental than conventional goods (potential strategies to mitigate the harmful effects of cigarettes include employing novel curing methods to decrease tobacco-specific nitrosamines, incorporating catalytic agents to minimize the production of aromatic polycyclic hydrocarbon cancerous substances in smoke, using genetically altered crops to minimize nicotine or nitrosamine content, or implementing filtering techniques in order to selectively decrease the overall quantity of toxic substances) and pharmacological interventions (tools that resembles cigarettes, such as ones that heat up instead of burning their tobacco content) to diminish tobacco consumption or mitigate associated health risks (75).

Several of the chemicals used to develop drugs in pharmaceutical companies have been linked to negative consequences and significant expenses (76, 77). Therefore, natural products like curcumin, propolis, aloe vera, and honey have garnered significant attention from the nutritional and pharmacological sectors. This is due to their easy accessibility and potential use in cost-effective therapies with minimum or no toxicity, in contrast to traditional techniques (78, 79). The abundance of bioactive chemicals has several benefits, such as anti-inflammatory, anticancer, antimicrobial, anesthetic, and wound-healing effects. These compounds can potentially disrupt multiple cellular signaling pathways, which could influence the development of oral mucositis and the behavior of cancerous cells (80).

Polyphenols have emerged as promising natural therapeutic agents for combating oral infections (81). Olives contain significant quantities of phenolic chemicals, with varying concentrations that range from 1% to 3% of the olive's total weight in its fresh state. Olives include a diverse array of phenolic chemicals, including flavonoids, phenolic alcohols, secoiridoids, and phenolic acid, with the latter being of particular significance. Phenolic compounds like tyrosol and hydroxytyrosol have the most significant levels of occurrence inside olives, and are very interesting for their antioxidant, anti-inflammatory, and anti-microbial activities (82). According to previous reported studies, olive leaf extract intake resulted in a significant reduction in oral mucositis, which may be attributed to the observed decrease in levels of IL-1β and TNF-α in saliva (83). Olive leaves contain polyphenols that exhibit anti-inflammatory properties and provide protection to DNA against oxidative damage caused by free radicals. Regular use of extra virgin olive oil, which contains many omega-3 fatty acids and monounsaturated fatty acids, has been shown to decrease the occurrence of macrovascular problems and to suppress the synthesis of inflammatory proteins, including interleukin-6 and C reactive protein. There is a need for more investigation into the molecular processes that are potentially responsible for the protective effects of polyphenols in relation to numerous health issues (84).

Conclusions

Maintaining high levels of research and innovation within the tobacco industry is essential for enhancing the health benefits of non-smoking consumption methods and for reducing smoking-associated risks. Microbiota manipulation opens up promising new possibilities for reducing the harmful effects of tobacco-related substances and for improving smokers' health.

Future Prospects

The increasing emphasis on fitness and balance compels us to reassess our stance towards cigarettes and other excesses. It is impossible to overemphasize the importance of tobacco-related research and development. We can try to create less harmful options for smokers by learning from other sectors' successes, like the availability of Coca-Cola Zero. The use of novel technologies and natural substances can reduce tobacco product toxicity and prioritize consumer health. The introduction of biodegradable cigarette filters, for example, is an excellent illustration of how research may play a significant role in mitigating the adverse consequences of tobacco use, while also ensuring environmental sustainability. Using such filters primarily aims at mitigating the adverse environmental impacts associated with removing cigarette butts by utilizing eco-friendly materials, specifically plant-based fibers. Preliminary investigations have yielded encouraging findings, demonstrating notable decreases in carcinogenic substances and other detrimental components inside filtered smoke. Additional investigation and improvement of these filters will have the potential to enhance the safety of smoking for individuals, and will be able to address environmental issues linked to tobacco waste. The potential advantages of natural substances in enhancing oral well-being have also received considerable study. According to existing research, integrating these natural components into oral sprays or alternative delivery systems can offer a safeguarding effect against oral health problems caused by smoking. Additional research will help in better understanding the appropriate dosage, effectiveness, and impact of these substances.

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Conflicts of interest statement

Authors declare no conflict of interest.

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